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Possible Link Between *Toxoplasma Gondii* and the Anosmia Associated With Neurodegenerative Diseases

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Abstract

Toxoplasma gondii is an intracellular protozoan infecting 30% to 50% of global human population. Recently, it was suggested that chronic latent neuroinflammation caused by the parasite may be responsible for the development of several neurodegenerative diseases manifesting with the loss of smell. Studies in animals inoculated with the parasite revealed cysts in various regions of the brain, including olfactory bulb. Development of behavioral changes was paralleled by the preferential persistence of cysts in defined anatomic structures of the brain, depending on the host, strain of the parasite, its virulence, and route of inoculation. Olfactory dysfunction reported in Alzheimer's disease, multiple sclerosis, and schizophrenia was frequently associated with the significantly increased serum anti–*T gondii* immunoglobulin G antibody levels. Damage of the olfactory system may be also at least in part responsible for the development of depression because *T gondii* infection worsened mood in such patients, and the olfactory bulbectomized rat serves as a model of depression.

Keywords

cerebral toxoplasmosis, neurodegeneration, impaired smell, anosmia, olfaction, autoimmune diseases, depression

The olfactory route for various infectious and/or toxic agents may initiate or exacerbate classical neurodegenerative and autoimmune diseases, especially in persons with genetic predisposition.[1-9] Several authors showed that many neurologic and neurodegenerative abnormalities are first demonstrable in the olfactory system with loss of smell (anosmia) up to 10 years before the onset of cognitive or motor dysfunction.[7] Neuroinflammation is a common feature of these diseases mostly emerging in the elderly individuals[9] and marked by activated glial cells that secrete numerous pro- and anti-inflammatory cytokines and other neurobiomediators.[10] For example, an exacerbation of Alzheimer's symptoms lasting for few months following a systemic infection was also capable of elevating serum interleukin (IL) 1β.[11] Recently, it was suggested that chronic *T gondii* infection may be the key infectious agent responsible for triggering and development of several neurodegenerative diseases associated with an increased generation of several pro- and anti-inflammatory cytokines, including IL-1β.[12-14]

Toxoplasmosis is one of the most frequent infections affecting both healthy and immunocompromised humans with approximately 6 billion people infected.[15,16] During its life cycle, the pathogen interacts with approximately 3000 host genes or proteins, and many of them represent an extensive *Toxoplasma gondii* host–pathogen interactome enrichment in several psychiatric and neurological diseases.[17] At present, in immunocompetent individuals *T gondii* infection is believed to be asymptomatic,[18,19] but an increasing body of literature strongly suggests that the parasite is slowly emerging as a global health threat,[16,19-22] especially in neurodegenerative diseases. Seroprevalence of the parasite measured by specific serum anti–toxo immunoglobulin G (IgG) antibodies varies widely in different countries depending on diagnostic tests used, environmental and socioeconomic conditions, including eating habits, health-related practices, and host susceptibility (Table 1). All these factors considerably hinder attempts to establish clear-cut connections between the highly prevalent infection of *T gondii* and the development of neurological diseases that are heralded by anosmia. In 1994, the National Health Interview Survey data obtained from 42 000 US households showed a 1.4% prevalence of self-reported olfactory dysfunction exponentially increasing with age.[24] Pregnancy is one of potential risk factors for olfactory disorders,[25] and the relationship between development of these abnormalities and chronic latent *T gondii* infection may be supported by the fact that at that time hormonal storm markedly affecting cellular

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Table 1. Seroprevalence of *Toxoplasma Gondii*–Specific IgG Antibodies in Pregnant Women in a Selected Number of Countries.[a]

Study Location	Year	Prevalence (%)
Mexico	2006	6.1
United Kingdom	2005	9.1
Norway	1998	10.9
Bangladesh	1997	11.18
India	1999	11.6
Thailand	1998	13.1
Sweden	1999	14
Finland	1992	20.3
Denmark	1993	27.4
Turkey	2005	30.1
The Nederlands	2004	40.5
Poland[b]	2012	40.6
Switzerland	1995	46.1
France	1996	54.3
West Indies	2006	57
Germany	1999	63.2
DRSTP	2007	75.2

Abbreviations: DRSTP, Democratic Republic of Sao Tome and Principe; IgG, immunoglobulin G.
[a] Adapted from Elsheikha[23]; with own modification.
[b] In Poland, between 2004 and 2012, the mean seroprevalence of IgG antibodies increased with age among 8281 pregnant women analyzed (mean age 26.7 vs 28.7 years; $P < .001$) with a yearly seroconversion rate of 0.8%.[24]

Table 2. Preferential Localization of *Toxoplasma Gondii* ME49 Strain Cysts in Different Regions of Murine Brain at 2 and 6 Months Postinoculation.[a]

Brain Region	2 Months After Inoculation[b]	6 Months After Inoculation[c]
Cerebral cortex	34	57
Hippocampus	10	25
Thalamus	5	–
Hypothalamus	6	3
Amygdala	25	9
Caudate putamen	12	6
Cerebellum	8	–

[a] Adapted from Melzer et al[33] with own modification.
[b] Total number of cysts observed = 67.
[c] Total number of cysts observed = 32.

and humoral immunity of pregnant woman may also exacerbate latent toxoplasmosis and increase the risk of congenital infection in the fetus. At present, one cannot exclude that isolated/syndromic congenital anosmia[26] is due to perinatal infection with the parasite, especially that structural differences in the brains of individuals with congenital anosmia are extending well beyond olfactory bulb and tract, including the piriform and orbitofrontal cortices.[27,28] Thus, from the first days/weeks of life, these neuroinflammatory processes may play an important role in the progress of pathophysiological abnormalities developing in the brain that finally lead to the olfactory system dysfunction also in neurodegenerative diseases.

Toxoplasma gondii tachyzoites may invade different types of brain cells including neurons, astrocytes, microglial cells, and Purkinje cells in the cerebellum. Intracellular tachyzoites manipulate signaling pathways and several signs for transduction mechanisms involved in apoptosis, immune cell maturation, and antimicrobial effectors functions.[29] It was demonstrated that in neurons infected by *T gondii* not only parasitic cysts but also the host cell cytoplasm and some axons were stained positive for the parasite antigens, thus supporting the notion that it may interfere with neuronal function.[20,30] It must be noted that in mice (at day 60 postinoculation with the parasite type II ME49 strain), a calculation of total cyst number per brain volume of various regions of the brain revealed that although cyst number decreased in cortex, thalamus, hippocampus, and striatum, their number slightly increased in olfactory bulb, hypothalamus, cerebellum, and brain stem.[30,31] The development of behavioral changes was paralleled by the preferential persistence of cysts in defined anatomic structures of the brain,[30-32] depending on the host, strain of the parasite, its virulence, and the route of inoculation.[32-34] Localization of *T gondii* cysts in different brain regions and cell types in both embryonal and adult animal brain tissues are presented in Tables 2 to 7. Immunochemistry study revealed that all major parts of neurons including the soma, dendrites, and axons harbored cysts, whereas intraneuronal *T gondii* antigen was present in the cytoplasm of cyst harboring neurons, and the parasite antigen–positive axons could be followed over long distances.[31] Astrocyte interactions with neuronal cysts were frequently observed.[33] Exposure of lipopolysaccharide (LPS) to neurons in the central nervous system (CNS) induced strong neurodegeneration in vivo and in vitro in substantia nigra and midbrain dopaminergic neurons[49-51] as well as in hippocampal and cortical neurons.[52,53] Similar neuronal cell death was also reported in the enteric nervous system (ENS).[54,55] It was found that the increased production of nitric oxide (NO) by inducible nitric oxide synthase was a major cause of cell death in LPS-treated cell cultures.[49,52] *Toxoplasma gondii* infection of different host brain cells was associated with an enhanced generation of various cytokines, including interferon (IFN) γ, tumor necrosis factor (TNF) α, IL-1β, NO, and reactive oxygen/nitrogen species[56,57]as well as with an increased production of many neurotic biomolecules (Table 8). These molecular disturbances could affect the sense of smell also in children with autism,[13,64] Asperger's syndrome,[65] and migraine patients[66,67] and result in olfactory impairment along with age[68-70](Table 9). This reasoning may be supported by the progressive decline in the levels of serum heat shock protein (HSP) 60 and HSP70 with age, whereas HSP70 antibody levels tend to increase (Table 10). On the other hand, it is known that host-derived HSPs play an important role in the development of innate immune defense against *T gondii* infection.[72] It must be noted that different strains of *T gondii* induced several constellations of cytokine responses[73] important for the development of various clinical signs and symptoms in the infected host. Virulence of the parasite has been linked with strain-dependent distinct dendritic cell responses and reduced number of activated $CD8^+$ T cells.[74] In animals, oral/peritoneal inoculation with *T gondii* genotypes I

Table 3. Distribution of Reactivation Foci in the Central Nervous System After Acute *Toxoplasma Gondii* Infection in Mice.[a]

	Cerebrum[b]					
Mice no.	Left	Right	Gray Matter	White Matter[c]	Cerebellum[d]	Meninges[e]
M1[f]	8	3	11	1	1	0
M2	20	19	37	2	0	0
M3	33	0	26	7	0	0
M4	3	5	5	3	0	0
M5	14	6	11	5	0	4
M6	19	29	24	22	0	2
M7	4	2	3	3	0	0
M8	13	15	17	10	2	3
M9	18	14	22	8	0	2
M10	4	6	10	0	0	0
Mean (SD)	13.5 (9.3)	9.7 (9.0)	15.2 (9.6)	7.2 (7.3)	0.3 (0.7)	1.0 (1.4)

Abbreviation: SD, standard deviation.
[a] Adapted from Dellacasa-Lindberg et al[35] with own modification.
[b] Number of foci detected in the left cerebral hemisphere.
[c] Markedly fewer number of foci was detected in gray matter than that in white matter ($P < .01$).
[d] Significantly fewer number of foci was found in the cerebellum than that in cerebrum ($P < .001$).
[e] Significantly fewer number of foci were found in the meningeal areas than in cerebrum ($P < .001$). Dellacasa-Lindberg et al[35] suggested that there was a striking resemblance in the distribution of parasitic lesions during acute toxoplasmic encephalitis in human and murine infections.
[f] Ten BALB/c mice (M1-10) were infected intraperitoneally with 5×10^4 freshly egressed *Toxoplasma gondii* tachyzoites. Mice were subjected to dexamethasone treatment and killed upon detection of central nervous system infection.

Table 4. The Number of Cysts Load in Brain Tissue and Congenital Transmission Rate From the Offspring.[a]

Group of mice	Number of Cysts in Brain	Congenital *Toxoplasma gondii* Transmission Rate (%)
Early-stage infection	$224 \pm 59^{b,c}$ (n = 18)	94.74
Intermediate-stage infection	202 ± 44^{b} (n = 19)	90.48
Late-stage infection	134 ± 31 (n = 22)	91.67

Abbreviations: ANOVA, analysis of variance; SD, standard deviation.
[a] Adapted from Wang et al[36] with own modification. Each group of mice was infected with 5 cysts of *Toxoplasma gondii* by oral inoculation on the 5th, 10th, and 15th day after gestation. Results are expressed as the mean number of cysts collected from each group ± SD, generated by using one-way ANOVA. The congenital *T gondii* transmission rate is shown at the age of 12 weeks after birth in the offspring from the infected group.
[b] $P < .01$ versus late-stage infection.
[c] $P > .05$ versus intermediate-stage infection group.

Table 5. Infection Rates of Different Cell Types From Embryonal Rat Cortices (E15) After In Vitro Infection With *Toxoplasma Gondii* Tachyzoites.[a]

Cell Type	mAb for Host Cell Identification	Frequency of Cell Type[b]	Rate of *T gondii* Infection[b]
Neurons	Anti-Nf 200 kDa	88.0 ± 1.3%	9.5 ± 1.1%
Astrocytes	Anti-GFAP	7.9 ± 2.1%	9.7 ± 3.3%
Microglia	Anti-CD71	4.1 ± 0.9%	31.5 ± 5.9%

Abbreviations: mAB, monoclonal antibody; GFAP, glial filament acidic protein; SD, standard deviation.
[a] Adapted from Lüder et al[37] with own modification.
[b] Determined 48 hours postinfection by double immmunofluorescence (at least 100 parasitophorous vacuoles were examined for each determination). Data represent means ± SD from 3 independent experiments.

Table 6. Replication and Morphology of *Toxoplasma Gondii* in Different Cell Types From Embryonal Rat Cortices (E15).[a]

Intracellular Replication (% PV)[b]	Neurons	Astrocytes	Microglia
1-2 parasites/PV	66 ± 2.6	67.2 ± 5.0	93.1 ± 4.5
4-8 parasites/PV	30 ± 2	26.2 ± 1.2	8.9 ± 4.5
16-32 parasites/PV	4.3 ± 1.5	5.3 ± 2.9	0
>32 parasites/PV	0	1.3 ± 1.2	0
Morphology of *T gondii*	Normal	Normal	Often degenerated

Abbreviations: PV, parasitophorous vacuole; SD, standard deviation.
[a] Adapted from Lüder et al[37] with own modification.
[b] Determined 48 hours postinfection by double immunofluorescence (at least 100 PV were examined for each determination). Data represent means ± SD from 3 independent experiments.

to III resulted in atrophy or hypoplasia of some segments of the gastrointestinal tract and death/hypertrophy of part of myenteric neurons.[75-77] Similar morphometric abnormalities of the ENS may be responsible for the development of gastrointestinal tract dysfunction reported in patients with autism, inflammatory bowel and/or autoimmune diseases, and in many other gastrointestinal tract disturbances.[55] Glial cells in the ENS appear to be very similar in origin, gross morphology, and ultrastructure to astrocytes of the CNS and bear similar relationships with neuronal cell bodies and processes to peripheral Schwann cells.[78] All these abnormalities in the brain and other organs associated with chronic *T gondii* infection strongly

Table 7. *Toxoplasma Gondii* Infection and Cyst Formation in Primary Cultures of Cells of the Central Nervous System.[a]

Parameters	Astrocytes	Microglial Cells	Neurons	Refs
Relative efficiency of infection	100[a]	50[b]	5-15[b]	39-42
Cytokine release	IL-1, IL-6, GM-CSF	IL-10, IL-6, TNF-α	TNF-α	43-45
Cyst formation	Yes	Limited	Yes	42,45
Size of cysts	Large (~50 μm)	Small (~10 μm)	Small (~ 10 μm)	43
Size of brain cells	100 μm (harbor several dozen tachyzoites)	5-10 μm	10-15 μm[c] (contain only few tachyzoites)	42
Effect of IFN-γ and TNF-α	Encystation	Parasite killing	?	39,44[46]
Inducible NOS	Low	High	Yes[d]	47,48

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; NOS, nitric oxide synthase; TNF, tumor necrosis factor.
[a] Adapted from Fagard et al[38] with own modification.
[b] Lüder et al[37] found that in rats only 30% of microglial cells were infected with *Toxoplasma gondii*, whereas 10% of neurons and astrocytes were invaded. Besides, parasites showed low replication rates, with only 1 or 2 degenerated parasites in 93% of the parasitophorous vacuole.
[c] Cerebellar granular neurons and pyramidal hippocampal neurons (when the size of a cell doubles, its volume increases 8-fold). It must be noted that *T gondii* size is 2 to 4 μm.
[d] Not documented for *T gondii* infection.
? Not established yet.

Table 8. Possible Consequences on Neurons of Cytokines and Biomolecules Secreted Upon *Toxoplasma Gondii* Infection.[a]

Cell Type	Secreted Biomolecules	Neurotic
Astrocyte	IL-6	−
	GM-CSF	−
	TNF-α	±
	IL-1β	−
	Arachidonic acid	+
Macrophage	IL-12	−
	NO	±
Microglial cells	RNI	+
	NO	±
	H_2O_2	+
	IFN-γ	−
	Glutamate	+
Neuron	NO	±
	TNF-α,	±
	Glutamate	+
Natural killer cell	IFN-γ	−
T cell	PAF	+
	IL-4	−
	IFN-γ	−
	IL-10	−

Abbreviations: RNI, reactive oxygen intermediates; PAF, platelet-activating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; NO, nitric oxide; TNF, tumor necrosis factor.
[a] Adapted from Fagard et al[38] with own modification. It must be noted that *Toxoplasma gondii* infection caused a significant increase in dopamine metabolism in neural cells, which may lead to psychobehavioral changes in humans infected with toxoplasmosis.[58] Dopamine concentrations were 14% higher in the brain of mice with chronic infections than in controls.[59] In addition, induction of indoleamine 2,3-dioxygnase expression and decreased levels of tryptophan and increased formation of kynurenine were found in the brain, lungs, and serum of mice infected with the parasite.[60] Moreover, dopamine stimulated tachyzoite proliferation in human fibroblast and primary neonatal rat astrocyte cell cultures,[61] thus further enhancing the harmful effects of the parasite on the brain function. In addition, chronic latent *T gondii* infection is associated with overproduction of various cytokines, and it was postulated that cytokines may induce changes in mood and behavior, leading to depressive illness in man.[62,63]

suggest that similar neuroinflammatory processes are also taking place in the olfactory system, leading to its progressing damage.

Xiao et al[79] showed that in male mice, infection with the parasite led mainly to modulation of genes associated with olfactory function, such as downregulation of the number of olfactory receptors and dopamine receptor D4. However, general olfactory tests and sensorimotor gating were normal in both male and female infection.[79,80] The discrepancy between the findings in rodents and impaired sense of smell reported in the patients with Alzheimer's disease, as well as in the individuals with various autoimmune diseases having chronic *T gondii* infection, may be at least in part explained by the markedly greater morphometric parameters of *rhinencephalon* in animals (*lobus olfactorius*) than in humans (*bulbus olfactorius*),[81] which must be clearly associated with a considerably smaller extent of the olfactory tissue subjected to neuroinflammatory destruction.[82] It must be emphasized that low olfactory bulb volumes have been found in patients with schizophrenia (left and right bulb) and their first-degree relatives (right bulb) as compared with healthy individuals (Table 11).[83] In 1 study, the significant atrophy was also reported in 43.9% of 150 patients with systemic lupus erythematous (SLE), with progression of reduction in right and left hippocampal volumes related to disease duration ($P < .001$).[84] Moreover, patients with neuropsychiatric SLE had amygdala damage.[85] In patients with Parkinson's disease, olfactory loss was considered as a marked early symptom that correlated with the progression of the disease,[86] and parkinsonian symptoms have been observed as an initial manifestation in a Japanese patient with acquired immunodeficiency syndrome and *T gondii* infection.[87] Olfactory dysfunction has also been reported in HIV-infected and AIDS individuals,[88,89] in patients with Alzheimer's disease,[90] in patients with Down's syndrome,[91] in patients with multiple sclerosis,[92] in patients with SLE,[93] in patients with schizophrenia[94] and their relatives,[95] and during several

Table 9. Percentage of *Toxoplasma Gondii*–Positive Individuals Among 214 Nonpsychiatrically Affected Controls Depending on Age Analyzed During a Large Epidemiologic Study of 869 Psychiatric Patients.[a]

	Age, years											
Percentage *T. gondii* Positive	18-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75
100												100
80									80		80	
60							58	58		60		
40		35	32	40	39	38						
20	19											
0												

[a] Adapted from Hinze-Selch et al.[70] In the control individuals 45 years or younger recruited from the same geographical region as the psychiatric patients admitted to the hospital, the serofrequency of *Toxoplasma gondii* infection ranged between 20% and 40% without any systematic age effect, whereas in the individuals older than 45 years, the serofrequency systematically increased with age from about 40% to almost 100%.[70]

Table 10. Changes in Serum Heat Shock Protein (HSP) and anti-HSP Antibody Levels in Aging.[a]

	Age group, years			
	<40	40-69	70-78	≥90
HSP60, ng/mL[b]	759 (239-1356)	383 (145-777)	221 (49-547)	294 ns (117-361)
HSP70, ng/mL	400 (60-1520)	80 (40-315)	50 (0-270)	20[c] (0-245)
Positive samples[d]	10/13; 77%	14/16; 88%	14/20; 70%	8/11; 73%
Anti-hHSP60, U/mL	482 (427-603)	439 (370-491)	389 (234-548)	577 ns (486-783)
Anti-hHSP70, U/mL	115 (102-144)	143 (130-172)	232 (134-269)	191 ns (146-267)
Anti-mHSP65, U/mL	119 (48-267)	201 (142-291)	138 (107-226)	268[e] (181-507)

[a] Adapted from Rea et al[71] with own modification.
[b] Data are presented as medians with interquartile ranges in parentheses.
[c] $P = .02$.
[d] All 60 serum samples contained detectable levels of HSP60 and anti-hHSP60, anti-HSP70, and anti-HSP65 antibodies. The numbers of samples with detectable levels of HSP70 is indicated.
[e] $P = .03$, nonsignificant versus <40 age group (independent samples *t* test on log-transformed data).

Table 11. Olfactory Bulb Volumes in Patients With Schizophrenia, First-Degree Relatives, and Healthy Controls.[a]

	Volumes, mm^3			
	Left Bulb		Right Bulb	
Group	Mean	SD	Mean	SD
Patients (n = 11)	70.82[b]	11.77	70.18[c]	14.11
Control individuals (n = 20)	81.62	16.91	85.97	13.75
Relatives (n = 19)	83.51	17.96	75.41[d]	13.56

Abbreviations: MANOVA, multivariate analysis of variance; SD, standard deviation.
[a] Adapted from Turetsky et al[83]with own modification.
[b] Significant difference between patients and relatives (MANOVA, $P < .05$, 2-tailed). [c] Significant difference between patients and controls ($P < .05$).
[d] Significant difference between relatives and controls ($P < .05$).

pregnancies,[96] that is, the clinical entities with significantly increased serum anti–*T gondii* IgG antibody levels compared with healthy controls.[23,97-104] Furthermore, the above-mentioned disturbed brain regions were consistently more infected than other sites in animals with toxoplasmosis.[31-33]

Depression is highly prevalent in various medical conditions, including infectious, autoimmune, and neurodegenerative diseases. It seems that damage of the olfactory system is at least in part responsible also for development of depression because it was found that *T gondii* infection worsened mood in pregnant women,[105] female veterans,[106] older persons,[107] and patients with multiple sclerosis.[108,109] Higher incidence of depression also preceded the onset of Parkinson's disease,[110] and the olfactory bulbectomized rat is usually serving as a model of depression.[111] Moreover, depression was reported in a sample of patients with obsessive–compulsive disorder,[112] and an important role of the parasite was suggested in the pathogenesis of this clinical entity.[113] Also, patients with

Table 12. Antidepressant Effects on the Host Immune System.[a]

Antidepressant	Source and Type of Effector Cells	Neuroendocrine Alterations
Fluvoxamine, reboxetine, imipramine	Murine glia cells	↓ NO levels after IFN-γ stimulation
Amitryptyline, nortriptyline	Rat glia cells	↓ IL-1 and TNF-α after LPS stimulation
Venlafaxine	Rat encephalogenic T-cell clones, splenocytes, peritoneal macrophages	↓ IL-12, TNF-α, and IFN-γ
Imipramine, mianserin, clomipramine, sertraline, and citalopram	Human peripheral white blood cells	↓ Proinflammatory cytokines; ↑ anti-inflammatory cytokines
Imipramine, venlafaxine, fluoxetine	Healthy human whole blood treatment resistant	↓ IL-10
Sertraline, citalopram, fluoxetine, fluvoxamine, paroxetine	Patients with depression	↓ TNF-α, CRP, and leukocyte count
Bupropion, mirtazapine, citalopram, paroxetine, venlafaxine	Patients with depression	↓ IL-6, TGF-β
Sertraline	Patients with depression	↓ IL-12, ↑ IL-4, TGF-β
Desipramine and fluoxetine	Rats	↓ IDO activity

Abbreviations: CRP, C-reactive protein; IDO, indoleamine 2,3-dioxygenase; TGF-β, transforming growth factor-β; LPS, lipopolysaccharide; IL, interleukin; ↓, decrease; ↑, increase ;TNF, tumor necrosis factor ;.NO, nitric oxide; IFN, interferon.
[a] Adapted from Antonioli et al[115] with own modification.

recurrent mood disorders with history of suicide attempt had higher *T gondii* antibody titers than nonsuicide attempters ($P = .004$).[114] It must be added that antidepressants act on the host immune system causing neuroendocrine alterations associated with an increased generation of several bioneurotic molecules (Table 12).[115] Thus, the relationship between chronic latent *T gondii* infection and brain damage resulting in the development of depression should be seriously taken into consideration. In such patients, treatment of the infestation together with estimation of clinical course of depression would be helpful in more beneficial modification of actual therapeutic regimens. This suggestion is in line with the finding that the antipsychotic haloperidol and the mood stabilizer valproic acid most effectively inhibited the parasite growth in vitro with synergistic activity.[29]

Interestingly, *T gondii* infection can convert the rodents' natural aversion to cat odors into attraction,[82,116,117] probably because of altered neuronal activity in limbic brain regions that is necessary for innate defensive behavior associated with the activation of adjacent sexual arousal pathways[79,80] and generation of various neurotransmitters.[115] It should be noted that a surface SAG1 antigen of *T gondii* combined with nontoxic mutants of cholera toxin and enterotoxin (powerful mucosal adjuvants) administered intranasally in mice provided a beneficial high-level protection after virulent challenge infection with the parasite cysts.[118] In addition, treatment with monoclonal antibody against IL-6 resulted in a remarkable decrease in inflammation and numbers of cysts in the brain of animals with toxoplasmic encephalitis.[119] This beneficial effect may be partly explained by the fact that IL-6 enhances intracellular replication of the parasite acting through interactions with IFN-γ and TNF-α molecular activities.[120] Unfortunately, despite development of many serological and molecular methods in recent years, diagnosis of toxoplasmosis still faces difficulties because most of the commercially available tests are not fully specific and sensitive, representing wide variations in accuracy due to the fact that the parasite exhibits several protein and LPS antigens depending on its virulence, strain type, infection stage (tachyzoites, bradyzoites, oocysts), innate and/or acquired host immunity, and so on.[121-123]

In summary, damage of the olfactory system caused by chronic latent *T gondii* infection may affect olfactory bulb volume and various olfactory functions, therefore being responsible for the smell impairment in patients with several neuropsychiatric and/or autoimmune diseases. In addition, it seems that damage of the olfactory system may also be at least in part responsible for development of depression, which is frequently observed in those individuals.

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