**Commentary**

# The Brain: Is it a Next Frontier to Better Understand the Regulation and Control of Hematopoiesis for Future Modulation and Treatment?

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Running Title: Brain, a Next Frontier to Regulate Hematopoiesis

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**Abstract**

We wish to suggest the possibility there is a link between the brain and hematopoiesis in the bone marrow and that in the future it may be possible to use such information for better understanding of the regulation of hematopoiesis, and for efficacious treatment of hematopoietic disorders.

## Introduction to Brain

As a very brief introduction to the brain we provide the following. The brain is highly complex, and is comprised of three major anatomical units: the brainstem, the cerebellum, and the forebrain. The brainstem consists of the medulla, pons, and midbrain. Collectively, these structures mediate voluntary and involuntary movement, communicate sensory information from the periphery, are essential for consciousness, and control the cardiovascular and respiratory systems. The brainstem also contains the cell bodies of nerve cells (neurons) that are involved in emotional, cognitive, and behavioral regulation. The cerebellum sits at the junction of the brainstem and forebrain, and is important for maintaining motor coordination and balance, and may influence cognition. The forebrain (also called the cerebrum) is divided into the telencephalon and diencephalon, both of which are further divided into multiple structures and subdivisions. The telencephalon is the cerebral cortex, which is the ultimate information processing center. A short list of its functions includes (but is not limited to) perception, comprehension, learning and memory, emotions, decision-making, language generation, and it serves as the overall behavioral control center. The dicencephalon contains several structures that integrate and process many types of information coming from both the brainstem and the cortex, including regulation of body functions (hypothalamus), multiple types of sensory information (thalamus), emotion generation and learning and memory (amygdala and hippocampus, respectively), and generation of directed movement and actions (basal ganglia). Despite the accumulating wealth of information and knowledge that the field of neuroscience has generated, there are still a myriad of functions that the brain performs that essentially remain a mystery.

## Why this Commentary?

The first author of this commentary, as have others, has been fascinated with the brain and its functions, exactly what it is capable of. We now ask how it may, in the future, be modulated/programmed for health benefit. After reading the book entitled: “When Einstein Walked with Gödel. Excursions to the Edge of Thought” (1), the first author, who originally started college as a math major, was intrigued by the third chapter entitled: “Numbers Guy: The Neuroscience of Math”. While this chapter dealt with the brain and mathematical prowess and the limited knowledge available in this area, it got the first author thinking about the brain and hematopoiesis. The following commentary is thus meant to serve as a provocative correspondence to stimulate thinking and work in the area of communication of the brain and hematopoietic interactions. The chapter in this book (1) resulted in the first author speculating about how and if we might be able to specifically link brain actions to the regulation and control of hematopoiesis, and vice versa. Such knowledge has the potential to help guide the development of better treatments for hematological disorders such as leukemia, myelodysplasia (MDS), myeloproliferative neoplasms (MPN), and other bone marrow (BM) disorders. Such knowledge could lead to the study of the Central Nervous System (CNS) control for beneficial treatment of disorders of other organ systems as well, should such possibilities be uncovered in the future.

**Possible Brain – Hematopoiesis Link**

The brain/hematopoietic regulatory link (2-11) hypothesis could initially be tested using sophisticated brain imaging methods to identify regions that are activated upon systemic cytokine/chemokine exposure (12-17), in order to assess BM microenvironment actions (2-11,

18-21), and during mobilization of Hematopoietic Stem (HSC) and Progenitor (HPC) cells from BM to the blood for hematopoietic cell transplantation (HCT) (22-27).

New information suggests how the BM microenvironment with interactions from nerves regulate mobilization of HSCs from the BM to blood (28), where nociceptive nerves detecting external signals, and involving G-CSF, are intimately involved in mobilization. Moreover purinergic signaling and extracellular ATP play a role both in neurogenesis and hematopoiesis, and that there is a role of catecholamines in HSC trafficking that play a pivotal role of ATP signaling as a mediator released in addition to that of catecholamines in synapses (29).

In support of the brain/hematopoietic regulatory link hypothesis is some evidence that the nervous system has a role in regulating HSC, HPC, and hematopoiesis (30-32), and that dipeptidylpeptidase (DPP)4/CD26 (24, 25, 33-39) is implicated in mobilization of HSC/HPC out from BM to the blood, and also for regulation of cytokine activity (39). DPP4 can cleave the neurotransmitter Neuropeptide Y (NPY), and recent work has shown that manipulation of endothelial NPY and its receptors alters behavior of HSC and HPC (24, 25). Although this work (24) involved peripheral endothelial NPY, effects of NPY is also integral to CNS function.

The above information, while of great interest, does not allow us to determine exactly how the brain-hematopoiesis might link, and led us to postulate that a brain/hematopoietic regulatory link is highly likely to exist. Such efforts to test this possibility will have to be multi-disciplinary in experimental attack, involving basic science researchers, neuroscientists, *in vivo* imaging scientists, and clinical investigators who are experts in blood cell production and the neurosciences. It is possible that experts in other interacting disciplines should also be

incorporated. The co-authors of this correspondence met on several occasions to discuss these concepts, and began to plan preliminary studies to address some of the questions regarding brain-hematopoietic links, as little or no empirical information on this topic is currently available. Unfortunately, the experiments were put on hold because of the pandemic, but fortunately are beginning again. This correspondence is meant to stimulate thought and feedback on this potential new area of future research.

**Need for Experimental Evidence for a Brain – Hematopoiesis Link**

We believe that the brain plays an important role in the production of blood cells in the BM. Blood Cell Production (Hematopoiesis) allows formation of all blood cells necessary for sustained health, including: the white blood cells including: neutrophils, lymphocytes, and other lymphoid and lymphoid-like cells (Natural Killer cells, (NK cells), and NKT cells, etc.). These cells are important for maintaining/sustaining immunity and fighting cancer/leukemia and pre-cancer/leukemia cells. These mature cells, including platelets are produced by immature subsets of HSC and HPC found and nurtured mainly in BM of newborns and young and old adults through communication between cytokines, chemokines, and the microenvironment, as well as cell-cell interactions (12, 13, 30-32). HSC are functionally defined by their capacity to make more of themselves (self-renew) and to differentiate to form HPC and more mature cells. HSC and HPC functional activities such as self-renewal, survival, proliferation, differentiation, and migration are controlled within the BM microenvironment of neonates and adults (12, 13). Much is yet to be learned regarding the cellular, molecular, and biochemical regulation of HSC and HPC functions, information of crucial importance for eventual translation of this work to a clinical translational situation for HCT using HSC and HPC found in BM, cord blood collected at the birth of a baby (which is highly enriched for these cells at birth) or mobilized peripheral blood (when cytokines can induce mobilization of HSC/HPC from BM to the blood, since steady state blood itself contains few HSC and HPC).

Better understanding of HSC and HPC function, and how the brain impacts these functions, could also provide the opportunity for the potential future use of such cells for regenerative medicine (an exciting, but not yet rigorously proven clinical treatment process), and this evaluation *ex-vivo/in vitro* using mouse and human embryonic stem cells and induced pluripotent stem cells.

Emerging evidence has linked neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, and traumatic brain injury to inflammatory processes arising from undesirable activation of cytokines (14-16). In addition, the gut-microbiota-brain-axis may play an important role in the brain function via inflammatory pathways (40-43) and impinge on hematopoiesis.

It is known that the nervous system plays an important role in regulating HSC, HPC, and hematopoiesis in the BM (30-32) which suggests a connection that might link brain activity with known neural-hematopoietic connections. Figure 1 diagrammatically summarizes some brain-hematopoietic possibilities (7, 19). Understanding patterns of brain activity after exposure to treatments that alter HSC/HPCs should direct us to mechanistic underpinnings of how the brain modulates HSC/HPCs. In turn, identifying these novel mechanisms may play important and crucial roles in learning how to control cytokine/chemokine-cell regulatory events within the BM. Thus, identifying potential links between the brain and signaling events within the BM would likely be important, as would be influences of the BM on brain function. Having a useful means such as neuroimaging to better understand CNS control of hematopoiesis will ultimately yield information of possible use for HCT and other clinical benefit by manipulating brain activity (perhaps via repeated transcranial magnetic stimulation, electric stimulation (44) or pharmacological manipulation). This putative ability to enhance desirable cellular responses, while possibly decreasing side effect profiles of such treatments would be far reaching and paradigm changing.

While at present, we do not have preliminary evidence for brain/BM regulatory control of HSC/HPC and hematopoiesis beyond the loose connections noted above, we propose some preliminary experiments that we believe, for the first time, may begin to elucidate such links.

**Beginning Experimental Suggestions for Establishing Potential Brain – Hematopoiesis Links**

In brief, examples of potential experiments would be: Determine if agents that are known to influence blood cell production originating in the BM and mobilization of HSC and HPC from the BM to blood have effects on brain activity assessed with functional magnetic resonance imaging (fMRI) and/or on cerebral blood flow measured with perfusion MRI (Figure 2; see reference 45). It should be possible to acquire functional and perfusion MRI data at baseline, and immediately after s.c. injection of cytokines, chemokines, or other growth modulating factors (12, 13) previously used in mice and man. Since we know that the effects of some cytokines, chemokines and other factors may occur very quickly (perhaps within 1-3 hours in the BM), it is possible that effects in the brain may be detected earlier, perhaps within minutes to early hours.

There might be changes in blood flow directly in response to exogenous administration to mice of cytokines/chemokines/other growth regulatory molecules. This is especially important to consider for fMRI, which indirectly measures neuronal activity via changes in blood oxygenation levels. This signal is flow-dependent, and could be confounded by direct effects of treatments on the vasculature. Thus, controlling for non-specific (non-neuronal) effects will be an important component in any experimental design. At a later time, when such effects are evaluated in humans, any effects of the various treatments on brain activity may be different in timing and

strength of the brain responses than what was initially observed in animals. Again, this speaks to the need to take such factors into account when designing human neuroimaging experiments. Regardless, this information could then serve as the first translational link between BM and brain responses. In turn, this would then drive research to help glean mechanistic insight into these phenomena, yet to be elucidated. As brain function and its links to the BM and other organs get better defined in a future technological advance context, it may be possible to define with more exactitude what neuronal circuitry is involved in the signals that the modulation of HSCs/HPCs elicit, and what intimate connections exist between the nervous system and BM microenvironment, HSCs, HPCs, and also the more mature myeloid, lymphoid, and stromal, endothelial, osteoblastic and osteomac cell types in the BM. As there are studies linking the nervous system to the mobilization of HSC/HPC from BM to blood (22-27), added insight into HSC/HPC mobilization may also be found.

**Additional Considerations**

It is important to understand that all cell regulation involves feedback loops (both negative and positive (12, 13)), and experiments can start with effects of modulation of BM cells to how the brain may respond, but also how the brain may elicit effects on the BM and other hematopoietic cell containing organs. This sequence (forwards and backwards) includes: the CNS (brain and spinal cord), the peripheral nervous system, neuronal endocrine involvement, microenvironmental effects, and BM and other cells. We already know that stress (46-50) and the microbiome (40-43, 51-55) has effects on both the brain and the BM. Moreover, other areas in the endeavor to uncover brain to/from regulation will need to eventually take into account enzymes, such as Dipeptidylpeptidase 4 (DPP4), known to regulate blood cell production and mobilization of HSCs,

HPCs, and more mature blood cells (33-39) and other enzymes. Sitagliptin, an orally active DPP4 inhibitor, has already been used to modestly enhance time to recovery of neutrophils for cord blood HCT (56, 57) with some decreased graft vs. host disease (GVHD) in cord blood HCT, and more recently to reduce the undesirable effects of GVHD in recipients of allogeneic mobilized peripheral blood HCT (58). Thus, it is possible that regulation of brain activity might be able to dampen GVHD. Hematopoietic studies evaluating HSC and HPC function should also entail the role of collecting BM and blood cells in an *in vivo* hypoxia oxygen tension (Physioxia) situation compared to that of ambient air collections (59, 60); the oxygen tension in the BM ranges from about 1-5%. Since the oxygen tension in the blood and other internal organs is lower than that of ambient air, it should be taken into consideration for a more physiological understanding of HSC/HPC numbers and functional activity when cells are collected outside the body, although it is clear that oxygen tension in the brain must be high to support cognitive and brain functions. Additionally, in relation of stress and the microbiome, it is likely that the aging process may elicit different effects from that of the young (61, 62).

**What is the Possibility of Getting Useful Brain – Hematopoiesis Information?**

Frank Wilczek, Nobel Laureate in Physics, 2004, noted that neurons are the basic units of human brains, with their numbers being in the range of one hundred billion ($10^{11}$) (63). This number of neurons is about equal to numbers of stars in our galaxy, a mind-boggling number. The neurons are wired together with many connections, perhaps hundreds or thousands with other neurons. With this vast complex number of neurons and their multipartite connections, can we ever make complete sense of how the brain-hematopoietic system and hematopoietic system-brain communicate with each other, and can these interactions/connections ever be used to control

hematopoiesis at a brain neuron level? Moreover, there are more glial cells in the brain than neurons, and they influence the function of neurons, another complication to investigating brain-hematopoietic and- other organ interactions. Difficult, yes. Impossible in the future, probably not if one takes an optimistic pioneering attitude. Einstein has been quoted as saying: “Everything should be as simple as possible, but not simpler” (63). It is likely that the study of brain-hematopoietic and other organ systems will get more complicated as they are analyzed, but ultimately, simple is the best solution if we are eventually ever able to take advantage of these links for therapeutic benefit in context of triggering the correct brain neural connections and their signaling, perhaps either physically or through next generation pharmacology.

Will linking the brain with that of hematopoiesis and vice versa be a next frontier to investigate for potential health benefits? We think and hope so, but information in this area will require beginning experiments in these areas and knowledge will continue to evolve as more advanced technologies to study the brain become available. Basic scientists in multi-disciplines working with clinical investigators will figure out the connections and how to utilize the knowledge either sooner rather than later, or perhaps later rather than sooner. Regardless, work in this direction, no matter how preliminary or simplistic at the beginning, is well-worth the effort. The longer we wait to start, the longer it will be before we get answers.

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All were involved in the preparation drafts and writing the commentary.

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Legends

Figure 1. Diagrammatic representation of possible reasons for suggesting links between the brain and regulation of hematopoiesis and vice versa. A) Simplistic picture of brain-neuronal connections; B and C) Simplistic overview of neural regulation of hematopoiesis, inflammation and cancer (7); and D) Simplistic rendition of the BM microenvironment (19).

Figure 2. Potential means to currently evaluate brain-organ links. A.) Diagrammatic representation of assessing the brain and organ responses. PNS: peripheral nervous system. ANS: autonomic nervous system. CNS: central nervous system. CBV: cerebral blood volume. CBF: cerebral blood flow. CMRO2: cerebral metabolic rate of oxygen. The hemodynamic response function is a parameter used in functional magnetic resonance imaging to estimate relative changes in blood oxygenation levels. B. Representative brain networks observed in human subjects with functional fMRI. C. Top: Representative maps of quantitative blood flow (cerebral blood flow, CBF, mL/100 g/min). Bottom: Representative maps of arterial transit time (ATT; m sec) from the same data acquisition. Data were acquired in a single subject with an MRI method called pseudo-continuous arterial spin labeling (pCASL). Similar technology can be applied to rodents with high-field small animal MRI systems, with the result being translational information about rodent and human brain networks and brain blood flow. See article by Khalili-Mahani et al (45).

Figure 1

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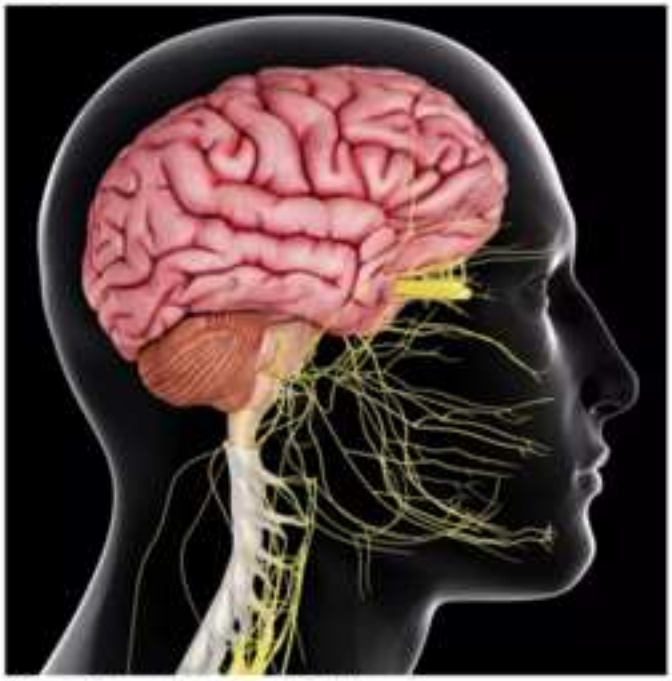
A)



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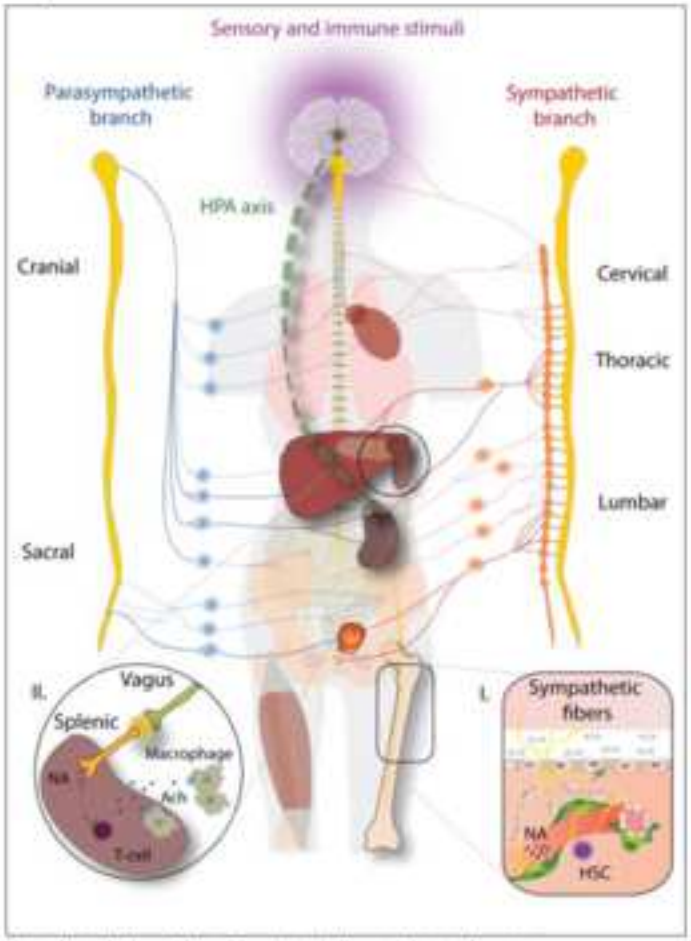
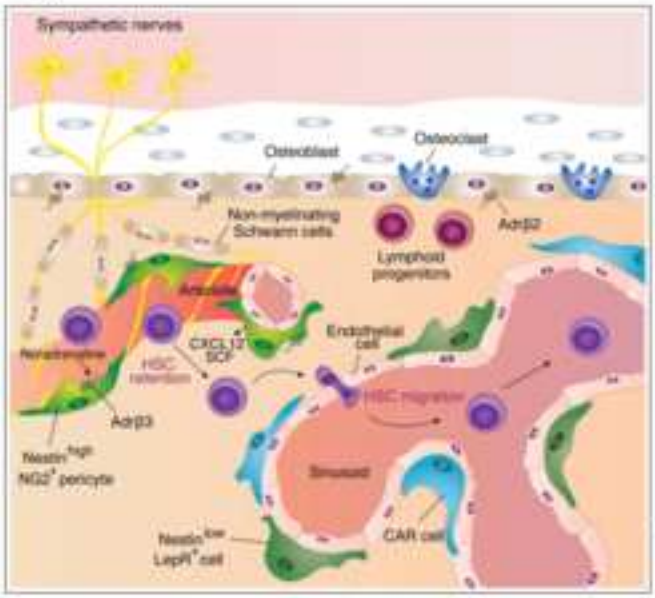



Neural regulation of hematopoiesis, inflammation and cancer. Hanoun et al, Neuron 86, 2015

C)

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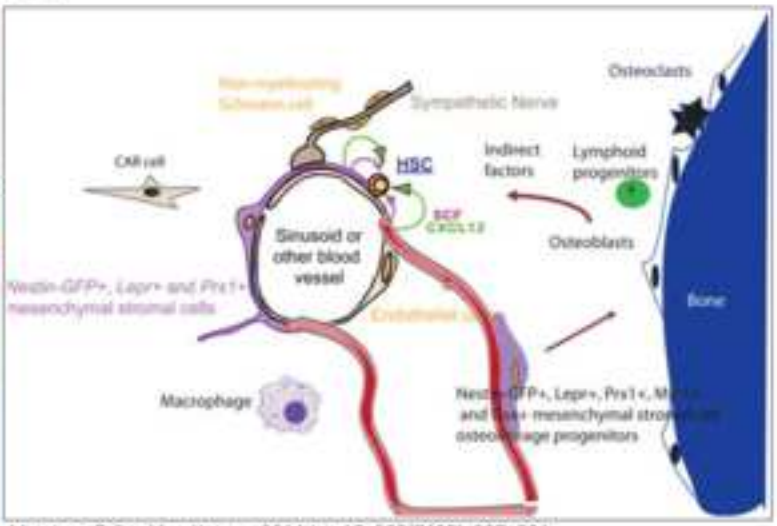


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Figure 1

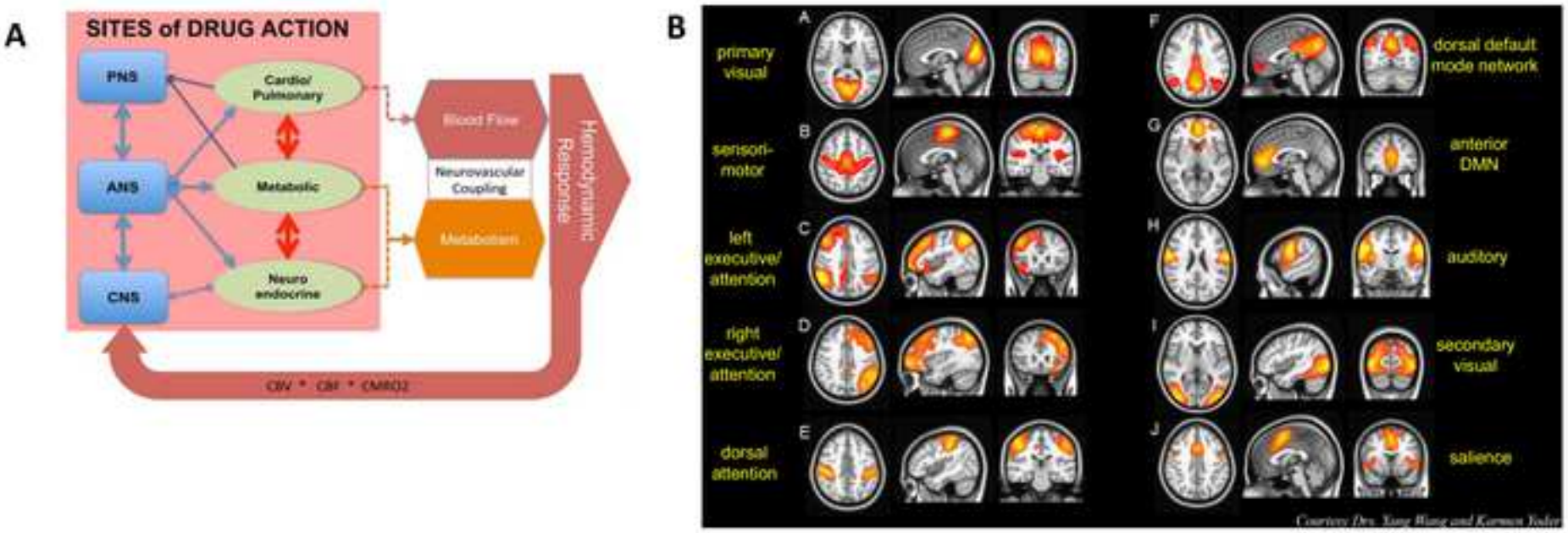


Figure 2

Graphical_Abstract