Neuropsychiatric Disease and Toxoplasma gondii Infection

S.A. Henriquez  R. Brett  J. Alexander  J. Pratt  C.W. Roberts
Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

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Abstract
Toxoplasma gondii infects approximately 30% of the world’s population, but causes overt clinical symptoms in only a small proportion of people. In recent years, the ability of the parasite to manipulate the behaviour of infected mice and rats and alter personality attributes of humans has been reported. Furthermore, a number of studies have now suggested T. gondii infection as a risk factor for the development of schizophrenia and depression in humans. As T. gondii forms cysts that are located in various anatomical sites including the brain during a chronic infection, it is well placed anatomically to mediate these effects directly. The T. gondii genome is known to contain 2 aromatic amino acid hydroxylases that potentially could directly affect dopamine and/or serotonin biosynthesis. However, stimulation of the immune response has also recently been associated with mood and behavioural alterations in humans, and compounds designed to alter mood, such as fluoxetine, have been demonstrated to alter aspects of immune function. Herein, the evidence for T.-gondii-induced behavioural changes relevant to schizophrenia and depression is reviewed. Potential mechanisms responsible for these changes in behaviour including the role of tryptophan metabolism and the hypothalamic-pituitary-adrenal axis are discussed.
may be asymptomatic or cause neurological and ophthalmological lesions [11]. Although approximately 30% of the world’s population have *T. gondii* infection and harbour cysts in the brain, overt disease symptoms such as encephalitis are only evident during immune suppression [10]. However, an increasing number of studies are now providing evidence that disease is associated with subtle changes in behaviour in animals and humans, and in some reports it has been noted that the incidence of mental diseases such as schizophrenia (see Appendix 1) is greater in *T. gondii*-infected individuals [11–16]. Herein, we review the evidence that *T. gondii* infection can cause these changes and discuss potential mechanisms that may account for these observations.

**T. gondii Initiates a Robust Innate Immune Response and Long-Term Immunity**

In spite of the complexity of the immune response to *T. gondii* and the number of murine models used to study it, there is now emerging a robust view of what constitutes protective immunity, how it functions, how it develops and how excessive inflammation is controlled [11, 17–19].

*T. gondii* is a potent stimulator of the innate immune system, which not only controls initial parasite growth, but also directs the developing adaptive immune response. To achieve this, *T. gondii* has a number of TLR ligands including GPI anchors (ligands for TLR-2 and TLR-4) [20], HSP70 (ligand for TLR-4) [21, 22] and an as yet unique profilin, which is a ligand for TLR-11, a molecule present only in certain mammalian species, including mice, but not humans [23]. Moreover, *T. gondii* cyclophilin 18 has been demonstrated to induce IL-12 production through ligation of the CCR-5 receptor [24]. These processes activate macrophages, dendritic cells and NK cells resulting in the production of IL-12, IFN-γ, TNF-α, and iNOS [21, 22, 24]. Together these mediators control parasite growth, induce Th1 cell expansion and the development of cytolytic CD8+ T cells [25–27]. Cytolytic CD8+ T cells have an essential role in controlling the development of tissue cysts and encephalitis, and resistance to this aspect of disease has been linked to the Ld region of MHC class I gene in mice [28–30]. While Th2 cytokines have been demonstrated to downregulate macrophage activation and thus the ability of these cells to control *T. gondii* growth [31], type 2 cytokines (including IL-4 and IL-13) would also appear to have a role in controlling the inflammatory response and preventing excessive pathology. The fine balance of controlling parasite growth while preventing pathology may account for the many contradictory reports on the role of IL-4 and other type 2 cytokines during *T. gondii* infection [32–37]. The role of IL-10 in vivo seems more defined as mice deficient in IL-10 are exquisitely sensitive to *T. gondii* infection due to cytokine shock. This is dependent on CD4+ T cells and is associated with increased production of IL-12, IFN-γ and TNF-α [31].

As well as systemic effects, *T. gondii* induces the production of a number of cytokines including IL-1β, IL-6, TNF-α, GM-CSF, IL-2, IL-4 and IFN-γ directly in the brain [38–42]. Microglial cells and astrocytes are associated with IL-1, IL-6, IL-10, IL-12 and TNF-α expression, while infiltrating CD4+ and CD8+ T cells are the presumed sources of IL-2, IFN-γ, IL-4, IL-10 and TNF-α. Expression of cytokines, specifically those associated with T cell expansion (IL-2 and IL-4), may be temporally or sequentially regulated. IL-10 is expressed during chronic infection and would appear necessary to regulate inflammation [40, 43]. It is now known that microglial cells can also produce IL-17 and IL-23, which may also contribute to inflammation, although the role of these cytokines in the brain of *T. gondii*-infected mice remains to be established [44, 55]. These cytokines may influence mood and behaviour through their ability to modulate neurotransmission including monoamine- and glutamate-dependent mechanisms [46–48] in the brain (see Appendices 1 and 2 for how this could affect schizophrenia and depression).

**Behavioural Changes in Humans Associated with *T. gondii* Infection**

The ability of *T. gondii* to alter human behaviours and personality has been investigated in recent years. Examination of 3 separate cohorts of subjects from the Czech Republic by Cloninger’s Temperament and Character Inventory revealed that irrespective of gender, people infected with *T. gondii* had reduced novelty seeking [49–53]. Nine out of 11 tests using various subject groups found gender differences between some of the factors assessed by Raymond Cattell’s 16 Personality Factors questionnaire. Men infected with *T. gondii* were generally found to have lower rule consciousness, but higher vigilance than uninfected males, whereas infected women had higher warmth and rule consciousness compared with uninfected women. Apprehension was increased in all infected subjects independent of gender. It is hard to determine if the observed correlations are due to infec-
tion or if certain personality types are more likely to become infected with *T. gondii* [49–53].

*T. gondii* infection has also been associated with a modest negative effect on reaction times which may account for the observation from 2 independent studies that *T. gondii*-infected individuals are more likely to be involved in road traffic accidents [54, 55]. However, causation criteria in the clinical field are not easy to achieve, and these associations may be due to other factors including the possibility that some personality types are more likely to be involved in road traffic accidents and to be infected with *T. gondii*.

**Association of Psychiatric Disorders in Humans and *T. gondii* Infection**

**Schizophrenia**

Several studies have demonstrated that schizophrenic patients have an increased incidence of *T. gondii* infection compared with control volunteers [14–16]. Importantly, a recent meta-analysis of 23 studies found an increased prevalence of *T. gondii* antibodies in patients with schizophrenia. Whilst the odds ratio of 2.73 is modest, it exceeds that of other environmental and genetic factors measured to date. This suggests that *T. gondii* infection is associated with a large number of cases of schizophrenia [12].

The reasons why only a proportion of individuals that have been infected with *T. gondii* develop schizophrenia are unclear. Possibilities include differences in genetic susceptibility, mode of infection (tissue or oocytes), and/or timing of infection (in utero, childhood or adulthood). Alternatively it has been suggested that behavioural traits associated with schizophrenia could result in increased infection with the parasite. For example, the transmission of the parasite could be related to a lack of personal hygiene, which is a characteristic of schizophrenic patients [15]. However, this is unlikely to explain all cases, and since *T. gondii* encysts in the brain, there is a clear potential to affect neuronal function directly. Evidence is accumulating for immune-mediated monoaminergic and glutamatergic interactions that could contribute to psychiatric disorders including schizophrenia [46–48]. Dysregulation of these neurotransmitter systems is long recognised to be important in behavioural deficits associated with schizophrenia (see Appendix 1). In addition, Hinze-Selch et al. [12] report an abnormal immune response to *T. gondii* in patients with schizophrenia, which could contribute to the increased vulnerability of this patient group.

**Depression and Other Neuropsychological Illnesses**

There is emerging evidence that *T. gondii* infection can cause depression (see Appendix 2) in certain individuals. For example, the incidence of *T. gondii* infection as determined by serology was greater in depressed patients compared with a control group [56]. Furthermore, in a case report, a patient was unresponsive to conventional antidepressants, but after treatment for an underlying *T. gondii* infection the depression was ameliorated [57]. Clearly more studies are required in this area to determine if there is a causal link between *T. gondii* infection and depressive illnesses. The general possibility that parasitic infections may contribute to depression also merits study.

**Animal Behaviour and *T. gondii* Infection**

*T. gondii* infection is relatively common among both wild and domestic animals [57, 58]. As *T. gondii* has a complex life cycle with predator-prey interactions, manipulation of the behaviour of the prey can facilitate parasite transmission [59, 60]. During the chronic phase of infection, the parasite resides in tissue cysts that are in various anatomical sites including smooth muscle, heart, lung and eye. However, it is the presence of the parasite within the brain that provides the greatest opportunity for manipulation of the host’s behaviour [57, 61].

A number of studies have demonstrated the ability of the parasite to manipulate the behaviour of rodents in relation to predator-prey interactions [59, 60, 62–70]. Early studies examined the ability of *T. gondii* infection to affect the behaviour of laboratory mice [62–66]. These studies found that infected mice were more active, explored novel areas of the apparatus and showed reduced grooming activity compared to uninfected animals. It was noted that some infected mice walked in circles while bending their head, leading to the suggestion that this may facilitate their capture by the cat host and transmission of the parasite [61]. Similar observations were reported in studies of rats, although these were not so pronounced, perhaps reflecting the generally reduced parasite loads in the brains of these rodents [61]. More sophisticated studies carried out recently in laboratory rats demonstrated *T. gondii* infection to reduce the natural aversion of rats and mice to cat odour, and even to attract the rats to the odour. Furthermore, this alteration was highly specific and not due to destruction of the olfactory regions of the brain, as neophobia towards food of novel scent remained unaltered [67]. These findings
have been corroborated in naturally infected and uninfected wild and wild/laboratory hybrid rats housed in semi-natural outdoor conditions [61]. In these studies, the innate fear normally exhibited towards cat urine was ablated or in some cases reversed so that T. gondii-infected rodents were attracted to the feline odour. This would serve to allow an increased exposure to feline attack and therefore an increased opportunity for T. gondii sexual reproduction in the definitive host [60]. No disturbance of the innate preference of the rodents to their own odour or that of rabbits was observed implying that the difference in odour perception may relate to impaired processing of emotionally relevant stimuli rather than a general olfactory impairment [60].

Further evidence supporting the ability of T. gondii to modulate behaviour is shown by the ability of the anti-psychotic drug haloperidol to inhibit growth of the tachyzoite form of T. gondii in vitro [71] and to reduce the altered neophobic behavioural response of rodents to cat odour [72].

**Potential Mechanisms whereby T. gondii Might Interfere with Neural Function**

**Direct Neuronal Modulation, Damage or Death**

In mice, T. gondii has been demonstrated to predominantly infect neurones [71]. Consequently, infection could directly affect neuronal function and thus explain neuropsychological deficits. Cysts are assumed to be present in the brain for the life of infected humans, although rarely reported at routine post-mortem examination. As encephalitis is the normal disease manifestation during reactivation of T. gondii infection in immunocompromised individuals, significant numbers of cysts are likely to be present in this tissue. Studies in at least certain strains of mice indicate that cyst number can decline with time, suggesting that individual cysts have a limited lifespan [28, 38]. This would suggest that cysts are perpetually turning over in the brain and causing neuronal cell death that could ultimately result in neurological impairment. Neurochemical changes have been demonstrated in mice with T. gondii infection. During acute infection, a 40% rise in homovanillic acid levels and a reduction in noradrenaline levels as compared with controls has been reported. Dopamine levels were unchanged during acute infection but were increased in the mice with chronic T. gondii infections. Serotonin and 5-HIAA levels were not found to be altered [74]. Whether these changes were directly due to T. gondii infection in the cells of the brain or a consequence of complex neuroimmunoendocrinological interactions is not known. However, the T. gondii genome is known to contain 2 aromatic amino acid hydroxylases (GenBank Acc. No. ACB99414) that potentially could directly affect dopamine and/or serotonin biosynthesis. Future studies will need to determine their substrate specificities, whether they are secreted by T. gondii, and their effects (fig. 1).

**Interference with the Hypothalamic-Pituitary-Adrenal Axis**

Immunological mediators interact with the brain at a number of different levels [73]. Neural mechanisms have been demonstrated to function through the vagus nerve from the abdominal organs directly to the brain [76]. Specifically, macrophages and dendritic cells in the perineuronal sheath of the vagus nerve have been demonstrated to respond to LPS through production of IL-1 that stimulates sensory activity on IL-1 receptors expressed by the nerve [75]. Surgical procedures that sever the vagus nerve are sufficient to prevent brainstem, hypothalamic and limbic activation following peripheral LPS or IL-1 administration [76].

Humoral mechanisms can also convey immunological signals to the brain. IL-1 produced in the periphery stimulates the endothelial cells that make up the cerebral blood vessels to induce prostaglandin E2 that acts on the hypothalamic area of the brain, stimulating the hypothalamic-pituitary-adrenal (HPA) axis [77]. Inhibitors of cycloxygenase 2, such as celecoxib, have been demonstrated to have beneficial effects for the treatment of major depression [78]. A number of cytokines are known to act directly on the HPA axis and include IL-1β, IL-6 and TNF-α [79], all of which are produced in abundance during T. gondii infection [38–40] (fig. 2).

Consequently, T. gondii infection in peripheral tissues may contribute to immunologically mediated events in the brain during T. gondii infection. However, as T. gondii is present within the brain, it can also directly induce the production of immunological mediators from within this site. Early studies demonstrated that a plethora of immunological transcripts are induced in the brains of infected mice [38–40]. Notably, a number of these mediators including IL-1β, IL-6 and TNF-α are able to stimulate prostaglandin E2 or act directly on the hypothalamus.

Although stimulation of the HPA axis has been linked to behavioural changes including depression, no mechanism has been definitively demonstrated [75]. It is indeed possible that the activation of the HPA axis may be indicative of immunological activity affecting the brain,
but not be the cause of behavioural changes. However, end products of the HPA axis are glucocorticoids. Glucocorticoids not only feed back to limit HPA stimulation, but affect a number of other systems [75]. Notably, glucocorticoids have profound effects on the immune system including macrophages, dendritic cells and T cells [75, 80, 81]. Glucocorticoid antagonists such as RU486 and ketoconazole have been demonstrated to function as antidepressants in certain individuals [82]. In addition, glucocorticoids affect tryptophan metabolism through increasing the levels of tryptophan 2,3-dioxygenase (TDO) in the liver and IFN-γ-induced indoleamine 2,3-dioxygenase (IDO) in immune cells [83, 84]. Therefore, tryptophan metabolism, the HPA axis and the immune system are inextricably linked (fig. 2).

**Tryptophan Metabolism**

Tryptophan is an essential amino acid in mammals that is not only required as a component of proteins, but is also the common precursor of the neurochemical mediators serotonin and melatonin. In a number of studies, depletion of tryptophan has been demonstrated to result in reduced brain serotonin levels and depression [85]. Although some micro-organisms are capable of de novo tryptophan synthesis from chorismate produced through the shikimate pathway, many including *T. gondii* are tryptophan auxotrophs and must therefore scavenge this amino acid from their host [86]. Potentially, for this reason the immune system has evolved a method to degrade tryptophan upon stimulation with IFN-γ which is effective in restricting the growth of many pathogens such as...
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This is achieved through the production of 1-L-tryptophan to N-formylkynurenine [87]. A similar system has been demonstrated to operate in the vicinity of the placenta during pregnancy and is thought to control the multiplication and action of T cells and contributes to the altered immunity observed during gestation that prevents fetal rejection [88]. Tryptophan can also be digested to N-formylkynurenine by TDO, an enzyme found predominantly in the liver, but also expressed in a variety of other tissues including astrocytes in the brain [75, 89].

IDO is produced in a number of cells including macrophages, dendritic cells and microglial cells in response to IFN-γ and has been specifically demonstrated to be induced in a number of cells and tissues during T. gondii infection [75]. TDO is induced predominantly, but not exclusively, in the liver by the action of glucocorticoids and therefore following stimulation of the HPA axis [75, 47, 89, 90]. In a similar manner, glucocorticoids have also been demonstrated to augment IDO induction in astrocytes following IFN-γ exposure [83]. Consequently, immunological activity inducing IFN-γ and/or the HPA axis serve to reduce tryptophan levels and are likely to have an effect on serotonin and melatonin levels [75]. Recent evidence has demonstrated that LPS-induced IDO is responsible for depression-like behaviours in mice inject-
ed with LPS, which would support the idea that *T. gondii* infection might alter serotonin levels through a similar mechanism and consequently affect behaviour [91]. Depletion of tryptophan conversely increases the production of a number of catabolites such as 3-hydroxykynurenine, and anthranilic, kynurenic, xanthurenic and quinolinic acids. Some of these catabolites have been demonstrated to affect neurones or their functions. For example, quinolinic acid is an agonist of the N-methyl-D-aspartate (NMDA) receptor [92]. 3-OH-kynurenine and quinolinic acid can cause neuronal death by a mechanism mediated by reactive oxygen species [93]. Quinolinic acid may also induce seizures, convulsions and muscle cramps [94]. Recent studies demonstrate that administration of L-kynurenine is capable of inducing depressive-like behaviour in mice [91].

*T. gondii* infection has been demonstrated to increase the levels of kynurenic acid (KYNA) in the brains of infected mice; KYNA has also been demonstrated to be increased in schizophrenia. This could be achieved via up-regulation of either IDO or TDO. Interestingly, TDO transcripts have been demonstrated to be increased in patients with schizophrenia and it has been suggested that this is due to a Th2-biased response [47, 90]. Acute *T. gondii* infection is normally associated with a Th1-biased response and consequently IDO expression early in infection, although Th2 cytokines can be found in the brains of chronically infected mice [40, 43]. Thus, it is possible that a disturbance of the Th1/Th2 balance in either direction could contribute to KYNA production and potentially contribute to schizophrenia.

Overall the literature demonstrates that *T. gondii* can affect animal behaviour, and the likelihood is that there is an association between infection and certain human personality features and psychiatric disorders. As there is also strong evidence in the literature that schizophrenia and depression can be precipitated by immunological events, such as those observed during toxoplasmosis, there is a rationale for further investigations to establish whether the causal link is directly attributable to the parasite or the immune response it generates, or both. Characterisation of the mechanisms responsible for ensuing neuropsychiatric disorders following *T. gondii* infection will direct future appropriate therapeutic intervention. Furthermore, information obtained from studies on toxoplasmosis may have relevance to other infectious diseases that may interact in a similar way with their mammalian hosts.

**Appendix 1: Schizophrenia: A Product of Genetics, Neurodevelopment and Environment**

Schizophrenia is a severe and debilitating psychiatric disorder that has a lifetime prevalence of 1% and is ranked as the ninth most prevalent cause of disability worldwide. It is a heterogeneous disease characterised by a diverse range of symptoms. The positive symptoms (such as hallucinations and delusions) are treated by antipsychotic drugs, whereas the negative symptoms (such as anhedonia, avolition, self-neglect and social withdrawal) and the cognitive deficits (including impairment in executive function, attentional processing and working memory) are not treated effectively by existing medications [95]. The onset of this illness can vary from late teens to early adulthood, and episodes of psychosis can occur throughout the life of the patient.

The causes of schizophrenia are beginning to be unravelled. Risk factors include genetic predisposition, neurodevelopmental insult and environmental factors [96]. It is becoming clear that these potential causes lead to dysfunction of interconnected brain regions involving the corticolimbobothalamic loop which results in the manifestation of symptoms. This circuitry utilises a variety of neurotransmitters including dopamine, 5-HT, GABA and glutamate. Dopamine was the first neurotransmitter to be implicated in schizophrenia. Drugs such as amphetamine (a dopamine-releasing agent), can exacerbate psychotic symptoms in patients and trigger psychosis in normal individuals. Direct evidence for dopaminergic involvement comes from imaging studies in patients which show enhanced release of dopamine in the limbic striatum [97]. Antipsychotic drugs ameliorate the patient’s hallucinations and delusions by blocking the dopamine D2 receptor [98]. Therefore, it is hypothesised that dopamine has an important role in schizophrenia [98].

Glutamate is also thought to have an important role in schizophrenia, due to the analysis of the effects of the psychotic drugs ketamine and phencyclidine [99]. These drugs are antagonists of the NMDA receptor subtype of the glutamate receptor and reproduce positive and negative symptoms as well as cognitive deficits associated with the disease [99]. The drugs also provide useful tools in preclinical studies for exploring disease mechanisms and identifying new drug targets [100, 101]. Indeed the therapeutic potential of drugs that modify glutamatergic transmission is emphasised by the recent report that an mGlu2/3 agonist is effective in treating the disease [102]. This may be the first successful treatment not based upon dopamine antagonism.

As noted above, there is a strong genetic predisposition to schizophrenia. Over 100 genes have been implicated although only a handful of these have been consistently replicated in genetic association and linkage studies. So far, the genes dysbindin, neuregulin 1, catechol-O-methyltransferase (COMT) and DISC 1 [103–106] have been most strongly implicated. The role and interaction of these genes in relation to disease pathology and symptoms are only beginning to emerge. Intriguingly, the neurobiological role(s) of several of these genes is/are to modify glutamate or dopamine neurotransmission and/or have a key role in neurodevelopment. Dysbindin, located on chromosome 6p22, is associated with glutamate neurotransmission [103]. Neuregulin 1, on chromosome 8p12–p21 [105], is implicated in the process of neuronal differentiation and migration. It acts on ErbB4 receptors which have a role in modifying NMDA receptor-mediated glutamate transmission [104]. COMT is situated on chromosome 22q11.
and is involved in the clearing of dopamine from the synaptic regions [104]. This region is of great interest since a deletion results in velocardiofacial syndrome. Disc 1 involves a 1;11 translocation of chromosome 1 between exon 8 and 9 and chromosome 11 [107]. Disc 1 appears to have a role in neurodevelopment processes which, if impaired, can lead to the development of schizophrenia.

In addition to genetic factors, environmental factors are also very important for the development of psychiatric disorders [96]. Some of these environmental factors may interact with the genetic factors to trigger the disease. Obstetric implications such as premature birth, low birth weight, pre-eclampsia, rhesus incompatibility, resuscitation at birth, emergency caesarean delivery and prenatal nutritional deficiency are considered environmental risk factors in the development of schizophrenia [108]. Recently, there has been a growing interest in the role of infectious agents as a factor in the development of psychiatric disorders. Immunological, epidemiological and neurological studies have shown an interaction and possible involvement with schizophrenia in cases of rubella, influenza, herpes simplex 1 and 2, cytomegalovirus, poliovirus, and the protozoan parasite T. gondii [109].

To date, studies observing the effects of infectious agents in schizophrenia have shown that the effect of the infection during postnatal and prenatal period is different [10]. Infections during pregnancy are not thought to be the immediate cause of brain development damage. Rather, the mother’s immune response to the infection is suggested to be responsible for the fetal damage [111]. One idea is that inflammatory responses to infection, especially responses that involve cytokines, may affect neurodevelopmental processes, such as synapse development, and programmed cell death [112, 113]. These impaired neurodevelopmental processes then increase the risk of developing the disease in adulthood. The mechanisms of psychiatric consequences due to infectious agents during postnatal periods are still unclear. However, recent studies suggest a relationship between immune system dysregulation, tryptophan metabolism and schizophrenia. People with schizophrenia have been demonstrated to have a Th2-biased immune response. This leads to inhibition of the enzyme IDO leaving tryptophan to be metabolised primarily by TDO. In the CNS, this occurs only in astrocytes where KYN is the final product. KYN is an endogenous NMDA receptor antagonist and also blocks the nicotinic acetylcholine receptor. Thus, the accumulation of this metabolite may lead to glutamatergic system hypofunction, which may be associated with the psychotic symptoms, as well as with cognitive dysfunction [47, 90].

**Appendix 2: Major Depression**

Major depression is a mood disorder that has been included in the larger group of affective disorders. Affective disorders have been considered to be less devastating than schizophrenia because they are largely characterised by an inappropriate exaggeration of mood rather than severe disruption of thought processes.

Major depression is the most common of these affective disorders, and it is characterised by an affective state of sadness that is pathological in relation to the intensity, duration and quality of the experience. The median onset of depression is at an age of around 40 years, but this disease can afflict the population at any age and can occur in people from any socio-economic background; however, it is most common in females [114]. The disease is characterised by episodes of depression that can last from 7 to 14 months if not treated and can result in suicide, despite the occurrence of long periods of normality [115]. The patient suffers from loss of appetite, sleep disturbances, loss of ambition, loss of sexual desire, recurrent crying episodes, digestive disturbances and difficulty in breathing. These episodes are recurrent and progressive characterising the disease more as a chronic and progressive illness rather than an episodic condition [115]. Depression may be triggered by stress, although genetic and environmental factors also play a role [116–118]. The exact relationship between these factors still remains unclear. However, it has been reported that adverse experience during the age of development contributes to this condition [119]. In addition, early manifestation of the disease is linked to a chronic condition, and long episodes of depression are associated with a low rate of recovery [120].

It has been suggested that a chemical imbalance in the brain occurs during depression, in particular a reduction in monoamine transmitters, such as 5-HT and noradrenaline (NA) not least because clinically used antidepressants all increase synaptic monoamine levels. However, since antidepressants can be shown to increase monoamine levels within hours of administration but take 2–3 weeks to be clinically effective, this monoamine hypothesis is undoubtedly an oversimplification [121]. In recent years, through imaging studies and other methods, a more global view of the involvement of the neuronal plasticity and regulation is developing [122, 123]. Studies have demonstrated the involvement of particular brain structures, such as the prefrontal cortex and limbic areas, in the pathology of depression. These structures are not only involved in mood regulation but also in learning, contextual and memory processes [124–126]. In particular, there has been an increasing interest in the role of the hippocampus in major depression [127]. Imaging and post-mortem studies have shown that the hippocampus in depressed patients is characterised by a reduced volume compared to age-matched normal controls [128–130], and it has been shown that recovery from depression is more difficult in patients characterised by a smaller hippocampus [131].

A dysfunction of the hippocampus leads to a neuroendocrine dysregulation via the HPA axis. High levels of cortisol are produced, and the consequences are reduced neuroplastic activity and low cellular resistance. In addition, an imbalance of the glucocorticoid, mineral corticoid and high-density glucocorticoid receptors is created and this promotes neuronal damage [132]. The loss of glucocorticoid receptor sensitivity is linked to stress and overproduction of glucocorticoids through an imbalanced regulation [133]. HPA overactivity generates an increase in the sympathetic tone, which leads to macrophage activation and the production of pro-inflammatory cytokines [134]. Moreover, major depression has been associated with both the humoral and cell-mediated immune responses [135].

Increased levels of the pro-inflammatory cytokines IL-1β, IL-6, TNF-α and IL-12 have been observed [135–137]. In fact, pro-inflammatory cytokines may be responsible for some of the symptoms of depression such as fatigue, loss of appetite and libido, and hypersensitivity to pain [138]. In particular, it has been suggested that the IL-1 and IL-1β receptor antagonist IL-1ra represents the
link between major depression and the immune system [139]. In fact, IL-1 upregulates corticotropin-releasing hormone, which participates in the HPA axis and is highly expressed in people experiencing depression. IL-1β, on the other hand, interferes with the activity of the serotonin transporter gene, related to depression by being a target of antidepressant drugs [140].

Pro-inflammatory cytokines can also downregulate insulin metabolism and ultimately decrease glucocorticoid receptor sensitivity [134]. In addition, pro-inflammatory cytokines reduce neurotrophic support [140]. This would lead to neuronal apoptosis and glial damage causing further increase in pro-inflammatory cytokine release. In this context, the neurotrophic hypothesis of major depression pathology can be located in the dysfunction of the hippocampus. In fact, brain-derived neurotrophic factor (BDNF) is an important neurotrophin of the hippocampus. It binds to tyrosine receptor kinase in order to provide cellular resilience and a long-term protection [141]. However, pro-BDNF, its precursor, binds to the p75NGFR receptor and mediates reduction of neuronal dendritic spines and cell death. Thus, the proportions of mature and pro-BDNF may determine the balance between cell death and cell protection. Dysregulation of BDNF is caused by chronic stress and depression [142]. Its activity is modulated by several neurotransmitters (glutamate, GABA, 5-HT, NA and acetylcholine) and hormones. In fact, monoamines such as 5-HT or serotonin and NA are thought to play an important role in major depression [143]. 5-HT and NA regulate mainly the limbic system and the prefrontal cortex. They are also associated with pain regulation and therefore with a symptom of depression [144].

Treatment involves the use of antidepressant drugs; the most common is fluoxetine (Prozac). Most of these drugs are selective serotonin reuptake inhibitors and NA reuptake inhibitors [145]. Therefore, the neurotransmitters are able to remain in the extracellular compartments for longer periods and maintain their activity. In addition, during chronic treatment with selective serotonin reuptake inhibitors or NA reuptake inhibitors there is an upregulation of cAMP which increases the levels of protein kinase A and finally increases the levels of BDNF [146].

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