Research Article

THE IMMUNOLOGY OF MIND CONTROL (PART IV)

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ABSTRACT

The brain reaches down into the bowels. That reality is shocking and not what neuroscientists want to hear. However, one has to develop a propensity for uncleanliness in order to hold the vulnerability of our existence in our hands. It is not just about neural connections and bacterial cross-talk. It goes far beyond that to the innate processes which revive our consciousness and programme our most primitive behaviour. Microbes affect our sleep. They also affect how we socialise and how we eat. They accomplish this through simple mechanisms, for example by lowering the threshold of the hypothalamic–pituitary–adrenal axis, and in this way disturbing the body and mind with cortisol and inflammation. Yet, it goes deeper than this. By gaining access to the homeostatic arsenal, microbes prevent the brain from regenerating during sleep and from laying down new memories. This throws the psyche and, eventually, the human spirit off course and the individual becomes isolated and depressed. This is wonderful news for a symbiont turned rogue.

Over the past 50 years, a few burning questions have been at the forefront of biological science. In textbook sketches, the lymphatic system stopped at the head. All along it felt wrong and there was a feeling that blushes were inevitable. We said things such as, 'Don't sneeze too hard – you're losing brain cells!' – almost taking every last sip from the cup of our predestined human potential. We were taught that nerves could never regenerate and that you should never bump your head. We had just mastered machines and begun to peer over the edge. We became fascinated with numbers. First it was, 'How many genes does each one of us possess?' After discovering that it was half that of the rice plant, we panicked a little, but had to find something to do with all those counting machines. So we counted something else and turned our attention to the microbes in our gut. To our horror, we realised that they made identical neurotransmitters to our own and used the same receptors to listen in on the cross-talk as we do. Genetics, epigenetics and artificial intelligence – the pebble was now skimming across the water. Yet did we ever ask, 'How do immune cells get into and out of the brain?'

Later, supercomputers began sending back some really big numbers – noughts and ones that made us realise that we would never touch down where we were planning to go. Our own infinity seemed to mirror that of the universe. The 100 billion neurons in our brain (and ten times more glial cells), the four billion thoughts that we receive each second and the trillion different odours that we smell at any given moment subdued the commentary, and teachers began to 'contemplate' while holding their cups of coffee.[1] Thought became contemplation because theoretical physics lacked theory. However, this forced us to 'debate' because the silence became too deafening. Only those who spoke with earphones and open collars became privy to what was mesmerising.

And all the while we had to listen and were denied what was real. In the haze, we learnt that each neuron was a Krakatoa and that each cell is engaged in 100 000 chemical reactions per second.[2] Yet we never asked, 'Who cleans up after the party?' We never realised that our brains were not created to think or do maths – they were created in order to help us to survive. The cerebral cortex does not register a tomorrow, nor does the cerebellum, and nor does the brainstem – and neither should we. The splendour of our vulnerability depends on how we get through each day.

During the day, the brain consumes energy voraciously as it explodes with crackling and electricity – billions of Krakatoas erupting simultaneously. As a result, huge mounds of toxic metabolic waste start piling up everywhere – Tau and beta-amyloid proteins, carbon dioxide, ammonia, and all the excitatory glutamate and potassium from the frenzied depolarisation that was spilled among the debris.[3] This is an extremely volatile situation because it takes only a spark to re-ignite all of the static. All that is needed now, is for mathematics to get in the way of things again:

- Equation One: the half-life of a single protein in the brain is 24–48 hours and each neuron produces 500 million proteins daily – now multiply this by 100 billion.
- Equation Two: it takes a single molecule of beta-amyloid, which weighs 3 kDa (kilo Dalton), 100 hours to be moved 1 mm across the interstitial space.

Therefore, how does the brain get all the moving done before the fires are lit the following day? And where does all of this glue, which is so noxious to neurons, disappear to at night?[4]

Whatever happens, the repair process must be 'cheap', because all of the adenosine-triphosphate (ATP) has been burnt. In addition it must also be simple. The secret lies in the anatomy of the pia mater of the meninges and the great cerebral arteries that it covers. A funnel-shaped space exists between the pia mater and the endothelial cell as the artery plunges into the depths of the brain parenchyma. During deep sleep, cerebrospinal fluid (CSF), which has drained from the basal cisterns and subarachnoid space, accumulates in this funnel and is forced down by the strong arterial pulsation of the great arteries.[5] At the nether reaches of the artery, its basement membrane fuses with that of astrocyte foot processes, which now skirt the arterial surface (Figure 1). Once the CSF has reached this region, it leaks through aquaporin-4 water channels in the foot processes of the astrocytes and out into the interstitium. CSF therefore permeates the brain without using energy. But how does it flush the brain without using energy?

Norepinephrine peaks during daily physical activity and inhibits CSF production by choroid-epithelial cells in the ventricles. At night, the negative feedback is released, which enables CSF production to continue.[6] Systolic blood pressure is significantly lower at night and is therefore insufficient to propel CSF across the interstitial space. In order to overcome this limitation, either the body needs to create a greater perfusion pressure by manipulating cardiac output or more space must be found in the brain in order for a low-pressure system to facilitate passive diffusion. Think of it as simple housekeeping: in order to vacuum the lounge, one has to rearrange the furniture. Almost unbelievably, a similar process occurs in your brain while you sleep. The solution lies in the ability of the astrocytes – which form the scaffolding upon which all cells in the brain are suspended – to contract, increasing the interstitial space by more than two-thirds.[7] In fact, the brain literally shrinks by 33–50% during deep sleep, allowing 500 ml of CSF to oscillate throughout the central nervous system (CNS) (Figure 2).[8]

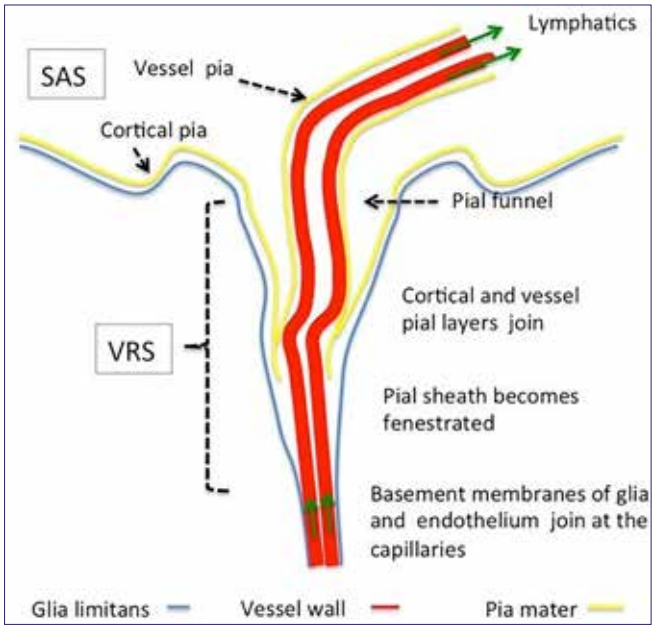

Figure 1: CSF accumulates in the pial funnel and is driven into the depths of the brain by the pulsation of the cerebral arteries. SAS - subarachnoid space; VR - Virchow-Robin space

The astrocytes contract as a result of ion fluxes in the interstitial fluid, which implies that this is not an energy-dependent system. Waves of CSF equally distribute glucose, lipids, amino acids, neurotransmitters and vital immune cells to even the most isolated neuron, while ammonia, beta-amyloid and other toxic metabolites are flushed out of the brain along the veins simultaneously.[9] Until now, the manner in which immune cells entered the brain was unknown. This process is called the 'glymphatic system'. It is a simple, brilliant and energy-efficient system that allows us to feel refreshed after a good night's sleep. It also protects against the build-up of beta-amyloid, which is central to the pathogenesis of Alzheimer's disease.[10]

Another recent discovery of immense significance accounted for the final step in the glymphatic system. In 2015, researchers at Virginia University discovered that a rich supply of lymphatic vessels exists in the dura mater, a thick, leathery membrane that envelopes the brain.[11] Until that point, the brain was believed to be devoid of lymphatic drainage, which posed an enormous dilemma in human physiology: a mechanism by which waste could be excreted from the brain could not be accounted for. With the discovery of these two systems that function in tandem – namely, the glymphatic system and the brain lymphatic system – it now becomes evident that all forms of microbe and their metabolites are able freely to access and influence the CNS. These are ground-breaking discoveries in the field of Immunology, and they create a myriad diagnosis and treatment options.[12]

If bacteria can pass into the depths of our brains along well-defined anatomical routes, then can they also access the

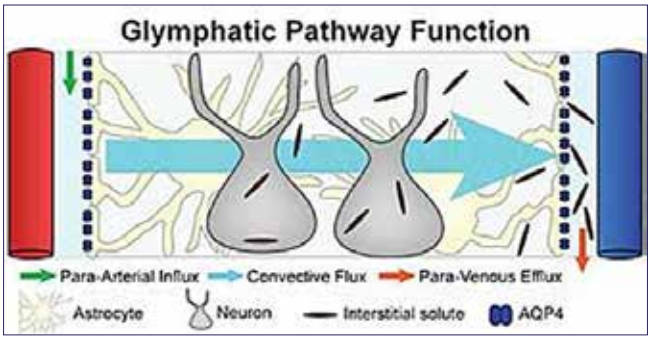

Figure 2: Astrocytes shrink by 33–50% during deep sleep in order to facilitate CSF flux

subconscious and in so doing, manipulate our behaviour? If specific food types are central to their survival, then bacteria will manipulate our behaviour in one of two ways: either by creating cravings for certain foods, or by inducing a sense of dysphoria in order to isolate the host, and in that way increasing the likelihood of foods that will benefit their fitness being ingested.[13] If this is true, then the limbic system, and in particular the hippocampus, becomes central to their cause. The hippocampus, which means 'sea monster' in Greek, can roughly be divided into two parts – the ventral hippocampus or the 'head' and the dorsal part representing the 'tail'. The hippocampus is critical to memory and learning, and at its core lies its role in mapping out the environment for the purpose of finding food.

Important visual cues pertaining to the environment – the topography or landscapes and significant objects or markers – are constantly relayed to the dorsal hippocampus in order for the brain to register change in the immediate surroundings.[14] Invariably, the environment can change only if the person is moving or walking. Should this occur, and the individual becomes more engaged in discovery or exploration, oxytocin is released. This oxytocin acts as a chemical switch and inactivates the ventral hippocampus.[15] It goes beyond feeling happy. Purposeful and strenuous endeavour, which is the combination of action and thought, creates a chemical surge of oxytocin and a sense of fulfilment (not reward).[16]

Conversely, if the environment is perceived as being stagnant and fresh visual cues are not being processed, this results in aberrant social behaviour.[17] The ventral hippocampus then activates the amygdala or 'emotional brain', which in turn hits the 'panic button' or stria terminalis, and a defensive response is initiated.[18] Cortisol is secreted by the hypothalamus and consequently sleep, appetite and immunity are adversely affected.

However, this is only the beginning of the problem. One of the most crucial scientific discoveries to have occurred over the past few decades has been the revelation that immature neurons are formed daily in the dentate gyrus of the hippocampus (Figure 3).[19] In fact, at least 700 (and possibly thousands of) neurons are nurtured and processed every 24 hours along a 'supply line' which is located in a distinct 'neurogenic niche' of the hippocampus.[20] It is an 'expensive' energy system that is maintained by the glymphatic system (which is relatively 'cheap'), and therefore the two can co-exist.[21] These new neurons are incorporated into the local circuitry at a very early stage of their development so that new 'hubs' in the network can aid visual memory and learning.[22,23] What, then, the reader may ask, has the formation of neuronal precursors got to do with movement and the visual exploration of the environment?[24] The secret lies in the 'brain fertiliser', or brain-derived neurotrophic growth factor (BDNF), which promotes the growth, differentiation and survival of this vulnerable sub-population of neurons.[25]

BDNF is released at the neuro-muscular junction during prolonged periods of significant motor activity.[26] In order to solidify the intimacy between the body and the brain, imagine a cattle rancher in the 'Old West' who has to acquire more and more land in order to sustain an ever-expanding herd. First, he will be forced to ride over greater distances in order to survey the terrain and map his territory. This will result in greater concentrations of BDNF being released from his muscles. Secondly, he will have to memorise the topography and landmarks of this new territory, so that he can quickly identify any threat to both himself and his cattle.[27] This will require enhanced levels of neurogenesis in his hippocampus, the site of memory and learning.[28,29] Object recognition and spatial learning (neurogenesis) cannot occur without BDNF.[30] The question may then be asked, 'Won't the stress of this exercise also elevate his blood cortisol levels and inhibit neurogenesis in the dorsal hippocampus?'[31] Fortunately, oxytocin, which protects against the effects of cortisol on the dorsal hippocampus and promotes neurogenesis, is also released during exercise (and sexual intercourse).[32,33] Therefore, the more an individual is mentally stimulated by a changing environment, the greater the possibility for that individual to reproduce.

To extrapolate further, if the brain is not being continuously stimulated and making new neurons, this 'stress' will activate the reverse pathway, and the amygdala will perceive the lack of 'positive' input as 'depression', even though no other (ancient) emotional circuits have been located in the brain.[34,35] The duration of neurogenesis is six weeks, the time required for antidepressants to become therapeutic. However, the adequate blood levels of antidepressants are attained within 72 hours.

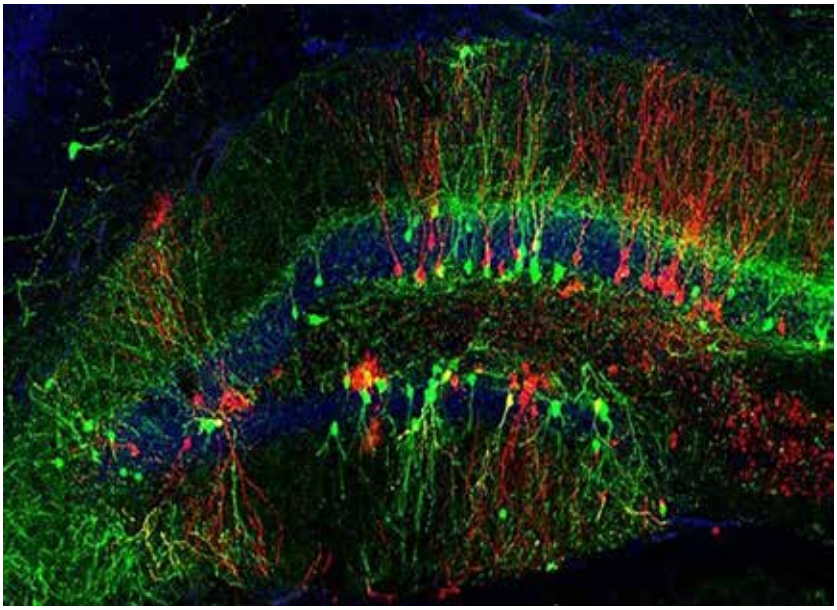

Figure 3: Nestin (green) and doublecortin-staining (pink) neuronal precursors in the neurogenic niche of the hippocampal dentate gyrus

This implies that the clinical effect is due to their direct influence on neurogenesis as opposed to a 'suppressive' effect on the amygdala.[36,37] Turmeric, blueberries and green tea produce a similar antidepressant effect, and are also known to promote neurogenesis.[38,39] Modern living revolves around the garage, the office and the lounge. Nothing changes – physically or spiritually – and our hippocampal neurons detect the emptiness.[40] With no walks outside in the open or talks around the supper table, depression is now the major cause of disability in the world, and novel therapeutics are drastically needed.[41,42,43] As the amygdala is also connected to the prefrontal cortex via the nucleus accumbens, the 'unhinged' hippocampus readily supports the 'reward pathway' and addiction that is rife in our society.[44,45]

To make things worse, eating is not controlled by will but by memory.[46] Once our brains get caught in this rut – and our self-esteem plummets even further – the amygdala disconnects from the mind (or the dorsal circuit) and concentrates on visceral 'feelings' from the body.[47] To our shame, three basic instincts grab hold of our behaviour: ingestion (feeding and drinking), sexual drive and defence or aggression, the primary inputs to the amygdala.[48] We begin to react to how we feel because the rumbling in our stomach or the sweaty palms must mean something – the body doesn't lie! So when we smell fresh bread in a bakery, that 'rumbling' tells us that we must be hungry, even though we aren't. See how quickly the brain seizes an opportunity and how slow it is in determining reason. However, there is often a reasonable explanation behind the ruse – 'rumbling' can increase mucous secretion and release digestive enzymes. Now the psychopathology has purpose and we delve deeper into ourselves: more shows on celebrity chefs, more alcohol and a greater desire for the body. Now filling the gap depends upon 'rediscovering' your inner potential, and all the while your hippocampus shrinks and you become more stressed – modern progress![49]

The gut–brain axis ('bottom-up') becomes the brain–gut axis ('top-down') and the mind is obscured by the disease of the body.[50,51] This strong correlation between psychiatric and gastrointestinal disorders is well known.[52] It was never meant to be this way: the gut was designed to support the brain through the microbiome. Bacteria make exactly the same neurotransmitters that we do, and they can sway our moods and way of thinking.[53,54] They also break down complex fibre to short-chain fatty acids, which not only grow the gut locally but reach the brain and open up chromatin so that DNA can be translated and converted into BDNF.[55] In this way, they get to the heart of what we focus on and how we react by ensuring that there is a constant supply of new neurons in the hippocampus for the rest of our lives.[56,57,58] Pathogens disrupt this process by generating cravings and converting low-quality starch into opiates and benzodiazepines.[59] As their numbers increase, they isolate the individual and flood the brain with inflammatory molecules from the systemic circulation, which then drive microglia to attack and destroy the neuronal precursors.[60,61,62]

In the result the host becomes more sedentary and less inclined to experiment. The mental decay spreads to the amygdala, where simple physiological sensations are elevated to 'emotions'. We become 'depressed' as a result of that 'gut feeling'. Tumour necrosis factor and substance-P start filling the abdomen, and nausea and pain confirm these 'thoughts'. Now the cycle is complete and the bacterial niche replaces the neurogenic niche.[63] Sweet and unrefined starch comes pouring in and inflammation abounds. The wrong signals keep on going up the vagal nerve to the brainstem and the threshold for the hypothalamic-pituitary axis (HPA) is lowered.[64,65,66] Cortisol flows freely and sleep cycles are fragmented. As cortisol supresses the gene for BDNF, sleep deprivation inhibits neurogenesis.[67,68] Less (deep) sleep means more time for eating and weaker memory consolidation. Balance is forgotten and loneliness creeps in – no more oxytocin and no more grass. Now work on your chest, phone your spouse and apologise for being late, and buy those chicken nuggets on the way home.

Stop! You, your spouse and your child, need walks and talks and normal bacteria for a normal brain.[69]

CONCLUSION

We have just entered the psychobiotic revolution, a worldwide phenomenon that is sweeping through our consciousness. Until now, we have never thought of ourselves as being inherently 'diseased' because our human structure and function were never viewed as being the culmination of a direct physical injury. The 'injury' was always 'external'. We are overcrowded and over treated. The injury was antibiotic resistance. We modernised and sterilised. The injury was autoimmunity. We praised convenience and stopped walking. We praised productivity and stopped talking. Insufficient brain cells were being made. We started to feel bad after the drain in oxytocin, and became infertile. The environment was not only meant to provide short chain fatty acids for our memory but cognitive flexibility for our endeavour. We didn't start the fire. Through abuse of the microbiome, we have become the 'fire', and therefore the world can no longer be controlled by will.

But we neglected the basics. Now we know that the glymphatic system disperses immune cells across the brain while we sleep. We know that pathogens and toxic metabolites can be drained through brain lymphatics. And we know that dysbiosis lowers the threshold of the HPA-axis and disrupts sleep cycles through elevated cortisol. We have to sleep more. We know that the right diet selects symbionts which increase BDNF and that exercise also promotes neurogenesis. We know that if you do not explore, in every sense of the word, your prefrontal cortex will disconnect and your perception of time will stand still. You become stuck in a rut. Time drags on and you feel socially isolated. You wait for the next text message so that dopamine can spike and activate the reward system. The brain becomes primed to seek the 'quick fix' so that satisfaction can shorten your day. The rumblings of your body become important. Ingestion and the body, lock you in.

What we didn't know is that pathogens want you to be like this. All that they need is sugar. They don't need sun or photosynthesis. They have been stuck in the depths of the large colon for billions of years, and depend on us entirely for their survival. What we didn't know is that these 100 trillion microbes are continually

'quorum sensing' and comparing their ecological fitness by means of a simple 'ticker-tape' counting system. They have found a way to programme our most innate behaviour using the identical neurotransmitters and receptors that we make in our brains. They want one person to eat the same thing over and over. And you probably thought initially that linking short-chain fatty acids (SCFAs) and movement to neurogenesis and depression, pathogens to starch and opioid cravings and oxytocin to infertility was extreme!

Forget 'artificial intelligence'. Don't focus on external 'injuries'. See the microbiome as your 'subconscious', and be disturbed by this. This is no longer fanciful thinking. This topic has flooded the latest issue of *National Geographic* magazine, and is a stern reminder for us to change the world one person at a time.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

This article has been peer reviewed.

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