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A Topological model of moderate exercise and chronic stress that produces counteractive effects on different areas of the brain

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Abstract
It is well known fact that, regular, "moderate", physical exercise is an established non-pharmacological form of treatment for depressive disorders. Brain lateralization has a significant role in the progress of depression. External stimuli such as various stressors or exercise influence the higher functions of the brain (cognition and affect). These effects often do not follow a linear course. Therefore, nonlinear dynamics seem best suited for modeling many of the phenomena, and putative global pathways in the brain, attributable to such external influences.
The well-known neurotransmitters serotonin (5-HT), dopamine (D) and norepinephrine (NE) all have various receptor subtypes. This topological model describes that 'Stress' increases the activity/concentration of some particular subtypes of receptors (designated nt_s) for each of the known (and unknown) neurotransmitters in the right anterior (RA) and left posterior (LP) regions (cortical and subcortical) of the brain, and has the converse effects on a different set of receptor subtypes (designated nt_h). In contrast, 'Exercise' increases nt_h activity/concentration and/or reduces nt_s activity/concentration in the LA and RP areas of the brain. These effects may be initiated by the activation of Brain Derived Neurotrophic Factor (BDNF) (among others) in exercise and its suppression in stress.

Keywords: Topological, chronic stress, counteractive

1. Introduction
Regular, "moderate", physical exercise is a non-pharmacological form of adjunctive treatment for depressive disorders. External stimuli such as various stressors or exercise influence the higher functions of the brain (cognition and affect). These effects often do not follow a linear course. Even though exercise itself can be seen as a stressor, in moderate doses it has been shown to reduce the effects of other stressors. To explain this model better, I need to elaborate on certain concepts – encompassing a wide range of biological and mathematical domains – of stress, depression, exercise, neurotransmitters along with their receptor subtypes, brain lateralization and nonlinear dynamics. All these concepts (and their interactions) are discussed broadly in the following paragraphs. The model is based on the numerous published data obtained from experimental research. The approach is more akin to systems biology (generalization) than to detailed characterization of any particular pathway of exercise and stress actions. A highly focused "linear" thought process may not be conducive to comprehending the underlying essential nonlinearities in this proposed model.

Background
Broadly: "Stress" refers to the mental or physical condition resulting from various disturbing physical, emotional, or chemical factors ("stressors"), which can be environmental or anthropogenic, and lead to a behavior or outcome that is commonly labeled "depressive". The effects of the stressors on the body constitute the "stress response", which may be measured by behavioral, biochemical, and genetic modifications. "Anxiety" may be defined as the emotional discomfort associated with "stress". "Depression" denotes a spectrum of disorders affecting many aspects of human physiology, and can be precipitated by various psychological (*e.g.*, mental trauma), biophysical (*e.g.*, loss of organ or function and genetic predisposition) and social (*e.g.*, loss of job) stressors. However, under-diagnosis in general medical practice is quite common [1].

Depression (including its various subtypes) is a common global disorder. Apart from newer pharmacotherapeutic management, some non-pharmacological interventions also play a significant part in its alleviation [1]. Regular, "moderate" physical exercise forms a pillar of such treatment. Our hypothesis concerns general mechanisms that give rise to the effects of exercise along with stress.

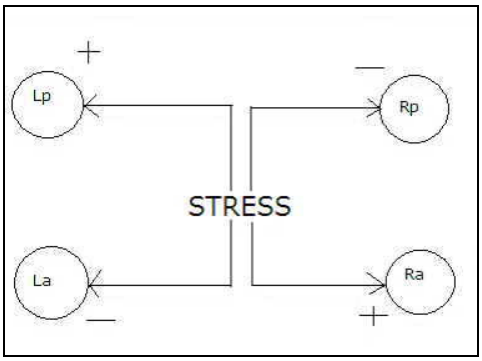

Fig 1: Demonstrates stress in brain

Impact of stress and depression in brain

Cerebral hemispheric lateralization alludes to the localization of brain function on either the right or left sides of the brain, and is an important factor in the progress of depression [2]. Incidentally, this lateralization is not confined to only the cerebral cortices, but also to the subcortical structures. A recent paper [3] indicates that mood state may be differentiated by lateralization of brain activation in fronto-limbic regions. The interpretation of fMRI (functional magnetic resonance imaging) studies in bipolar disorder is limited by the choice of regions of interest, medication effects, comorbidity, and task performance. These studies suggest that there is a complex alteration in regions important for neural networks underlying cognition and emotional processing in bipolar disorder. However, measuring changes in specific brain regions does not identify how these neural networks are affected. New techniques for analyzing fMRI data are needed in order to resolve some of these issues and identify how changes in neural networks relate to cognitive and emotional processing in bipolar disorder.

The relationship between exercise and stress is not a simple one. As succinctly pointed out by Mastorakos and Pavlatou [4]: "Exercise represents a physical stress that challenges homeostasis. In response to this stressor, the autonomic nervous system and hypothalamus-pituitary-adrenal axis are known to react and participate in the maintenance of homeostasis and the development of physical fitness. This includes elevation of cortisol and catecholamines in plasma. However, physical conditioning is associated with a reduction in pituitary-adrenal activation in response to exercise." In our present model, we shall start at the point at which chronic moderate exercise has already led to the "baseline adaptive changes" and behaves in a different way from any other stressor. In future modifications, changes in the model's threshold for exhibiting this particular (bimodal) behavior can also be incorporated. This bimodal or hormetic response is characterized by low dose stimulation, high dose inhibition, resulting in either a J-shaped or an inverted U-shaped (nonlinear) dose response. A chemical pollutant or toxin or radiation showing hormesis therefore has the opposite effect in small doses to that in large doses. Therefore, we can assume regular moderate exercise as the mild, repeated "stressful" stimulation (which is good for health). While excessive and prolonged stress (as in heavy exercise) can lead to depression, mild and irregular (non-linearly applied, hormetic) stress can actually improve depression. Radak *et al*. [28] extend the hormesis theory to include reactive oxygen species (ROS). They further suggest that the beneficial effects of regular exercise are partly based on the ROS-generating capacity of exercise, which is in the stimulation range of ROS production. Therefore, they suggest that exercise-induced ROS production plays a role in the induction of antioxidants, DNA repair and protein degrading enzymes, resulting in decreases in the incidence of oxidative stress-related diseases.

External stimuli such as various stressors or exercise influence the higher brain functions, i.e., cognition and affect. These effects often do not follow a linear course. In nonlinear dynamics the rate of change of any variable cannot be written as a linear function of the other variables. Therefore, it may be better suited to modeling many phenomena, and putative global pathways, in the brain, that are attributable to such influences [7, 8, 12-15].

Neurotransmitters convey the information to be passed and processed through some 10^{14} to 10^{16} interconnections linking approximately 10^{10} to 10^{11} neurons in the human brain. Each of the many neurotransmitters acts through a receptor, which in general will have numerous subtypes [16].

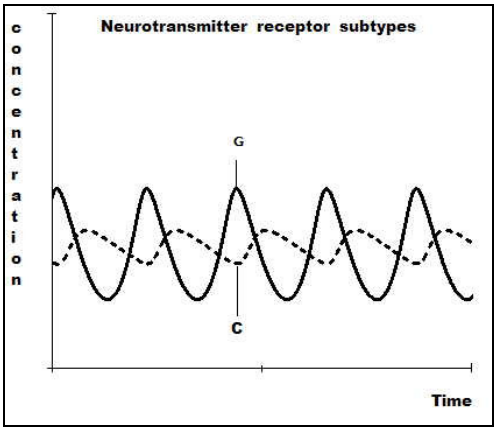

Fig 2: Demonstrates Neurotransmitter receptor subtypes

The same neurotransmitter acting through two different receptor subtypes may have opposing actions. Most psychotropic drugs exert their therapeutic effects through various neurotransmitters, mainly through specific receptor subtypes. Some neurotransmitter receptor subtype interactions are depicted properly. It may be noted that 5-HT_2 class receptors couple to Gq/G11 and do not primarily signal through cAMP pathways. Similarly, 5-HT_3 receptors are ligand-coupled ion channels and do not primarily signal through cAMP. However, this only proves the existence of additional intracellular pathways such as the Gq/G11 coupled intracellular calcium/protein kinase C pathway, and also highlights the fact that signaling is much more complex than this model allows. Our oversimplification is essential for trying to grasp the overall complexity of all possible (known and as yet unknown) underlying mechanisms of the brain. The basic purpose of this figure is to show that (irrespective of the mechanisms of action) any neurotransmitter is capable of exerting opposing effects

(e.g., increasing anxiety or 'anxiogenesis' and decreasing anxiety or 'anxiolysis') by acting through its diverse receptor subtypes.

It is important to note that, Protein kinase C, commonly abbreviated to PKC (EC 2.7.11.13), is a family of protein kinase enzymes that are involved in controlling the function of other proteins through the phosphorylation of hydroxyl groups of serine andthreonine amino acid residues on these proteins, or a member of this family. PKC enzymes in turn are activated by signals such as increases in the concentration of diacylglycerol (DAG) or calcium ions (Ca^{2+}). Hence PKC enzymes play important roles in several signal transduction cascades.

Cell type	Organ/system	Activators ligands --> G_q-GPCRs	Effects
smooth muscle cell (gastrointestinal tract sphincters)	digestive system	• prostaglandin $F_{2\alpha}$[6] --> • thromboxane[6]	contraction
smooth muscle cells in: • iris dilator muscle (sensory system) • urethral sphincter (urinary system) • uterus (reproductive system) • arrector pili muscles (integumentary system) • ureter (urinary system) • urinary bladder (urinary system)[7][8]	Various	• adrenergic agonists --> α1 receptor	contraction
smooth muscle cells in: • iris constrictor muscle • ciliary muscle	sensory system	acetylcholine --> M3 receptor	contraction
smooth muscle cell (vascular)	circulatory system	• 5-HT --> 5-HT2A receptor • adrenergic agonists --> α1 receptor	• vasoconstriction[9][10][11][12]
smooth muscle cell (seminal tract)[9][10][11]	reproductive system	• adrenergic agonists --> α1 receptor	ejaculation
smooth muscle cell (GI tract)	digestive system	• 5-HT --> 5-HT2A or 5-HT2B receptors[9][10] • acetylcholine (ACh) --> M3 receptor	• contraction[11]
smooth muscle cell (bronchi)	respiratory system	• 5-HT --> 5-HT2A receptor • adrenergic agonists --> β_{2A} receptor • acetylcholine --> M3[12] and M1 receptor[11]	bronchoconstriction[9][10]
proximal convoluted tubule cell	kidney	• angiotensin II --> AT1 receptor • adrenergic agonists --> α1 receptor	• stimulate NHE3 --> H^+ secretion & Na^+ reabsorption[14] • stimulate basolateral Na-K ATPase --> Na reabsorption[14]

Fig 3: Demonstrates Cell-specific function of Protein Kinase-C

The PKC family consists of fifteen isozymes in humans. They are divided into three subfamilies, based on their second messenger requirements: conventional (or classical), novel, and atypical. Conventional (c) PKCs contain the isoforms α, β_I, β_{II}, and γ. These require Ca^{2+}, DAG, and a phospholipid such as phosphatidylserine for activation. Novel (n) PKCs include the δ, ε, η, and θ isoforms, and require DAG, but do not require Ca^{2+} for activation. Thus, conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase C. On the other hand, atypical (a) PKCs (including protein kinase Mζ and ι / λ isoforms) require neither Ca^{2+} nor diacylglycerol for activation. The term "protein kinase C" usually refers to the entire family of isoforms.

Interestingly, there is a greater right-sided EEG abnormality in depression owing to impaired cerebral lateralization [2]. Therapeutically, too, better antidepressant results are obtained with non-dominant unilateral electroconvulsive shock. It is generally believed that "affect" processing is a right hemisphere (RH) function. It is also believed that RH dysfunction is characteristic of depressive illness. Both these beliefs are oversimplified because the relationship between affect processing and affective illness, in terms of intra- and inter-hemispheric role-play, is not straightforward. There is exchange of information and action between the two hemispheres (inter-hemispheric, *i.e*., between left and right; intra-hemispheric *i.e*., between anterior and posterior; and also cross-hemispheric coupling *i.e*., similarities between the left anterior and right posterior quadrants). Very broadly, a sad mood is a function of positive coupling (stimulation) between the left posterior and right anterior areas and/or negative coupling (depression) between the left anterior and right posterior areas of the brain [2].

Brain functions are lateralized to the right or the left sides and there are observed differences in the expression of neurotransmitter receptor subtypes [16-22]. Some of these results [21] are supported by a meta-analysis of various studies reported in the literature. Neuroanatomical asymmetries are known to be present in the human brain, and disturbed neurochemical asymmetries have also been reported in the brains of patients with schizophrenia [22]. Not only neuroanatomical but also neurochemical evidence supports the loss or reversal of normal asymmetry of the temporal lobe in schizophrenia, which might be due to a disruption of the neurodevelopmental processes involved in hemispheric lateralization.

Neuropsychological research provides a useful framework for studying emotional problems such as depression and their correlates. Shenal *et al*. [25] review several prominent neuropsychological theories focusing on functional neuroanatomical systems of emotion and depression, including those that describe cerebral asymmetries in emotional processing. Following their review, they present a model comprising three neuroanatomical divisions (left frontal, right frontal and right posterior) and corresponding neuropsychological emotional sequelae within each quadrant. It is proposed that dysfunction in any of these quadrants could lead to symptomatology consistent with a diagnosis of depression. Their model combines theories of arousal, lateralization and functional cerebral space and lends itself to scientific investigation. Shenal *et al*. [25] conclude: 'As the existing literature appears to be somewhat confusing and controversial, an increased precision for the diagnostic term "depression" may afford a better understanding of this emotional construct. Future research projects and innovative neuropsychological models may help to form a better understanding of depression.' Their proposed model 'combines theories of arousal, lateralization, and functional cerebral space to better understand these distinct clinical pictures, and it should be noted that these regions may be differentially activated following various therapies to depressive symptomatology.' However, their excellent neuropsychological model does not take into account the different neurotransmitter receptor subtype distribution and functions.

Neuropharmacological investigations aimed at understanding the electrophysiological correlates between drug effects and action potential trains have usually involved the analysis of firing rate and bursting activity. Di Mascio *et al*. [29] selectively altered the neural circuits that provide inputs to dopaminergic neurons in the ventral tegmental area and investigated the corresponding electrophysiological correlates by nonlinear dynamic analysis. The nonlinear prediction method combined with Gaussian-scaled surrogate data showed that the structure in the time-series corresponding to the electrical activity of these neurons, extracellularly recorded *in vivo*, was chaotic. A decrease in chaos of these dopaminergic neurons was found in a group of rats treated with 5, 7-dihydroxytryptamine, a neurotoxin that selectively destroys serotonergic terminals. The chaos content of the ventral tegmental area dopaminergic neurons in the control group, and the decrease of chaos in the lesioned group, cannot be explained in terms of standard characteristics of neuronal activity (firing rate, bursting activity). Moreover, the control

group showed a positive correlation between the density-power-spectrum of the interspike intervals (ISIs) and the chaos content measured by nonlinear prediction S score; this relationship was lost in the lesioned group. It was concluded that the impaired serotonergic tone induced by 5, 7-dihydroxytryptamine reduces the chaotic behavior of the dopaminergic cell-firing pattern while retaining many standard ISI characteristics. However, some difficulties remain. There is a suspicion that the determinism in the EEG may be too high-dimensional to be detected with current methods. Previously [30], ISIs of dopamine neurons recorded in the substantia nigra were predicted partially on the basis of their immediate prior history. These data support the hypothesis that the sequence-dependent behavior of dopamine neurons arises in part from interactions with forebrain structures. ISI sequences recorded from unlesioned rats demonstrated maximum predictability when an average of 3.7 prior events were incorporated into the forecasting algorithm, implying a physiological process, the "depth" of history-dependence of which is approximately 600–800 ms.

It has been repeatedly confirmed that the brain acts nonlinearly, especially when complex interactions are required, as in cognition or affect processing. In a cognitive study [31], although the nonlinear measures ranged in the middle field compared to the number of significant contrasts, they were the only ones that were partially successful in discriminating among the mental tasks. In another cognitive study [32], initial increase in complexity of both episodic and semantic information was associated with right inferior frontal activation; further increase in complexity was associated with left dorsolateral activation. This implies that frontal activation during retrieval is a non-linear function of the complexity of the retrieved information.

A broader view of stress is that not only do dramatic stressful events exact a toll, but also the many events of daily life elevate the activities of physiological systems and cause some measure of wear and tear. This wear and tear has been termed "allostatic load" [33], and it reflects the impact not only of life experiences but also of genetic load (predisposition); individual habits reflecting items such as diet, exercise and substance abuse, and developmental experiences that set life-long patterns of behavior and physiological reactivity. Hormones and neurotransmitters associated with stress and allostatic load protect the body in the short term and promote adaptation, but in the long run allostatic load causes changes in the body that lead to disease. These have been observed particularly in the immune system and the brain.

The beneficial role of exercise is evident in many neurodegenerative disorders [40]. Despite the paucity of human research, basic animal models and clinical data overwhelmingly support the notion that exercise treatment is a major protective factor against neurodegeneration of various etiologies. The final common pathway of degradation is clearly related to oxidative stress, nitrosative stress, glucocorticoid dysregulation, inflammation and amyloid deposition. Exercise training may be a major protective factor but in the absence of clinical guidelines, its prescription and success with treatment adherence remain elusive. In the present model, Moderate Exercise: 3.0 – 6.0 METs (3.5 – 7.0 kcal/min) [41] is assumed for the purpose of modeling.

It is not known whether the complex dynamics are an essential feature or if they are secondary to internal feedback and environmental fluctuations [13]. Because of the complexity of biological systems and the huge jumps in scale from a single ionic channel to the cell to the organ to the organism, all computer models will be gross approximations to the real system for the foreseeable future. There is a rich fMRI literature on affect, stress and depression and this, together with a wealth of preclinical data, will enable the very general model proposed in this paper to be refined in the future. At present, our concern is to determine whether a broadly testable nonlinear dynamic model can be elaborated and to outline the preliminary experiments required to validate it. Only after this task is completed will detailed refinement, producing a more practically helpful model, become appropriate. It may be noted that the basic purpose of the model is to provide direction for experimental research, since there is a paucity of real life data, which we feel to be essential for understanding the precise role of neurotransmitter receptor subtypes in different areas of the brain.

The effects of concomitant stress and exercise on the four different quadrants of the brain

As a non-pharmacological intervention, we have introduced 'exercise' into the stress dynamics. The schematic diagram shown in represents the functional characteristics of brain dynamics in presence of stress-induced exercise activities. In this particular schema we assume that both stress and exercise are acting simultaneously where the stress activity (not counting "moderate" exercise itself as a stressor, whereas "heavy" exercise may qualify as a stressor) develops independently from various sources and/or systems over which the individual has no control.

A person who is not under the influence of stress can do exercise. On the other hand one can do the exercise when one knows that one is under influence of stress. We call this situation 'stress-induced exercise activity'. In the present study, our approach is based on the latter scenario.

In this scenario, the effects of exercise positively activate the left-anterior and right-posterior of the brain but they negatively activate (feedback mechanism) the left-posterior and right anterior of the brain. As such, the exercise effect conteracts the stress effect on the brain.

Summary of the hypothetical models

The models described in this article show one of the likely mechanisms for the action, on the brain, of concomitant stress and exercise. They mathematically prove our assumptions that 'Stress' nonlinearly increases the activity/concentration of particular subtypes of receptors (designated nt_s) for each of the known (and unknown) neurotransmitters in the right anterior (RA or R_a) and left posterior (LP or L_p) regions of the brain, and/or nonlinearly decreases the activity/concentration of another set of receptor subtypes (designated nt_h) for each of these neurotransmitters in the left anterior (LA or L_a) and right posterior (RP or R_p) activity areas. Exercise elicits the opposite (nonlinear) effects.

It is established that the intensity of exercise, the level of fitness, and various individual differences (which may be due to "nature" or "nurture"), impact acute affective responses to exercise [51, 52]. Also, Bixby *et al*. [51] have shown that exercise intensity impacts the affective response

during and after exercise, with higher intensity exercise being associated with more negative affect during exercise. These aspects will be dealt with in the future models.

Furthermore, exercise can also influence other brain parameters such as blood flow, antioxidant activities, neuronal apoptosis, receptor sensitization, glutamate secretion and many other unknown factors, which in various combinations can have some effect on depression. Our model does not explicitly deal with any of these effects in detail.

According to Dishman *et al*. [53], "Chronic voluntary physical activity also attenuates neural responses to stress in brain circuits responsible for regulating peripheral sympathetic activity, suggesting constraint on sympathetic responses to stress that could plausibly contribute to reductions in clinical disorders such as hypertension, heart failure, oxidative stress, and suppression of immunity. Mechanisms explaining these adaptations are not as yet known, but metabolic and neurochemical pathways among skeletal muscle, the spinal cord, and the brain offer plausible, testable mechanisms that might help explain effects of physical activity and exercise on the central nervous system." This model provides one possible direction towards solving some of the puzzles.

Greenwood *et al*. [54] suggest that the central 5-HT system is sensitive to wheel running in a time-dependent manner. The observed changes in mRNA regulation in a subset of raphe nuclei might contribute to the stress resistance produced by wheel running and the antidepressant and anxiolytic effects of physical activity. We believe that more than one or two neurotransmitter systems are simultaneously involved in leading to the observed nonlinear behaviors of stress and exercise.

Implications of the Topological Model

To sum up the information gathered in this paper, we can see that many anti-depressive interventions exert their therapeutic effects through various neurotransmitters, mainly acting nonlinearly through their several specific receptor subtypes. The final common pathway (biological cascade) is at the cellular and subcellular levels. Therefore, to achieve therapeutic benefit, lower level targets are now being selected, *e.g*., adenosine (A_{2A}) and calcium (Ca^{2+}) channels, as well as genes for BDNF and CREB. The underlying neural networks function on the basis of the inputs received from the various neurotransmitter receptor subtypes. Detailed expositions are given elsewhere [26, 27].

Experiments may be devised to measure changes in concentrations and activity levels of various neurotransmitters and of growth factors such as BDNF in different regions of the brain, followed by identification of specific receptor subtypes in these regions. It may be noted that it is beyond the capacity of a single researcher or even a single group to validate all the experimental possibilities predicted from this model.

Conclusion

As per Etevenon's [66] proposal, more than two decades ago, a model for cross-coupling of diagonal quadrants of the brain in affect processing – but there was hardly any empirical data to support the proposal. With the advance of technology and its applications in the healthcare domain we are in a better position to construct a more realistic model.

Numerous other contemporary scientists [67, 68] have demonstrated that mathematical modeling is a useful tool for diagnosing and assessing the prognosis of depression.

Future models are bound to be modified and refined as more and more experimental evidence is gathered owning to advances in technology. We have tried to integrate diverse domains of knowledge about depressive disorders and exercise physiology. It may not currently be possible to test the hypothesis holistically, but there is an immediate need for domain experts to come together from various disciplines such as neuropsychology, computational neuroscience, exercise science, molecular biology, clinical psychophysiology, bedside clinics, experimental neurophysiology, behavior therapy and nonlinear dynamics. The necessity for this theoretical modeling arose because of the lack of experimental data relating to all aspects of our hypothesis. We hope that by using the outcomes of these models, experimental biologists will be able to devise experiments involving diverse subtypes of the same neurotransmitters, acting differently in localized areas of the brain (in health and disease), reinforce (or refute) our assumptions, and enable more refined and practically applicable versions of the present hypothesis to be elaborated.

Authors's contribution

Author has extended in depth research and exclusive study regarding the present spectrum that has been manifested to write him this review in favour of mankind and well being of health science and cultivation.

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It is an established fact that every mission needs a spirit of dedication and hard work but more than anything else it needs proper guidance. In fact, author feels proud in taking this opportunity to express his heartiest regards and deep sense of gratitude to his beloved wife Mrs. Ranita Kar for her evergreen inspiration as well spirit for progress, research and all kinds of pursuit of excellence in author's life and achievements.

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