Journal of Advanced Pharmacy Research

Impacts of Immune System in an Experimental Social Behavior Model: Review Article

Amal M. Mahfoz*

Department of Pharmacology, Faculty of Pharmacy, Modern University for Technology and Information, Cairo, Egypt

**Corresponding author: Amal M. Mahfoz, Department of Pharmacology, Faculty of Pharmacy, Modern University for Technology and Information, Cairo, Egypt.   Tel. +201064794983
Email address: mahfozamal@gmail.com*

ABSTRACT

There is growing evidence supports the regulatory role of the immune system in neuronal function and mental health. Many studies have demonstrated the impact of the immune system in neurodegenerative disorders. There are beneficial therapeutic effects of targeting the immune system in the management of these disorders. However, there are gaps in the available knowledge and many steps are needed to move forward. Sensory contact model (SCM) is an experimental social behavior model which allows the formation of different psychopathological conditions which are originated between male mice by the repeated agonistic interactions; resemble those in human. SCM has been developed to investigate aggression and submission behaviors. It gives the chance to study the pharmacological actions of novel psychoactive drugs. The current study aims to review the possible relations between the immune system and social behavior; using the SCM as an experimental model of aggression and depression. To encourage the production of novel psychoactive drugs target the immune system and inflammatory pathways.

Keywords: Behavior; Social behavior; Sensory contact model, Immune system

INTRODUCTION

The immune system

The immune system is a complex array of organs, cells, and soluble factors that constitute a defense mechanism aiming at the preservation of integrity being charged with the ability to identify self and nonself [1]. The outcomes of the functional immune system are in most times desirable, as in termination of infection, acquiring resistance against further infection and identifying new antigens such as those expressed by newly arising tumors. However, in some instances the outcomes are undesirable. When integral body tissue performs defensive and destructive abilities against its tissues; it results in autoimmune disease, transplant rejection, or hypersensitivity reactions [2].

Based on their function, organs of the immune system can be classified into:
a. Central organs (Primary lymphoid tissues): These are organs that provide the microenvironments that support the initial development of immune cells and their priming by expressing their first antigenic receptors during the process of tolerance and attaining phenotypic and functional maturity. In mammals, primary lymphoid tissues include bone marrow, where all lymphocytes, including B lymphocytes, and blood stem cells are generated; and the thymus where T lymphocytes are generated and mature [3].

b. Peripheral organs (Secondary lymphoid tissues):
These are organs that provide sites where the antigen-specific lymphocytes respond to their cognate antigens efficiently, and where proper cellular interactions occur to provide a well-regulated immune response. They include lymph nodes, spleen, mucosal-associated lymphoid tissues, and Waldeyer's ring, which in turn includes tonsils and nasal associated lymphoid tissues. Besides, there are less well-defined clusters of lymphoid and other hematopoietic cells associated with genitourinary, gastrointestinal, and respiratory tracts [4].

Experimental Indicators of Immunomodulation
A battery of tests was selected to serve as indicators of the immunomodulatory potential of the different immunomodulatory candidate substances. These indicators are supposed to give the primary profile of the immunomodulatory potential that might be subjected to further investigation by more specific and detailed studies.

1. Total and differential leucocyte counts
Leucocytes are concerned with many different defensive and reparative activities in the body, essentially in destroying invading antigens as well as the production and distribution of antibodies [5]. The alterations in normal leukocyte blood pictures may provide diagnostic clues to specific diseases both benign and malignant [6,7].

The types of leucocytes enumerated in the differential count are the lymphocytes, monocytes, neutrophils, basophils, and eosinophils. The following section includes a brief description of the roles of each type and its participation in the immune system.

a. Lymphocytes
1. B lymphocytes
The defining feature of B lymphocytes is their ability to synthesize and secrete immunoglobulins. Mature B lymphocytes express immunoglobulins in two different forms. In the effector B lymphocytes lineage (called plasma cells) immunoglobulins are secreted in large amounts into their surrounding milieu. By contrast, in the resting (virgin or memory) B lymphocytes, immunoglobulins are expressed only on the cell surface, where they serve as membrane-bound receptors for specific antigens and therefore may be referred to as handicapped B cells [8]. When activated B lymphocytes divide, some of its progeny become B lymphocytes, while the remainders differentiate into plasma cells. The memory cells enable the immune system to encounter high-affinity responses to subsequently encountered antigens in a faster and more efficient manner [9, 10].

2. T lymphocytes
T lymphocytes, which mature in the thymus gland, localize in particular lymphoid tissues throughout the body such as the paracortex of lymph nodes and the periarterial lymphoid sheath in the splenic pulp [11]. When a specific antigen is encountered in the tissues, the T lymphocytes which are programmed to recognize that particular antigen return to the specific T lymphocytes domain of the lymphoid tissue where they transform to lymphoblasts (T immunoblasts) that divide repeatedly by mitosis. Its result is the production of activated T lymphocytes which enter the circulation and migrate to the site of antigenic stimulation [12, 13]. These cells can split the antigen into smaller peptides display them on their surface MHC molecules to form the required ligands with T lymphocyte receptors [14].

3. Null (Natural Killer) cells
This is the third major class of lymphocytes. This class expresses markers of neither B nor T lymphocytes and was, therefore called the null cell population. It is now apparent that most null cells are large lymphocytes with numerous cytoplasmic granules that are able of lysing a variety of virus-infected and tumor cells without overt antigenic stimulation. As a result, they are called large granular lymphocytes or natural killer cells [15].

b. Monocytes
Their principal function is phagocytosis which is mediated by their surface receptors Fc fragment of immunoglobulin G [14]. Monocytes also participate in processing antigens and presenting them to T lymphocytes in conjunction with MHC II molecules. Moreover, monocytes have a secretory function, where they produce several cytokines including interleukins (ILs) as IL-1, IL-6, IL-10, and tumor necrosis factor (TNF) [14].

c. Neutrophils
These cells are also called polymorphonuclear (PMN) leucocytes. They can respond rapidly to chemotactic stimuli and effectively perform their main function namely to phagocytosis of the stimulating foreign particle [16]. Neutrophils are capable of extracellular killing of other cells if coated with the proper opsonins, mainly immunoglobulin (IgG). They attach to the protruding Fc piece utilizing their Fcγ receptors and kill the attached cell. A well-known example is killing schistosomula in vitro [17].

d. Eosinophils
Eosinophils have also a phagocytic function that starts by their adhesion to post venular capillary with their adhesion receptors to the ligand on the

endothelial cells. Eosinophils also express IgG, A, D, and E receptors, and can, therefore, undertake several IgE-dependent functions including killing helminths coated by IgE. Eosinophils are abundant at sites of immediate hypersensitivity reactions where they contribute to tissue injury and inflammation. This effect is due to their capacity to secrete several potent mediators including lipid mediators, basic proteins, and oxygen burst components including hydrogen peroxide [18].

e. Basophils

These cells have similar functions to those of mast cells. Both types have high-affinity receptors for IgE (FcεRI), therefore, avidly bind free IgE molecules. Upon interaction with specific antigens, granular contents are released, which are namely the chemical mediators of immediate hypersensitivity. Thus, these granulocytes are effector cells of IgE-mediated immediate hypersensitivity [19].

All blood cell types originate from several multipotential hematopoietic stem cells that undergo processes of proliferation and maturation in the bone marrow under the influence of cytokines [20]. They include granulocyte, macrophage, and granulocyte/macrophage colony-stimulating factor (G, M, and GM-CSF, respectively); erythropoietin and thrombopoietin. Other hematopoietic cytokines that are not colony-stimulating factors include IL-3, IL-5, IL-7 and stem cell factor [21]. The bone marrow also provides a microenvironment that is particularly supportive of the differentiation and maturation of B lymphocytes and natural killer cells [22,23]. Therefore, B lymphocytes cannot be produced in vitro unless they are placed onto layers of bone marrow stromal cells [24]. The cultured stromal cells selectively support the differentiation of hematopoietic stem cells into myeloid lineage [25] or B cell lineages. [26, 27]

Different behavioral aspects

Social behavior

It is the behavior that is directed to society, between members of the same species. In sociology, "behavior" means an activity free of social meaning, contrary to "social behavior" that has both together. Social behavior is accompanied by social actions that are directed toward others and induced a response. So, social behavior is a process of communication[28]. Behavior comes in many forms; blinking, eating, reading, dancing, shooting, rioting, and warring….etc. Such social behavior towards others apprehends another as thinking, perceiving, moral, and intentional. Consider the meaning of the other's fields of expression [28].

Conflict behavior

Tendency towards conflict is an elementary component of human nature. Conflict may arise due to competition for scarce resources. Conflict and struggle may promote human social survival by guaranteeing that the strongest survive [29]. According to Marxian theory; conflict is the basic structural condition of society. It is an inherent part of human relationships and existence. Freud's theory stated that; self-interest is the basic to human nature; however, it is managed by conscience. There is also an aggressive unconscious force that seeks expression. The social reality is dualistic; it includes forces that promote social orders and social conflicts [29]. There is an organizational network between individual parties (as individuals, subunits, groups) together with their mutual relations. Besides, the task-oriented and socio-emotional relations are combined with aspects of scarce resources [30]. These aspects often result in conflict situations that may harm working environment [31]. Poorly handled conflict reduces productivity, and increase relations problems [32]. An individual becomes emotional throughout the conflict, he loses focus on tasks and becomes less effective, which results in lack of performance [33]. Sometimes organizational conflict has positive outcomes that include; better ideas; higher interest; and creativity [34]. The previous study had stressed aggression as an important result of dysfunctional conflict. Excess conflicts hinder the success of a group or organization, thus resulting in less satisfaction, increase turnover rates, and decrease productivity [35]. However, the optimal level of conflict enhances motivation through the creation of challenges and questions with vitality which makes the work environment interesting [36]. Approximately 21% of managers' time spends on managing conflict [37]. "Conflict handling", "conflict resolution" and "conflict management" are different concepts [38-40]. The styles of handling conflict are differentiated on two basic dimensions: concern for self and concern for others [41]. A combination of these two concepts results in five different specific styles of handling interpersonal conflict [38, 42]: 1. **Integrating:** Focuses high concern for self and others. 2. **Obliging:** Involves withdrawal, ignoring, and low concern for self and others. 3. **Dominating:** High concern for self and low concern for others. 4. **Compromising:** Moderate concern for self and others; give and take. **5. Avoiding:** Low concern for self as well as other parties.

Aggression

Aggression may be considered as a heterogeneous phenomenon as far as motivations, context, behavioral patterns of attack and presumed functions are concerned. Wilson, 1981 [43] demonstrated that aggression was classified into different types with different various endocrine bases. Maternal aggression that protects the offspring from intruders is mediated by

hormonal changes during the production of offspring [44; 45]. However territorial aggression, inter-male aggression, and sex-related aggression are mediated by steroidal hormones and androgens [46]. Other types of aggression as learned aggression and defensive aggression seem to have different underlying neuronal mechanisms [46].

Learned aggression

Social conditions requiring the expression of prolonged aggression often appear in communities (war, sports, social security). This type of aggression in humans is known as premeditated (learned) aggression [47].

In the sensory contact model (SCM); aggressive behavior is made by repeated experience of victories in regular daily agonistic interactions in male mice. The development of learned aggression in male mice is like those in humans. Positive daily fighting experience in social conflicts modifies many features of individual and social behaviors. Physiological parameters are also changed in both winners and losers [47; 48]. Neurochemical records confirm the stimulation of brain dopaminergic systems and inhibition of the serotonergic system, in the winners under the effect of repeated aggression. This creates a low threshold for aggressive behavior in a weakly provoking environment. Alterations in opioidergic systems as a result of aggression abuse in male mice. Similarities in mechanisms of learned aggression in humans and animals are discovered. Understanding the brain neurochemical basis of learned aggression as well as pathological aggressiveness can be useful for pedagogics, the science of law, and Centers of rehabilitation for war' participants [47].

Depression and anxiety

Stress resulted in psychoemotional negative effects in humans as anxiety, depression, and phobias. Repeated defeat in daily agonistic interactions results in dramatic changes in the social behaviors of losers, which were close to human depression regarding etiology, vulnerability to treatment, symptoms, and neurochemical changes. A significant behavioral deficit, meaninglessness, depression, anxiety, alcohol addiction, in addition to weight loss, reduction of stress reactivity, and sexual dysfunction were found also in the losers [47].

Anxiolytics or antidepressants had positive effects. Chronic social stress is considered as an important pathogenic factor, which aggravates the development of mixed depression/anxiety state in experimental animals. The study of brain neurotransmitters in the losers allowed imagining the dynamic changes in the brain serotonergic and dopaminergic systems; depending on the depth and

duration of depressive disorder. The SCM is a unique experimental model since it permits the examination of neurochemical, behavioral changes, and to suggest specific pharmacological treatments. This model of anxious depression produced by social stress and permanent anxiety is the most adequate and productive one at the present time and can be used for many aims of biological psychiatry [48].

Experimental models for different types of behaviors
Sensory Contact Model (SCM):

The effects of stressful events on the development of psychopathologies have been investigated in animal studies. It was demonstrated that different types of stressors, duration, and intensity produce different responses [49; 50]. The most common stressors in humans are social [51; 52]. So, using the social animal conflict model has an evident advantage over other animal models that require physical stimuli as restraint, electric foot shock, food or water withdrawal, or cold exposure. Previous studies had shown that social defeat stress is an important factor that results in psychopathological impacts [52].

In the first agonistic encounter; behavioral differences often appear between dominant and subordinate animals. One animal begins to win, and the other to lose in the first fight. Successive fights usually occur more quickly, till fighting is avoided overall by the withdrawal of the subordinate. The changes between the behavior of two strangers to the behavior of dominant and subordinate can happen quickly within minutes of their first encounter. These behavioral states can persist for periods, from hours to a lifetime [53].

It was demonstrated that repetitive experience of aggression in winners is accompanied by the stimulation of the brain dopaminergic, and opioidergic systems along with inhibition of the serotonergic system [54,55]. However, repeated experience of depression by social defeats in losers results in a reduction of the activity of all these mediators [56]. Therefore, the winners and losers have been found to show significant differences in emotions, motor activities, gonadal function, level of sociability, and the state of the immune system [57].

Therefore the sensory contact model is important in generating different psycho-emotional disturbances in animals. In this respect, it would be useful to outline possible applications of the proposed experimental method for detecting therapeutic and protective effects and efficacy of prospective novel psychotropic drugs [58, 59].

Locomotor activity is required for many complex behavioral tasks. Thus, it should be measured before performing any other behavioral characterization. Several aspects of locomotion could be measured, for example, response to novelty,

exploratory behavior, and locomotor response to drug treatment. It should be considered that all measures of activity are sensitive to the circadian clock. Therefore, the experiments should be performed daily at the same time [60].

Open field test (OFT) is a test used to evaluate both locomotion activity and emotionality of the animal when exposed to either square or circular open arena under standard conditions [61; 62; 63, 64]. In the OFT; the situation induces anxiety behavior in rodents by two factors; 1. The animal is separated from its social group; 2. Agoraphobia; as the area is very large relative to the animals' environment [65].

Mahfoz, 2019 [48] reported that the winner partner in SCM had higher motor activity in OFT which was demonstrated by a significant increase in ambulation & grooming and a decrease in latency. The higher aggression is associated with the higher motor activity [66]. Aggression contains more features of motor activity [45].

Higher aggression in winners is accompanied by higher anxiety. This was manifested by lower time spent in the open arm of the elevated plus maze (EPM) test [48]. This may be due to fighting for dominance which leads to high fearfulness and anxiety and neurotransmitters imbalance [57; 67].

The EPM is a test used to measure anxiety and emotionality. It represents the natural conflict between the tendency of mice to explore a novel environment and the fear from brightly lid open places [68; 62].

Losers exhibited many behavioral changes; include low motility accompanied by a parallel reduction in DA levels which indicates the depression state of defeated mice [48]. Rygula et al. (2005) [69] also reported that chronic stress in rats resulted in higher immobility in forced swimming test and low preference for a sweet solution.

Impacts of Different Behavioral Aspects on Neurotransmitters
Social information processing in the mammalian brain

Sensory information is processed in the fusiform area, accessory olfactory bulb, or superior temporal gyrus. This signal comes to be instantiated as marked or silent in a successive multimodal projection to defined fields in the temporal cortex, prefrontal cortex, and amygdala, where social status, emotion, or familiarity may be programmed. However, social attachment as pair bonding, maternal behavior, and infant attachment involves enrolment of the mesolimbic dopamine pathway together with the ventral tegmental area. In conclusion, social behavior implicates the stimulation of the neuroendocrine hypothalamus, plus the medial preoptic area, in addition to, motor and autonomic centers [76].

Other brain regions have been reported to be involved in aggression. The elimination of the temporal lobes leads to a passivity syndrome. Lesions in some brain areas as the lateral septum, olfactory bulbs, dorsal and medial raphe, medial accumbens, and amygdala increase defensiveness but didn't affect social aggression [77; 78].

Aggression is salient stressors for both the aggressor and the victim. It is accompanied by stimulation of the mesocorticolimbic region, but not the striatal dopamine. It has been reported that targeting the D_2 receptor family, may affect aggressive behavior in both animals and human patients, this suggesting that the mesocorticolimbic dopamine pathway may have significant enabling or permissive functions[79]. Aggression in winners is associated with increase brain NE and DA levels; while repeated social defeats resulted in attenuation of 5- HT; NE; and DA. This indicates the obtained physiological state in losers and winners [55].

Developments in our information about the neurobiology of pathological aggression have led to the discovery of rational pharmacological treatments for these behaviors. Many biological systems are known to be involved; such as serotonin (5HT), testosterone, opioid peptides, gamma-aminobutyric acid (GABA), dopamine [DA], and Norepinephrine [NE][80-85]. The pathological aggression is associated with low levels of the serotonin metabolite 5-hydroxy-indoleacetic acid in the cerebrospinal fluid and low blood level of serotonin[80; 83].

Moreover, others reported on a Dutch family in which a gene mutation in the monoamine oxidase enzyme (MAOA), resulting in a defect in the breakdown of DA, 5HT, and NE, was associated with markedly increased aggressive behaviors in teenagers [81].

Enhancing catecholamine function by treatment with alpha-2 adrenergic receptor antagonists' was found to increase aggressive responses to intruders [86]. Further experiments [87] in rodents revealed that tricyclics and MAO inhibitors, which increased both DA and NE activity, also enhanced aggressive behavior in these animals. In humans, the NE metabolite 3-methoxy-4-hydroxyphenylglycol correlated with a positive history of aggressive behavior [88].

Acute isolation–induced fighting in mice produced a striking "dose–dependent" increase in dopamine uptake in mesocortical nerve endings (synaptosomes) but no significant changes for these uptake constraints in nigrostriatal terminals[89]. Moreover, the DA metabolite 3-4- dihydroxy-phenylacetic acid (DOPAC) was significantly lower in muricidal rats compared to nonmuricidal animals. The hippocampus of muricidal rats (rats which killed mice)

showed significantly higher DA levels, and higher levels of the NE metabolite homovanillic acid (HVA) were found in the hippocampus of muricidal rats [90].

Behavior and immunity

The endocrine, immunological, and nervous 'super-systems' are engaged in various connections during the reaction of the body to acute or chronic stress [91]. This network bonds relevant ligands with their cognate receptors [92]. Whether or not a healthy balance of protective or damaging effects of stress responses is achieved, it is affected by the concept of allostasis [93]. Allostasis; is known as the adaptation of the endocrine, immune, and nervous systems to keep stability throughout psychological changes, for example unpredictable events: as social conflict, competition for resources, or predictable events: as seasonal changes[93].

Neurotransmitters, neurohormones, neuropeptides, and neurotrophins stimulate a series of adaptation responses in response to stress. These include cardiovascular, metabolic, behavioral, and immunological changes [94] the immunological changes are ranged from immunosuppression to inflammation [95; 96].

These reflect the multifunctional role of the immune system in the stress response. The immune system also controls the central nervous system (CNS). Inflammatory mediators and cytokines influence behavior and complex body reactions. Proinflammatory cytokines can induce sickness behavior or depressive symptoms [93]. Several diseases have been recognized to be aggravated by psychological stress. Such as: migraine, inflammatory bowel disease, allergic encephalomyelitis, and multiple sclerosis[97].

Central hypothalamic-pituitary-adrenal (HPA) axis and corticotropin-releasing hormone (CRH) have a major role in controlling and coordinating complex responses to psychological stress [97]. Relevant examples for the pro-inflammatory actions of CRH had been introduced; include carrageenan-induced arthritis and aseptic inflammation [97; 98].

Histamine release from mast-cells increases the expression of CRH mRNA in the hypothalamus, this activates the HPA, Moreover CRH release could be triggered by IL-1 and IL-6, both are released also from mast cells. On the other hand, CRH stimulates IL-6 release [99].

In humans, positive correlations have been observed between the development of infectious episodes and depressive state [100; 101; 102, 103]. Chronic activation of the cytokines network (e.g., multiple sclerosis and rheumatoid arthritis) has also been correlated with a propensity to develop a depressed mood [104; 105, 106]. A correlation has also been shown in women between the increased liberation of cytokines occurring at childbirth and a post-partum depressive mood [107-109].

Previous studies have demonstrated that the administration of IL-2 or Interferon (IFN) induces depression symptoms in cancer patients. Besides, patients with major depression have reported a higher level of central cytokines [110].

It has been demonstrated that the behavior of patients with viral or bacterial infection changes dramatically. They often feel nauseated, ignore food, and lose interest in their physical and social environments. Furthermore, they are irritated and feel depressed, they can experience mild cognitive disorders ranging from impaired attention to difficulties in remembering recent events. Despite their negative impact on well-being, these symptoms of sickness are usually ignored [91].

Regarding the immunological parameters; it was reported that winners had a significant increase in lymphocytes counts; and viability [70]. **Line et al., (1996)**[71] reported that aggression is associated with the strong immune response which may be due to NE elevation[72]. However, losers have shown weaker immune response demonstrated by the reduction in lymphocytes counts, and viability [70]. This may be due to higher corticosterone levels in losers with depressive behavior, which is immunosuppressant, thus induced cell destruction and lymphocytopenia [73; 74; 75].

It had been reported that cellular and humoral immunity is suppressed in the losers partners in SCM. This means that depression state in loser results in psychogenic immune deficiency. Therefore, the sensory contact model can be used to study the neurochemical and physiological mechanisms of immune suppression along with the possible pharmacological interventions [59].

The brain is considered an immune-privileged organ. It contains immune cells, like macrophages, and dendritic cells, which present in the meninges and choroid plexus. The brain parenchymal macrophages, which known as microglial cells, are more inert as compared to other tissue macrophages; but can respond to inflammatory stimuli by pro-inflammatory cytokines and prostaglandins production [110]. Neuroinflammation is a significant biological event that increases the risk of major depressive episodes [110].

Variables details about how the immune system can influence the brain function had been elaborated. The immune system has a vital role in neurodegeneration and the development of various psychiatric disorders. Autism may result from maternal or host autoantibodies that disrupt neurons that regulate social behavior [111]. Schizophrenia represents overactive immune response which results in neurotransmitters dysregulation [112]. Many studies have reported the impact of the immune system and inflammation

pathways in neurodegeneration occurred in epilepsy [113,96,70,114]. **Niraula et al, 2017** [115] have reviewed the impact of chronic stress on the aging of immune cells. He described age-related hyperresponsiveness and pro-inflammation those have been consistently associated with neurodegeneration and accelerate the aging process.

In line, Eisenberger et al. (**2017**) had discussed the co-regulations between inflammation, and social behavior through neural circuits that stimulates the adaptation to social environments throughout durations of sickness or stress. Acute inflammation raises threat-associated neural sensitivity to negative social experiences. However, increasing reward and motivation associated neural sensitivity toward positive social experiences like care or support during sickness. On the contrary, social behavior may similarly regulate features of inflammatory activity for preparing the body for stress situations [116].

Michopoulos et al, (2017) [117] had also evidenced the role of immune system activation in phobias, posttraumatic stress disorder, panic disorder, and generalized anxiety disorder. Stress or trauma exposure is associated with dysregulation of the autonomic and neuroendocrine systems; these precipitate the release of cytokines which increase symptoms severity through effects on brain circuits critical for the regulation of fear and anxiety (eg, prefrontal cortex, insula, amygdale, and hippocampus). These effects of inflammation on neurotransmitters and neurocircuits are further extended in the review by Brundin et al. (2017) [118] who reported an association between inflammatory activation and suicidal behavior reported through psychiatric disorders. On the basis of this association, they propose that biomarkers of inflammation and its downstream mediators including metabolites of the kynurenine pathway, which relate to both glutamate and serotonin and, provide a mechanism by which suicidal behavior happens. These findings suggested that the immune system affect fundamental pathways which regulates social behavior and in that way represents a critical pathway to the pathophysiology of different neuropsychiatric diseases.

CONCLUSION

On the basis of this review, it could be concluded that the immune system has a strong impact on neurons, brain function, and social behavior. Neuroinflammation is involved in many neuro-degenerative disorders. Novel pharmacological treatments that target autoimmunity, anti-inflammatory, and neuroprotective strategies may have a potential impact on both developmental and neurodegenerative psychiatric disorders.

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

REFERENCES

1. Delves, P. J. and Roitt, M. The immune system, First of two parts. *N. Engl. J. Med.,* **2000**, *343*, 37-49.
2. Karras, J. G., and Holsapple, M. P. Mechanisms of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induced disruption of B lymphocyte signaling in the mouse: a current perspective. *Exp. Clin. Immunogenet.,* **1994**, *11*,110–118.
3. Owen, J. J. T. and Jenkinson, E. J. Ontogeny of the immune response. *In: Clinical aspects of immunology,* volume 1, 5th ed. Lachmann, P.J.; Peters, S.K.; Rosen, F.S. and Walport, M. J., eds. Blackwell Scientific Publications., Boston. **1993**, 3-12.
4. Chaplin, D. Lymphoid tissues and organs. *In: Fundamental Immunology*. 5th ed. Paul, W., ed. Lippincott William & Wilkins, Philadelphia. **2003**, 419-453.
5. Junqueira, L. G.; Cameiro, J. and Long, J. A. *Basic Histology*. 5th ed. Lang Medical Publications, Los Altos, California. **1986**, 270-325.
6. Ravel, R. *Clinical Laboratory Medicine: Clinical Application of Laboratory Data*. 6th ed. Mosby, London. **1995**, pp 56-62.
7. Wheater, P.R.; Burkitt, H.G.; Daniel, V.G. *Functional Histology: A text and colour atlas*. Churchill Livingstone, London. **1987**, 36-51; pp. 225-232.
8. Khan, W. N. Regulation of B lymphocyte development and activation by Bruton's tyrosine kinase. *Immunol. Res.,* **2001**, *23*, 147-156.
9. Herzenberg, L.A.; Black, S.J. and Tokuhisa, T. Memory B cells at successive stages of differentiation. Affinity and the role of IgD receptors. *J. Exp. Med*., **1980**, *150*, 1071-1087.
10. Parslow, T. G. Lymphocytes and lymphoid tissues. *In: Medical Immunology*. 9th ed. Stites, D.P.; Terr, A. I.; Parslow, T.G., eds. Librairie du Liban, Lebanon. **1997**, pp.43-62.
11. Mackay, C.R. Homing of naïve, memory and effector lymphocytes. *Curr. Opin. Immunol.,* **1993**, *5*, 423-427.
12. Weiss, A. and Samelson, L. E. T-lymphocytes activation. *In: Fundamental Immunology*. 5th ed. Paul, W., ed. Lippincott William & Wilkins, Philadelphia. **2003**, pp. 321-363.
13. Marrack, P. and Kappler, J. T cells can distinguish between allogeneic major histocompatibility complex products on different cell types. *Nature*, **1988**, *332*, 840-843.

14. Davies, P. Macrophages. *In: Text book of Immunopharmacology*. 3rd ed. Dale, M.M.; Foreman, J.C. and. Fan, T.D., eds. Blackwell Scientific Publications, Oxford. **1994**, 64-74.

15. Norris, S.; Collins, C.; Doherty, D.G.; Smith, F.; McEntee, G.; Traynor, O.; Nolan, N.; Hegarty, J.; and O'Farrell, C. Resident human hepatic lymphocytes are phenotypically different from circulating lymphocytes*. J. Hepatol.,* **1998**, *28*, 84-90.

16. Lekstrom-Himes, J. A. and Gallin, J. I. Immunedeficiency diseases caused by defects in phagocytes. *N. Engl. J. Med.,* **2000**, *343*, 1703-1714.

17. Fitzer-Attas, C. J.; Lowry, M.; Crowly, M. T.; Finn, A. J.; Meng, F.; DeFranco, A. L. and Lowel, C. A. Fcγ receptor- mediated phagocytosis in macrophages lacking Src family tyrosine kinase Hck, Fgr, and Lyn. *J. Exp. Med*., **2000**, *191*, 669-682.

18. Wardlow, A.J.; Moqbel, R. and Kay, A.B. The eosinophil leukocyte*. In: Text book of Immunopharmacology.* 3rd edn.; Dale, M. M.; Foreman, J.C. and Fan, T.D., eds. Blackwell Scientific Publications, Oxford. **1994**, pp. 55-63.

19. Fung-Leung, W. P.; Sousa-Hitzler, J. D.; Ishaque, A.; Zhou, L.; Pang, J.; Ngo, K.; Panakos, J. A.; Chourmouzis, E.; Liu, F. T. and Lau, C. Y. Transgenic mice expressing human high affinity immunoglobulin (Ig) E receptor alpha chain respond to human IgG in mast cell degranulation and in allergic reactions*. J. Exp. Med.,* **1996**, *183*, 49-56.

20. Kondo, M.; Weissman, I.L. and Akashi, K. Identification of clonogenic common lymphoid progenitors in mouse bone marrow. *Cell,* **1997**, *91*, 661-672.

21. Mantovani, A.; Dinarello, C.A. and Ghezzi, P. (Eds). *Pharmacology of cytokines.* Oxford University Press, U. K. **2000**, pp. 1-18.

22. Lu, M.; Kawamoto, H.; Katsube, Y.; Ikawa, T. And Katsura, Y. The common myelolymphoid progenitor: A key intermediate stage in hemopoiesis generating T and B cells. *J. Immunol*., **2002**, *169*, 3519-3525.

23. Silvennoinen, O.; Renkonen, R. and Hurme, M. Characterization of natural killer cells and their precursors in the murine bone marrow. *Cell Immunol*., **1986**, *101*, 1-7.

24. Whitlock, C.A. and Witte, O.N. Long-term culture of B lymphocytes and their precursors from murine bone marrow. *Proc. Natl. Acad. Sci. U.S.A.,* **1982**, *79*, 3608-3612.

25. Zipori, D.; Duksin, D.; Tamir, M.; Argaman, A.; Toledo, J. And Malik, Z. Cultured mouse marrow stromal cell lines. II. Distinct subtypes differing in morphology, collagen types, myelopoietic factors and leukemic cell growth modulating activities. *J. Cell Physiol.,* **1985**, *122*, 81-90.

26. Dorshkind, K.; Johnson, A.; Collins, L.; Keller, G.M. and Phillips, R.A. Generation of purified stromal cell cultures that support lymphoid and myeloid precursors. *J. Immunol.* Methods, **1986**, *89*, 37-47.

27. Namen, A. E.; Lupton, S.; Hjerrild, K.; Wignall, J.; Mochizuki, D.Y.; Schmierer, A.; Mosley, B.; March, C.J.; Urdal, D. and Gillis, S. Stimulation of B-cell progenitors by cloned murine interleukin-7. *Nature,* **1988**, *333*, 571-573.

28. Rummel R.J. *Understanding Conflict and War:* Vol. 2: The Conflict Helix. 2000.

29. Farrington, K., and Chertok, E. Social conflict theories of the family. *In: P.G. Boss, W. J. Doherty, R. LaRossa, W. R. Schumm, & S. K. Steinmetz (Eds.), Sourcebook of family theories and methods: A contextual approach* New York: Plenum. **1993**, pp. 357-381.

30. Mastenbroek, W.E.G. *Conflict management and organizational development.* New York: John Wiley and Sons **1993**.

31. Bodtker, A. M. and Jameson, J.K. "Emotions in conflict formation and its transformation: Application to organizational conflict management." *Int. J. of Conf. Manag.,* **2001**, *12* (3): 223- 226.

32. Tjosvold, D. and Chia, L.C. "Conflict between managers and workers: The role of cooperation and competition. *J. of Soc. Psych.,* **1988**, *129*, 235-247.

33. Jehn, D.A. A qualitative analysis of conflict types and dimensions in organization groups. *Administ. Sci. Quat*., **1997**, *42*, 530-557

34. Pelled, L.H.; Eisenhardt, K.M. and Xin, K.R. Exploring the black box: An analysis of group work diversity, conflict and performance. *Administ. Sci. Quat*., **1999**, *44*, 1-28.

35. Opotow, S. Aggression and violence. *In: Deutsch, M. And Coleman, P. T. The handbook of conflict resolution.* San Fransisco: Jossey-Bass Publishers. **2000**.

36. Robbins, S. P., Odendaal, A. and Roodt, G. *Organisational behaviour: Global and South African Perspectives.* Cape Town: Pearson Education Inc. **2003**, *28*, 161-168.

37. Nelson, D. and Quick, J. *Organizational behaviour: Foundations, realities and challenges*. Cincinnatti: South- Western College Publishing. **2001**, *373*, 561-573

38. Rahim, M.A. "Toward a theory of managing organizational conflict". *Int. J. Conf. Manag.*, **2002**, *13* (3), 206-235.

39. Thomas, K.W. and Killman, H.R. *Thomas-Killman conflict MODE instrument.* NY.; Xicom. **1974**.

40. Thomas, K.W. and Killman H.R. Conflict and conflict management." *(In Dunette, M.D. (ed.) Handbook of Industrial Organizational Psychology*. Chicago: Rand McNally. **1976**.

41. Rahim, M.A. and Bonoma, T.V. Managing organizational conflict: A model for diagnosis and intervention. *Psychol. Rep*. **1979**, 44.

42. Van de Vliert, E and Kabanoff, B. Toward theory-based measures of conflict management, *Acad. of Manag. J.* **1990**, *33*,199-209

43. Wilson. E.O. *Sociobiology.* Cambridge: Harvard University Press. **1981**, pp. 343.

44. Bridges, R.S. Biochemical basis of parental behavior in the rat. *In: Rosenblatt, J.S.; Snowden, C.T., editors. Parental Care: Evolution, Mechanisms, and Adaptive Significance.* San Diego: Academic. **1996**, pp. 215-237.

45. Gammie, S.C. and Nelson, R.J. Maternal aggression is reduced in neuronal nitric oxide synthase-deficient mice. *J. Neurosci*., **2003**, *19*, 8027-8035.

46. Bouissou, M.F. Androgens, aggressive behavior and social relationships in higher mammals. *Horm. Res.,* **1983**, *18*, 43-61.

47. Kudryavtseva, N. N. The sensory contact model for the study of aggressive and submissive behaviors in male mice. *Aggress. Behav*., **1991**, *17*.

48. Mahfoz, A. M. "Social behavior effects of diphenyl dimethyl bicarboxylate (DDB) in the sensory contact model." *Naun. Schm. Arch. Pharmacol* **2019**, *392* (3), 313-326.

49. Puglisi-Allegra, S.; Kempf, E.; Schleef, C. and Cabib, S. Repeated stressful experiences differently affect brain dopamine receptor subtypes. *Life Sci.,* **1991**, *48*,1263–1268.

50. Cabib, S. and Puglisi-Allegra, S. Stress, depression and the mesolimbic dopamine system. *Psychopharmacol. (Berl).,* **1996**, *128*, 331–342.

51. Kessler, R.C. Price RH, Wortman CB. Social factors in psychopathology: stress, social support, and coping processes. *Annu Rev Psychol*. **1985**, *36*, 531–572.

52. Bjorkqvist K. Social defeat as a stressor in humans. *Physiol Behav*., **2001**, 73:435–442.

53. Shih-Rung Yeh; Barbara E. Musolf and Donald H. Edwards. Neuronal Adaptations to Changes in the Social Dominance Status of Crayfish, *J. Neurosci*., **1997**, *17* (2), 697–708

54. Kudryavtseva, N.N. Neurobiological correlates premeditated (learned) aggression: seeking new experimental approaches. *Usp Fiziol Nauk.,* **2001**, *32* (4), 23-35.

55. Kudryavtseva, N.N. *Psychopathology of repeated aggression: a neurobiological aspect. Perspectives on the Psychology of Aggression* . Ed. J.P. Morgan. NOVA Science Publishers, **2006**, 35-64.

56. Avgustinovich D. F.; Alekseenko O.V.; Bakshtanovskaia I. V.; Koryakina L.A.; Lipina T.V.; Tenditnik M.V.; Bondar N.P.; Kovalenko I.L. and Kudryavtseva N.N. Dynamic changes of brain serotonergic and dopaminergic activities during development of anxious depression: experimental study. *Usp Fiziol Nauk*. **2004**, *35*, 19-40.

57. Kudryavtseva, N. N. Agonistic behavior: model, experiment, perspectives. *Ross Fiziol Zh Im I M Sechenova.*, **1999**, *85*(1), 67-83.

58. Kudryavtseva, N.N.; Bakshtanovskaya, I.V. and Koryakina, L.A. Social model of depression in mice of C57BL/6J strain // *Pharmacol. Biochem. Behav*., **1991**, *38*(2), 315-320.

59. Kudryavtseva, N.N. and Avgustinovich, D.F. Behavioral and physiological markers of experimental depression induced by social conflicts (DISC) *Aggress. Behav*., **1998**, *24*, 271-286.

60. Karl, T.; Pabst, R. and von Horsten, S. Behavioral phenotyping of mice in pharmacological and toxicological research. *Exp. Toxic. Pathol.,* **2003**, *55*, 69-83.

61. Satinder, K.P. Open-field emotional reactivity and alcohol intake in rats. Pharmacol. Biochem. Behave., **1982**, *17*, 961-965.

62. Trullas, R. and Skolnick, P. Differences in fear motivated behaviors among inbred mouse strains. *Psychopharmacol. (Berl),* **1993**, *111*, 323-331.

63. Van Gaalen, M.M. and Steckler, T. Behavioral analysis of four mouse strains in an anxiety test battery. *Behave. Brain Res*., **2000**, *115*: 323-331.

64. Prut, L. and Belzung, C. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. *Eur. J. Pharmacol*., **2003**, *463*, 3-33.

65. Bhattacharya, S.K. and Satyan, K.S. Experimental methods for evaluation of psychotropic agents in rodents: I- Antianxiety agents. *Indian J Exp Biol.,* **1997**, *35*, 565-75.

66. Sandnabba, N.K. Selective breeding for isolation-induced intermale aggression in mice: associated responses and environmental influences. *Behav. Genet.,* **1996**, *26* (5), 477–88.

67. Cases, O.; Seif, I.; Grimsby, J.; Gaspar, P.; Chen, K.; Pournin, S.; Muller, U.; Aguet, M.; Babinet, C. and Shih, J.C. Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA , *Sci.,* **1995**, *268*, 1763-1766.

68. Pellow, S. and File, S.E. Anxiolytic and anxiogenic drug effects on exploratory activity in an elevated plus-maze: a novel test of anxiety in the rat. *Pharmacol. Biochem. Behav.*, **1986**, *24*, 525-529.

69. Rygula, R.; Nashat Abumaria; Gabriele, Fl¨ugge; Eberhard Fuchs; Eckart R¨uther; Ursula Havemann-Reinecke. Anhedonia and motivational

deficits in rats: Impact of chronic social stress, *Behav. Br. Res*. **2005**, *162*, 127–134.

70. Mahfoz, A. M., A. F. Abdel-Wahab, M. A. Afify, N. Shahzad, I. A. A. Ibrahim, N. A. ElSawy, G. A. Bamagous and S. S. Al Ghamdi. "Neuroprotective effects of vitamin D alone or in combination with lamotrigine against lithium-pilocarpine model of status epilepticus in rats." *Naun. Schmied. Arch. Pharmacol.* **2017**, *390* (10), 977-985.

71. Dhabhar, F. S., Miller, A. H., McEwen, B. S., and Spencer, R. L.. Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms. *J. Immunol.,* **1995**, *154*, 5511–5527.

72. Line SW; Jay R. Kaplan; Eugene R. Heises; Julia K. Hilliard; Sheldon Cohen; Bruce S. Rabin and Stephen B. Manuck. Effects of social reorganization on cellular immunity in male cynomolgus monkeys, *Am. J. Primatol*., **1996**, *39*, 235 – 249.

73. Bloemena E.; Koopmans RP. and Weinreich S. Pharmacodynamic modeling of lymphocytopenia and whole blood lymphocyte cultures in prednisolone-treated individuals. *Clin Immunol Immunopathol.,* **1990b**, *57*, 374.

74. Bloemena E.; Weinreich S. and Schellekens PT. The influence of prednisolone on the recirculation of peripheral blood lymphocytes in vivo. *Clin Exp Immunol*., **1990a**, *80*, 460.

75. Braat, M.C.; Oosterhuis, B. and Koopmans R.P. Kinetic-dynamic modeling of lymphpcytopenia induced by the combined action of dexamethasone and hydrocortisone in humans, after inhalation and intravenous administration of dexamethasone. *J Pharmacol Exp Ther,* **1992**, *262*:509.

76. Thomas, R. Insel and Russell D. Fernald. How the brain processes social information: Searching for the Social Brain, *Annu. Rev. Neurosci*., **2004**, *27*, 697–722.

77. Kluver, H. and Bucy, P.C. Preliminary analysis of functions of the temporal lobes in monkeys. *Arch. Neurol. Psychiatry,* **1939**, *42*, 979-1000.

78. Albert, D.J. and Walsh, M.L. Neural systems and the inhibitory modulation of agonistic behavior: A comparison of mammalian species. *Neurosci. Biobehav. Rev.,* **1984**, *8*, 5-24.

79. Klaus, A. Miczek; Eric, W. Fish; Joseph, F. de Bold and Rosa, M. de Almeida. Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and γ-aminobutyric acid systems, *Psychopharmacol. (Berl.)* **2002**, *163* (3-4), 434-458.

80. Linnoila, M.; Virkkunen, M.; Scheinin, M.; Nuutila, A.; Rimon, R. and Goodwin, F.K. Low cerebrospinal fluid 5- hydroxyindoleacetic acid concentration differentiates impulsive from nonompulsive violent behavior. *Li. Sci.,* **1983**, *33*, 2609-2614.

81. Brunner, H. G., Nelen, M.; Breakfield, X.O.; Ropers, H.H. and van Oost, B.A. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Sci.,* **1993**, *262*, 578-80.

82. Muhlenkamp, F.l.; Lucion, A. and Vogel, W.H. Effects of selective serotonergic agonists on aggressive behavior in rats. *Pharmacol Biochem Behav.,* **1995**, *50*, 671-674.

83. Yaryura-Tobia, J. A.; Nezoroglu, F.A. and Kaplan, S. Selfmutilation, anorexia, and dysmenorrhea in obsessive compulsive disorder. *Int. J. Eating Disord*., **1995**, *17*, 33-38.

84. Fischer, S.G.; Ricci, L.A. and Melloni, R.H. Jr. Repeated anabolic/androgenic steroid exposure during adolescence alters phosphate-activated glutaminase and glutamate receptor 1 (GluR1) subunit immunoreactivity in Hamster brain: correlation with offensive aggression. *Behav Brain Res*., **2007**, *180*, 77-85.

85. Jacobs, C.; Van Den Broeck, W. and Simoens P. Neurons expressing serotonin -1B receptor in the basolateral nuclear group of the amygdale in normally behaving and aggressive dogs. *Brain Res*., **2007**, *1136*, 102-109.

86. Haller, J.; Makara, G. B.; Kovacs, J. L. The effect of alpha 2 adrenoreceptor blockers on aggressive behavior in mice: implications for the actions of adrenorector agents. *Psychopharmacol (Berl).,* **1996**, *126*, 345-350.

87. Eichelman, B. and Barchas, J. Facilitated shock–induced aggression following anti-depressive medication on the rat. *Pharmacol Biochem Behav*., **1975**, *3*, 601-604.

88. Brown, G. L.; Goodwin, F.K.; Ballenger, J.C.; Goyer, P.F. and Major, L.F. Aggression in human correlates with cerebrospinal fluid amine metabolites. *J Psychiatr Res.,* **1979**, *1*, 131-139.

89. Hadfield, M. G. Dopamine: mesocortical vs. nigrostriatal uptake on isolated fighting mice and controls. *Behav Brain Res* **1983**, *7*, 269-281.

90. Broderick, P.A.; Barr, G.A.; Sharpless, N.S. and Brodger, W.H. Biogenic amine alterations in limbic brain regions of muricidal rats. *Res Comm Chem Pathol Pharmacol.,* **1973**, *48*, 3-15.

91. Fleshner, M.; Laudenslager, M. L. Psychoneuro-immunology: then and now. *Behav. Cogn. Neurosci. Rev*., **2004**, *3*, 114–130.

92. Steinman, L. Elaborate interactions between the immune and nervous systems. *Nat. Immunol.*, **2004**, *5*, 575–581.

93. Dantzer, R. Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate

immunity. *Eur. J. Pharmacol.,* **2004**, *500*, 399–411.

94. Viswanathan, K. and Dhabhar, F.S. Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation. *Proc. Natl. Acad. Sci. U. S. A.,* **2005**, *102*, 5808–5813

95. Padgett, D.A. and Glaser, R. How stress influences the immune response. *Trends Immunol.,* **2003**, *24*, 444–448.

96. Borham, L. E., A. M. Mahfoz, I. A. A. Ibrahim, N. Shahzad, A. L. AA, A. A. Labib, B. Bin Sef, A. Alshareef, M. Khan, A. Milibary and S. Al Ghamdi. "The effect of some immunomodulatory and anti-inflammatory drugs on Li-pilocarpine-induced epileptic disorders in Wistar rats." *Brain Res.* **2016**, *1648* (Pt A), 418-424.

97. Chrousos, G.P. Stressors, stress, and neuroendocrine integration of the adaptive response: the 1997 Hans Selye Memorial Lecture. *Ann. N. Y. Acad. Sci.,* **1998**, *851*, 311–335.

98. McEvoy, A. N. Corticotropin-releasing hormone signaling in synovial tissue from patients with early inflammatory arthritis is mediated by the type 1a corticotropin-releasing hormone receptor. *Arthritis Rheum*., **2001**, *44*, 1761–1767.

99. Venihaki, M. et al. Corticotropin-releasing hormone regulates IL-6 expression during inflammation. *J. Clin. Invest.* **2001**, *108*, 1159–1166.

100. Greenwood, R. Residual mental disorders after herpesvirus infections. *In: Kurstak, E., Lipowski, Z.J., Morozov, P.V. (Eds.), Viruses, Immunity and Mental Disorders*. Plenum Press, New-York, **1987**, 65–80.

101. Hendler, N. Infectious mononucleosis and psychiatric disorders. *In: Kurstak, E., Lipowski, Z.J., Morozov, P.V. (Eds.), Viruses, Immunity and Mental Disorders*. Plenum Press, New-York, **1987**, 81–94.

102. Meijer, A.; Zakay-Rones, Z. and Morag, A. Pos-inXuenzal psychiatric disorders in adolescents. *Acta Psychiatr. Scand*. **1988**, *78*, 176–181.

103. Brown, R.; King, M.G. and Husband, A. J. Sleep deprivation-induced hyperthermia following antigen challenge due to opioid but not interleukin-1 involvement. *Physiol. Behav.*, **1992**, *51*, 767–770.

104. Minden, S.L. and Schiffer, R.B. Affective disorders in multiple sclerosis. Review and recommendations for clinical research. *Arch. Neurol.,* **1990**, *47*, 98–104.

105. Parker, J.; Smarr, K.; Anderson, S.; Hewett, J.; Walker, S.; Bridges, A.; Calwell, W. Relationship of changes in helplessness and depression to disease activity in rheumatoid arthrisis. *J. Rheumatol.,* **1992**, *19*, 1901–1905.

106. Marshal, P.S. Allergy and depression: a neurochemical threshold model of the relation between the illnesses. *Psychol. Bull*., **1993**, *113*, 23–43.

107. Parry, B. L. Mood disorders linked to the reproductive cycle in women. In: *Blomm, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress.* Raven Press, New-York, pp., **1995**, 1029–1042.

108. Hall, S. and Smith, A. Investigation of the effects and after-effects of naturally occurring upper respiratory tract illnesses on mood and performance. *Physiol. Behav.,* **1996,** *59*, 569–577.

109. Yirmiya, R. Endotoxin produces a depressive-like episode in rats. *Brain Res*., **1996**, *711*, 163–174.

110. Maes, M. Evidence for an immune response in major depression: a review and hypothesis. Prog. Neuropsychopharmacol. *Biol. Psychiatry.,* **1995**, *19*, 11–38.

111. Meltzer A, Van de Water J. The role of the immune system in autism spectrum disorder. *Neuropsychopharmacol.* **2017**, *42*, 284–298.

112. Miller, B. J.; Goldsmith, D. R. Towards an immunophenotype of schizophrenia: progress, potential mechanisms, and future directions. *Neuropsychopharmacol.* **2017,** *42*, 299–317.

113. Abdel-Wahab, A. F.; Afify, A. M.; Mahfouz, N.; Shahzad, G. A. Bamagous and S. S. Al Ghamdi. "Vitamin D enhances antiepileptic and cognitive effects of lamotrigine in pentylenetetrazole-kindled rats." Brain Res 1673: 78-85. *Neuropsychopharmacol.* **2017**, *42*, 318–333.

114. Mahfoz, A. M.; N. Shahzad. "Neuroinflammation impact in epileptogenesis and new treatment strategy." *Behav. Pharmacol.* **2019**, *30* (8), 661-675.

115. Niraula A, Sheridan JF, Godbout JP. Microglia priming with aging and stress. *Neuropsychopharmacol.* **2017**; *42* (1), 318-333. doi: 10.1038/npp.2016.185.

116. Eisenberger NI, Moieni M, Inagaki TK, Muscatell KA, Irwin MR. In sickness and in health: the co-regulation of inflammation and social behavior. *Neuropsychopharmacol.* **2017**, *42*, 242–253.

117. Michopoulos, V.; Powers, A.; Gillespie, C. F.; Ressler, K. J.; Jovanovic, T. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. *Neuropsychopharmacol.* **2017**, *42*, 254–270.

118. Brundin, L.; Bryleva, E. Y.; Thirtamara Rajamani K. Role of inflammation in suicide: from mechanisms to treatment. *Neuropsychopharmacol*. **2017**, *42*, 271–283.