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IMMUNE SYSTEM AND DESTRUCTIVE BEHAVIOR

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Abstract. When microglia is maladaptive activated in the brain, may be the origin of the unconscious drive such as death drive in the unconscious mind, and induce emotional reactions such as anxiety, fear, aggression envy, and suicidal thoughts and behaviors. Beyond its traditional role in defending the body, the immune system is now considered a diffuse sensory organ and metabolic regulator that works in concert with the nervous system to achieve and maintain body homeostasis; the involvement of immune cells, in the first place the microglia cells and their products of secretion, such as the cytokines, in brain physiology and pathology. The bidirectional communication between the brain and the immune system via cytokines has important consequences for behavior.
Keywords: brain, behavior, emotion, immune, microglia, unconscious.

INTRODUCTION

A century ago, Freud proposed designing of mind structure models consisting of the following three components: id (unconscious /instinctual drives), ego (conscious mind exclusive device), and the super ego (which represses ID to avoid any disruption to rational thinking). In the process of clarifying id and super ego unconscious components, Freud also developed economic models of the following energy units / unconscious drives, primarily "life instinct"(Lebenstrieb) - tendency to survival and development, and other creative life-producing creative drives lifeforms producing units, and later "death drive " (Todestrieb) described in "Beyond the Pleasure Principle" (Freud, 1920) and death instinct, one of the key concepts of psychoanalysis, believed to form the basis of various emotions / behaviors - anxiety, fear, aggression and envy, and problem behaviors, including violence and suicide (Freud, 1933,

Historically speaking, Freud asserted the unity of death from clinical phenomena such as backlash treatment, repetition - constraint, dreams of anxiety in people with war neurosis, and masochism. Freud considered that the life instinct and death instinct coexist since the early stages of life, Freud, 1924). Freud called the death drive outward directed destructive instinct (drive wishes of affection and / or objects) and the death drive (destruction and aggression), and these units are expressed as relationships internal / external object object (Klein, 1957).

DESTRUCTIVE BEHAVIORS. DESTRUCTIVE EMOTIONS.

Researchers such as Heinz Hartmann, Otto Kernberg, and Jaak Panksepp discussed the concept of instincts and drives / drives of psychoanalysis in relation to biology and affective neuroscience. Hartmann, one of the founders of ego psychology, developed the theory of aggression based on unit death (Hartmann, 1939) from experience in neurobiology and neuropsychoanalysis and Panksepp has recently developed SEEKING system that links units / drives and emotions (Wright and Panksepp, 2012).

We use the term death drive as virtual destructive instinct/ drive that induce negative emotions and destructive behaviors outside. In the next part, we present the theory of unconscious units in order to integrate psychoanalytic and biological model (Kato ,2013).

COMMUNICATION BRAIN / IMMUNE SYSTEM. CYTOKINES AND BEHAVIOR

Beside the critical role of defending the body, the immune system on the brain level has fundamental roles both in normal processes "homeostatic" and in pathological processes when molecular disorders occur.Ketteman,2011

Primary immunocompetent cells of the CNS, microglia and astrocytes are involved in every major aspect of development and brain function.

CNS glial cells produce cytokines involved both in the processes of trauma / / injury and repair. Evidence from animal studies and human data involve the immune system in a number of disorders with known or suspected origins in the period of initial growth and development of the body as schizophrenia, anxiety / depression and cognitive dysfunction. Infection during the perinatal period acts as a vulnerability factor for subsequent changes in cytokine with important consequences for the behavior of the rest of your life. Bilbo hypothesizes that long-term changes in brain glial cell function underlie this vulnerability.Bilbo,20o9

Experiences during the perinatal period can modulate or "program" the normal course of development, with the result that adults outcomes , including behavior, are significantly and often permanently modified (Bennet and Gunn, 2006). There is strong evidence that the perinatal exposure to infectious agents has a number of further influences on the human body, including the reactivity of stress, disease susceptibility, and in particular, to develop high vulnerability of cognitive and / or neuropsychiatric disorders including Alzheimer's disease, Parkinson's disease, schizophrenia, , and autism (. Nelson and Willoughby, 2000. Rantakallio et al, 1997).

Beyond its traditional role in defending the body, the immune system is now considered a diffuse sensory organ and metabolic regulator that works in concert with the nervous system to achieve and maintain body homeostasis (Husband, 1995; Vitkovice, 2000) . Immunocompetent cells are located along nearly every organ of the body, including the brain, and sophisticated interactions occur between these cells mainly by soluble protein messengers called cytokines. What I'd like to underline here is that the bidirectional communication between the brain and the immune system via cytokines has important consequences for behavior. For example, sick animals has several well-characterized behavioral changes , including reductions in food and water intake , activity , exploration, and social and sexual interactions (Hart , 1988; . Kent et al, 1992).

Importantly, these so-called "sickness behavior" are not mediated by infectious pathogens themselves, but rather are orchestrated by the body by cytokines (Dantzer and Kelley, 2007). Numerous studies have now shown that these behaviors are organized adaptation strategies critical for survival (Dantzer and Kelley, 2007; Nesse and Williams, 1994). Thus, the behavior of the disease reflects the total change in motivational state of the individual.

IMMUNE RESPONSE

Cytokines are produced in the brain during normal development of the brain, but are expressed at much higher levels during an immune response. Increased exposure of cytokines during key periods of brain development can act as a factor of "vulnerability" for a potential subsequent pathology, the neural substrates awareness and change the way the brain responds to a subsequent immune challenge. In turn, this altered immune response is important and lasting consequences in the behavior, including the social, cognitive, and affective skills. There have been discussions about a mechanism responsible for persistent changes in the cytokines that may be chronic activation of microglia, the primary CNS immunocompetent cell.

CYTOKINES AND GLIAL CELLS

One of the most significant changes associated with perinatal infection is the glial activation. Interestingly, one of the first doctors who suggested relationship between infection and psychosis at the end of the 19th century cites "changes in the land" as one of four primary anatomical changes in the brain (Kraepelin, 1919). Glial cells are described as critical to "every major aspect of the development, function and brain pathology (Barres, 2008), the central cells in cerebral homeostasis, so that brain

pathology is pathology of glial cells," brain pathology is, to a very great extents, the pathology of glial cells "(Giaume, 2007).

Microglia cells are the primary immunocompetent cells of the brain, existing even in non-pathological conditions in a resting state, with ramified morphology, with low or non-detectable expression on the cell surface markers of "activation" (eg, CD11b [3 complement receptor / CR3] major histocompatibility complex MHC II). However, the term "activation" marker is rather unsuitable, since the resting cells are in no way dormant or inactive. However, in response to an injury or stimulation / challenge of the immune system microglia cells are more active and express an increased number of surface receptors. Once activated, glial cells produce a number of cytokines, chemokines (e.g., Monocyte chemoattractant protein, MCP-1), and other factors (e.g., nitric oxide - NO, superoxide), which, in turn, influence neuronal function.

All these data concludes the involvement of immune cells, in the first place the microglia cells and their products of secretion, such as the cytokines, in brain physiology and pathology.Bilbo,2009

I have argued here that the early life of an individual is very important in shaping how the immune system and therefore the brain develops, with important consequences for brain and behavior during lifetime.

Available data indicate a range of influences from perinatal life going toward adulthood regarding the activation of the immune system in the brain and on behavior, through mechanisms such as cytokine production and glial activation. On the other hand, the data suggest that a number of challenges performed in certain specific times of development during pregnancy affects the brain in its entirety. Infectious early experience can help adjusting an appropriate immune response, and this has significant consequences, both adaptive and maladaptive for the complex behavioral responses throughout life.Bilbo,2009

The immune system is critically involved in normal brain function and conversely in the cognitive / behavior pathology on a large scale. Studies have shown extremely complex influence immune activity in neural development, immune response and the role the brain plays in adaptive behavior, both in sickness and in health states.

MICROGLIA AND UNCONSCIOUS DRIVES

Brain imaging and histological studies showed microglial activation in the brains of people with mental disorders such as schizophrenia, depression, a microglial contribution to mental disorders (Monji, 2009, Kato, 2011).

Immune / inflammatory activators such as lipopolysaccharide (LPS) and interferon - γ, which are induced by infection, and stressful life events, can activate microglia in the brain. Activated microglia release proinflammatory cytokines and free radicals (Block and Hong, 2005). Into the brain of patients with mental disorders, these mediators can cause brain pathology such as neuronal degeneration, white matter abnormalities, and decreased neurogenesis (Uranova, 2004, 2007; Jarskog, 2005; Lieberman, 2005; Girgis, 2006; Glantz, 2006; Macritchie, 2010). Such interactions remodeling of neuron - microglia could be an important factor in the pathophysiology of mental disorders (Monji, 2009, 2011; Kato, 2011).

Microglia is activated not only in inflammation but also in terms of physical stress (Frank et al, 2007; Sugama, 2007, 2009) and psychosocial stress conditions, such as social isolation (Schiavone 2009), chronic stress constraint type (Tynan, 2010; Hinwood, 2012) and defeatist social situations (Wohleb et al, 2011).

Microglia may be involved in physical and emotional disorders. Human postmortem studies have shown microglial activation in the brains of suicide victims (Steiner et al., 2006, 2008). Suicide was generally regarded as a consequence of emotional disorders, and also in psychology and psychoanalysis, suicide was considered to be the result of maladaptive unconscious drives.

THEORY OF CONNECTION BETWEEN MICROGLIA AND UNCONSCIOUS DRIVES. MICROGLIA INVOLVED IN MENTAL ACTIVITIES THAT ARE AT THE ORIGIN OF UNCONSCIOUS DRIVES

Death drive internal reasons have not been clarified in terms of molecular neuroscience. It is necessary to be clarified the mechanism underlying the unconscious drive according to modern understandings of microglia and its immunological roles in the brain. Clearly, Freud did not know these cells, however surprisingly, he assumed a link between immunity and suicide in the following sentence:

"… It is noteworthy that the obsessional neurotic, in contrast to the melancholic, never in fact takes the step of self-destruction; it is as though he were immune against the danger of suicide, and he is far better protected from it than the hysteric (Freud, 1920)."

Today, the role of microglia has been understood with greater clarity than in the era of Freud. Synaptic responses have been considered having a role in human mental activity and that severe stress, including psychosocial stress would activate microglia (Frank et al, 2007; Schiavone et al, 2009; Sugama et al, 2009; Tynan et al , 2010; Wohleb et al, 2011; Hinwood et al., 2012). In addition, human studies suggest that microglial activation is observed in the brain of suicide victims and psychiatric patients (Steiner et al, 2006, 2008; Van Berckel et al, 2008; Doorduin et al, 2009; Takano et al , 2010). In the microglia activated state, the unconscious drives may be highly active in psychoanalytic terms.

In conclusion, a new hypothetical theory appears: "When microglia is maladaptive activated in the brain, may be the origin of the unconscious drive such as death drive in the unconscious mind, and induce emotional reactions such as anxiety, fear, aggression envy, and suicidal thoughts and behaviors". Northoff, 2012

There are better alternative approaches to clarify the functions of microglia in social work / human mind. Early life events can activate human microglia, to establish a relation to neuro-synaptic, and this may result in the formation of personality and social behavior by personality later in life (Kato et al., 2013).

The above assumptions shed new light on the dark side of mental functions modulated by cytokines from microglial level, particularly emphasizing the role of microglia in understanding the unconscious. In the same way that Freud suggested that our behavior must be controlled by the unconscious world, microglia can control our behavior unconsciously. Neuroscience focusing on microglia could be a new key for investigating social / mental human work.

MICROGLIA AND AMBIVALENCE

Microglial cells serve both for protection as well as pathology. For example, they produce neurotrophic factors that help repair cell and recruit immune cells in the brain, helps eliminate self-limiting infection and cellular debris, aid in cellular repair, and recruit immune cells into the brain, which aid in clearing infection or cellular debris (Lalancette-Hebert et al., 2007). Moreover, selective ablation of microglia after stroke is worsening the clinical status (Lalancette-Hebert et al., 2007). Unlike these benefits, exaggerated microglial chronical activation is associated with neuroinflammatory and neurodegenerative diseases, including Parkinson's disease, multiple sclerosis, Alzheimer's disease and Huntington's disease (Perry, 2004).

Microglia play an interesting role as a double-edged sword in brain (Henkel et al, 2009 . Graeber and Streit , 2010). Microglia activation could be seen not only as maladaptive factors such as tumor necrosis factor (TNF) - α , but also as protective factors such as n - derived neurotrophic factor (BDNF) , which means that microglia are both bad and good actors alternating in the brain. The "destructive" function of microglia may play a vital role in the death instinct. On the other hand , the function of " trophic " of microglia may play an equally crucial role in the life instinct . It remains controversial as to whether the origin of the two units is the same in terms of psychotherapy.

Based on the theory of microglial origin and determining factor may be the composition and direction of microglia. Changing balance of trophic / destructive in microglial expression may explain the origin of the base of the two units in mind. The existence of two directional microglial in the same region could induce ambivalence, which is a dilemma between the two opposite emotions like "love and hate." The direction of microglial activation could cause our behaviors towards life or death.

Terms "trophic" and "destructive" should not be taken in a strictly literally manner. The proposed theory may be too simplified which means that the function of microglia is easily divided ("trophic" = preservation = instinct of life, and "destructive" = destroy = death instinct). This dichotomy is not always true in real world situations. Certain microglia may have a destructive effect on synaptic level, which long term is a of trophic result for the brain, to conserve power to run populations of neurons and to rebuild appropriate neural networks. Aging is known to be one of the key factors microglial switching characteristics. Generally speaking, aging tends to activate maladaptive microglia (Dilger and Johnson, 2008; Jang and Johnson, 2010; Norden and Godbout, 2012).

MICROGLIAL CONTRIBUTION IN CONSCIOUS /UNCONSCIOUS SYSTEM

To understand the current state of neuroscience one of the main issues is understanding the biological importance of unconscious / conscious and also to understand the emotional and unconscious reactions in the brain. It is a challenge to consider the role of microglia in the emotional and unconscious reactions. Neural systems and neurotransmitters have been considered to have an important role in emotions " unconscious " modulated and in motivational behavior (Solms and Turnbull , 2002). In addition, microglia may be a possible source of negative “unconscious” emotions. There is a hypothesis of a possible role for microglia in emotional reactions. Following three processes may be occurring in at least some biological pathways of unconscious / conscious (1) microglia can be activated by modulation of neurotransmitter emotional reactions based on perceptual information , (2) microglial activation can modulate synaptic responses by neurotransmitters as a result of emotional reactions , and (3) a combined process of the first and second may occur in particular during emotional responses of high intensity and duration , the primary emotional reactions can activate the neuronal systems and synapse modulation of neurotransmitters which result in microglial activation , and ultimately activation of each other can occur by microglial neurotransmitters and mediators such as radicals and / or free cytokines . The third process could be one of the possible causes of emotional disorders , symptoms of various mental disorders and also suicide .Kato,2013

The relationship between conscious and unconscious has long been considered in the context of neural systems. Microglial cells are now known to be unique dynamic cells in the brain that can move and are usually independent. Microglial activation itself is not directly related to emotional reactions, but it is possible that microglial activation may be one of the primary factors of crucial priming unconscious emotional reactions by affecting neural business systems. Glial involvement theory of unconscious processes can bring new insights into understanding the emotional reactions of internal causes (derived from the unconscious). Interestingly, recently there has been studied the contribution of microglia in the development of delirium, which induces consciousness disorder by internal causes such as systemic infections (Van Gool et al., 2010). All these can put in a new light Freud's theory of conscious and unconscious system.

CONCLUSIONS. FUTURE PERSPECTIVES

- possibility that microglial activation in the brain to activate the unconscious mind.
- possibility that microglial activation direction and meaning to be key factors in complex behavioral and mental activities presentation mechanisms "unconscious drives" in both psychoanalytic and neuroscience perspectives.
- Microglia may have the potential to reduce the enormous gap between neuroscience, biological psychiatry, psychology, psychoanalysis. . To investigate the theory of microglia, there is a need for in vitro and in vivo animal studies, based on neuropsychoanalytical approach.
- Clinical studies involving microglia could lead to new strategies in the therapy of mental disorders
- clarifying the mutual interaction of neuron - glia may lead to deeper understanding of the theory of the unconscious and theories neuropsychoanalytice in the brain.

REFERENCES

Barres, B. A. The mystery and magic of glia: a perspective on their roles in health and disease. Neuron 60, 430–440,2008

Bennet, L., and Gunn, A. The fetal origins of adult mental illness. In Early Life Origins of Health and Disease (Advances in Experimental Medicine and Biology), M. Wintour-Coghlan and J. Owens, eds (New York, Springer), pp. 204–211.,2006

Bilbo, S. D., and Schwarz, J. M. (2009). Early-life programming of later-life brain and behavior: a critical role for the immune system. Front. Behav. Neurosci. 3:14. doi: 10.3389/neuro.08.014..2009

Block, M. L., Zecca, L., and Hong, J. S. . Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat. Rev. Neurosci. 8, 57–69.,2007

Dantzer R., O'Connor J. C., Freund G. G., Johnson R. W., Kelley K. W. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.10.1038/nrn2297 ,2008

Dilger, R. N., and Johnson, R. W. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J. Leukoc. Biol. 84, 932–939.,2008

Doorduin, J., De Vries, E. F., Willemsen, A. T., De Groot, J. C., Dierckx, R. A., and Klein, H. C. Neuroinflammation in schizophrenia-related psychosis: a PET study. J. Nucl. Med. 50, 1801–1807,2009

Feldman, M. (2000). Some views on the manifestation of the death instinct in clinical work. Int. J. Psychoanal. 81, 53–65.

Frank M. G., Barrientos R. M., Biedenkapp J. C., Rudy J. W., Watkins L. R., Maier S. F. mRNA up-regulation of MHC II and pivotal pro-inflammatory genes in normal brain aging.Neurobiol. Aging 27, 717–722.10.1016/j.neurobiolaging.2005.03.013,2006

Freud, S. (1920). “Beyond the pleasure principle,” in The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XVIII (1920–1922): Beyond the Pleasure Principle, Group Psychology and Other Works, ed J. Strachey (London: Hogarth Press), 1–64.

Freud, S. (1924). “The economic problem of masochism,” in The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XIX (1923–1925): the Ego and the Id and Other Works, ed J. Strachey (London: Hogarth Press), 155–170.

Freud, S. (1933). “New introductory lectures on psycho-analysis,” in The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XXII (1932-1936): New Introductory Lectures on Psycho-Analysis and Other Works, ed J. Strachey (London: Hogarth Press), 1–182.

Freud, S. (1933). “Why war?” in The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XXII (1932-1936): New Introductory Lectures on Psycho-Analysis and Other Works, ed J. Strachey (London: Hogarth Press), 195–216.

Girgis, R. R., Diwadkar, V. A., Nutche, J. J., Sweeney, J. A., Keshavan, M. S., and Hardan, A. Y. Risperidone in first-episode psychosis: a longitudinal, exploratory voxel-based morphometric study. Schizophr. Res. 82, 89–94.,2006

Giaume, C., Kirchhoff, F., Matute, C., Reichenbach, A., and Verkhratsky, A. Glia: the fulcrum of brain diseases. Cell Death Differ. 14, 1324–1335,2007

Glantz, L. A., Gilmore, J. H., Lieberman, J. A., and Jarskog, L. F. . Apoptotic mechanisms and the synaptic pathology of schizophrenia. Schizophr. Res. 81, 47–63.,2006

Graeber, M. B. Changing face of microglia. Science 330, 783–788. ,2010

Graeber, M. B., and Streit, W. J. Microglia: biology and pathology. Acta Neuropathol. 119, 89–105,2010

Hanisch, U. K., and Kettenmann, H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat. Neurosci. 10, 1387–1394.,2007

Hart B. L. Biological basis of the behavior of sick animals. Neurosci. Biobehav. Rev. 12, 123–137.10.1016/S0149-7634(88)80004-6 ,1988

Hartmann, H.. Ego Psychology and the Problem of Adaptation. New York, NY: International Universities Press.

Henkel, J. S., Beers, D. R., Zhao, W., and Appel, S. H. (2009). Microglia in ALS: the good, the bad, and the resting. J. Neuroimmune Pharmacol. 4, 389–398.,1939

Hinwood, M., Morandini, J., Day, T. A., and Walker, F. R. Evidence that microglia mediate the neurobiological effects of chronic psychological stress on the medial prefrontal cortex. Cereb. Cortex 22, 1442–1454.,2012

Jang, S., and Johnson, R. W. Can consuming flavonoids restore old microglia to their youthful state? Nutr. Rev. 68, 719–728.,2010

Jarskog, L. F., Glantz, L. A., Gilmore, J. H., and Lieberman, J. A.. Apoptotic mechanisms in the pathophysiology of schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 846–858.,2005

Kato TA and Kanba S (2013) Are microglia minding us? Digging up the unconscious mind-brain relationship from a neuropsychoanalytic approach. Front. Hum. Neurosci. ,2013.

Kato, T. A., Yamauchi, Y., Horikawa, H., Monji, A., Mizoguchi, Y., Seki, Y., et al. (2013). Neurotransmitters, psychotropic drugs and microglia:

clinical implications for psychiatry. Curr. Med. Chem. 20, 331–344.,2013

Kent S., Bluthe R. M., Kelley K. W., Dantzer R. Sickness behavior as a new target for drug development. Trends Pharmacol. Sci. 13, 24–28.10.1016/0165-6147(92)90012-U,1992

Kernberg, O. F. (2012). The seeking system and Freud's Dual-Drive Theory Today.Neuropsychoanalysis 14, 50–52.,2012

Kettenmann, H., Hanisch, U. K., Noda, M., and Verkhratsky, A. Physiology of microglia. Physiol. Rev. 91, 461–553.,2011

Klein, M. . "Envy and Gratitude," in The Writing of Melanie Klein, Volume 5. Envy and Gratitude and Other Works (1946–1963), ed R. E. Money-Kyrle (London: Hogarth Press), 176–235.,1957

Kraepelin E. Dementia praecox and paraphrenia (Foundations of Modern Psychiatry) [FACSIMILE], 1st Edn, July, 2002. Thoemmes Press.,1919

Lalancette-Hebert M., Gowing G., Simard A., Weng Y. C., Kriz J. Selective ablation of proliferating microglial cells exacerbates ischemic injury in the brain. J. Neurosci. 27, 2596–2605.10.1523/JNEUROSCI.5360-06.,2007

Lieberman, J. A., Tollefson, G. D., Charles, C., Zipursky, R., Sharma, T., Kahn, R. S., et al. (2005). Antipsychotic drug effects on brain morphology in first-episode psychosis.Arch. Gen. Psychiatry 62, 361–370.,2005

Macritchie, K. A., Lloyd, A. J., Bastin, M. E., Vasudev, K., Gallagher, P., Eyre, R., et al. White matter microstructural abnormalities in euthymic bipolar disorder. Br. J. Psychiatry 196, 52–58.,2010

Monji, A., Kato, T., and Kanba, S. Cytokines and schizophrenia: microglia hypothesis of schizophrenia. Psychiatry Clin. Neurosci. 63, 257–265.,2009

Nelson K. B., Willoughby R. E. Infection, inflammation and the risk of cerebral palsy.Curr. Opin. Neurol. 13, 133–139.10.1097/00019052-200004000-00004 ,2000

Nesse R., Williams G. Why we get sick. New York, Vintage Books.,1994

Northoff, G. (2012). Psychoanalysis and the brain - why did freud abandon neuroscience? Front. Psychol. 3:71. doi: 10.3389/fpsyg.2012.00071

Panksepp, J. Affective Neuroscience: the Foundations of Human and Animal Emotions. New York, NY: Oxford University Press USA.,2004

Panksepp, J. . Neuro-psychoanalysis may enliven the mindbrain sciences.Cortex 43, 1106–1107. discussion: 1116–1121.,2007

Panksepp, J., and Solms, M. . What is neuropsychoanalysis? Clinically relevant studies of the minded brain. Trends Cogn. Sci. 16, 6–8.,2012

Perry V. H., Cunningham C., Boche D. Atypical inflammation in the central nervous system in prion disease. Curr. Opin. Neurol. 15, 349–354.10.1097/00019052-200206000-00020 ,2002

Perry V. H., Newman T. A., Cunningham C. The impact of systemic infection on the progression of neurodegenerative disease. Nat. Rev. Neurosci. 4, 103–112.10.1038/nrn1032,2003

Schiavone, S., Sorce, S., Dubois-Dauphin, M., Jaquet, V., Colaianna, M., Zotti, M., et al. Involvement of NOX2 in the development of behavioral and pathologic alterations in isolated rats. Biol. Psychiatry 66, 384–392.,2009

Solms, M., and Lechevalier, B. (2002). Neurosciences and psychoanalysis. Int. J. Psychoanal. 83, 233–237.,2002

Steiner, J., Mawrin, C., Ziegeler, A., Bielau, H., Ullrich, O., Bernstein, H. G., et al. (2006). Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization. Acta Neuropathol. 112, 305–316.,2006

Sugama, S., Fujita, M., Hashimoto, M., and Conti, B. . Stress induced morphological microglial activation in the rodent brain: involvement of interleukin-18. Neuroscience 146, 1388–1399.,2007

Sugama, S., Takenouchi, T., Fujita, M., Conti, B., and Hashimoto, M. . Differential microglial activation between acute stress and lipopolysaccharide treatment. J. Neuroimmunol. 207, 24–31.,2009

Takano, A., Arakawa, R., Ito, H., Tateno, A., Takahashi, H., Matsumoto, R., et al. Peripheral benzodiazepine receptors in patients with chronic schizophrenia: a PET study with [11C]DAA1106. Int. J. Neuropsychopharmacol. 13, 943–950.2010

Tynan, R. J., Naicker, S., Hinwood, M., Nalivaiko, E., Buller, K. M., Pow, D. V., et al. Chronic stress alters the density and morphology of microglia in a subset of stress-responsive brain regions. Brain Behav. Immun. 24, 1058–1068.,2010

Uranova, N. A., Vostrikov, V. M., Orlovskaya, D. D., and Rachmanova, V. I. . Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr. Res. 67, 269–275.,2004

Uranova, N. A., Vostrikov, V. M., Vikhreva, O. V., Zimina, I. S., Kolomeets, N. S., and Orlovskaya, D. D. The role of oligodendrocyte pathology in schizophrenia.Int. J. Neuropsychopharmacol. 10, 537–545.,2007

Van Berckel, B. N., Bossong, M. G., Boellaard, R., Kloet, R., Schuitemaker, A., Caspers, E., et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biol. Psychiatry 64, 820–822.,2008

Van Gool, W. A., Van De Beek, D., and Eikelenboom, P. . Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 375, 773–775.,2010

Vitkovic L., Bockaert J., Jacque C. "Inflammatory" cytokines: neuromodulators in normal brain? J. Neurochem. 74, 457–471.10.1046/j.1471-4159.2000.740457.x,2000

Wake, H., Moorhouse, A. J., Jinno, S., Kohsaka, S., and Nabekura, J. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. J. Neurosci. 29, 3974–3980.,2009

Wohleb, E. S., Hanke, M. L., Corona, A. W., Powell, N. D., Stiner, L. M., Bailey, M. T., et al. . Beta-adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. J. Neurosci. 31, 6277–6288.,2011

Wolpert, L., and Fonagy, P. There is no place for the psychoanalytic case report in the British Journal of Psychiatry. Br. J. Psychiatry 195, 483–487.,2009

Wright, J. S., and Panksepp, J. An evolutionary framework to understand foraging, wanting, and desire: the neuropsychology of the SEEKING system .Neuropsychoanalysis 14, 5–39.,2012