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Abstract

A large database documents the role of inflammatory processes in the development of neuropsychiatric symptom dimensions that are common to multiple psychiatric conditions. Mechanisms mediating these effects are believed to involve disturbances in monoamine and glutamate metabolism and function, through the action of inflammatory factors on two distinct enzymatic pathways, including the indoleamine-2,3-dioxygenase (IDO) and GTP-cyclohydrolase I (GCH-I) pathways. Alterations in these pathways contribute to profound structural and functional brain abnormalities associated with specific symptom dimensions. Increasing knowledge on immune-to-brain interactions is expected to facilitate the development and implementation of novel and innovative therapeutic interventions against inflammation targeting, at distinct levels of integration, mechanisms, processes and brain circuits underlying the expression of specific clinical profiles. These strategies are crucial for a precision medicine in Psychiatry, tailored to the clinical and biological phenotypes of patients.

Keywords: Inflammation; Depression; Neuropsychiatric Symptom Dimensions; Enzymatic Pathways; Monoamine; Glutamate; Brain Structural Abnormalities; Precision Medicine; Research Domain Criteria.

Introduction

Psychiatric disorders are frequent in the general population, with an estimated lifetime prevalence of 30% (1). Generally characterized by symptoms of severe intensity and recurrent/chronic course, they substantially impact the patient daily functioning and quality of life and are responsible for life-years lost due to premature deaths, including suicide. Their socioeconomic repercussions are elevated, with substantial indirect costs, primarily related to the high rate of workplace absenteeism and loss of productivity at work, as well as direct medical costs mainly attributed to medical consultations, medications and hospital admission. Based on data from the Global Burden of Disease Study, major depression is the most common of mental disorders, representing one of the top leading causes of years lived with disability (YLDs) (2, 3).

Over the last five decades, significant advances in the development of pharmacological strategies have modified the poor prognosis of psychiatric diseases, notably in major depression. Controlled research has provided high-level evidence for the efficacy of a large panel of medications sharing common mechanisms of action primarily targeting monoamine systems in the management of mental disorders. However, a significant number of psychiatric patients still fail to respond successfully to these pharmacological treatments, experiencing insufficient clinical improvement after several weeks or months of administration. Side effects may also occur therefore limiting the gradually increasing dosage regimen classically recommended until optimal therapeutic response is obtained. These issues highlight the necessity to improve current knowledge on the biological determinants of psychiatric diseases. Such a scientific approach is expected to ensure the promotion and use of innovative therapeutic alternatives that can be particularly helpful in psychiatric patients who are unresponsive to conventional treatments. This implies a better phenotyping of patients so as to match specific clinical profiles to biomarkers in the perspective to propose more adapted treatments targeting biological substrates intimately related to clinical symptoms. This research strategy is in line with the Research Domain Criteria

(RDoC) project introducing a conceptual and methodological breakthrough in mental health by emphasizing the need for a "*biosignature*" of clinical symptomatology enabling to define distinct and homogenous patient subgroups and therefore improve therapeutic management (4, 5). In this context, a growing attention has been paid to the critical role of the immune system in the emergence of neuropsychiatric symptoms with the aim of establishing close relationships between identified inflammatory pathways and key clinical symptom dimensions for the further development of appropriate and individualized therapies.

A. The role of inflammation in the development of neuropsychiatric symptom dimensions

Compelling evidence for a role of inflammation in the development of neuropsychiatric symptoms comes from preclinical and clinical findings indicating that treatment with inflammatory agents, including pro-inflammatory cytokines and endotoxins, induces behavioral alterations that resemble symptoms of major depression (6, 7). The model of interferon (IFN)-alpha-induced depression in clinical settings has particularly highly contributed to demonstrate the causal role of cytokines in the pathophysiology of major depression in vulnerable subjects (7, 8). In addition, large clinical observations have indicated that chronic inflammatory conditions, such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, obesity, diabetes or cardiovascular diseases, are frequently characterized by depressive symptoms that can be relieved by pharmacological anti-inflammatory or anti-cytokine interventions (7, 9). Similarly, basal and stimulated-levels of inflammatory markers, including the acute phase protein, C-reactive protein (CRP), or the pro-inflammatory cytokine, Interleukin (IL)-6, have been associated with an increased risk for the development and persistence of depressive symptoms (10-15). Four recently published meta-analyses based on 20 to 80 studies examining peripheral cytokine profile reported concordant results, with circulating concentrations of the pro-inflammatory cytokines IL-6 and Tumor Necrosis

Factor (TNF)-alpha found to be higher in depressed subjects (16-19). Increased levels of IL-6 were also found in the cerebrospinal fluid (CSF) of depressed patients (20).

Strong relationships have been established with the clinical severity of neuropsychiatric symptoms. Accordingly, peripheral concentrations of high-sensitive (hs) CRP were found to correlate with the intensity of depressive manifestations (21-25). Interestingly, correlations were the strongest with the dimensions of anhedonia, loss of interest, apparent sadness, cognitive disturbances and suicidality (22). Similarly, higher levels of IL-6 were associated with more severe symptoms of anhedonia (26), slowness of thought and movement (27) and cognitive impairment on sustained attention in depressed patients (28). In large cohort studies of non-pathological populations, relationships between hsCRP and symptom dimensions were also established, but rather with non-specific symptoms including fatigue, reduced appetite and sleep alterations (29).

Semiological, temporal and clinical specificities were reported regarding the relationships between systemic inflammation and neuropsychiatric dimensions, allowing deconstructing inflammation-driven symptom dimensions based on their phenomenological aspects. This particularly relies on clinical evidence showing that IFN-alpha treatment in medically ill patients induced two distinct sets of symptoms that differed by their time-course and responsiveness to classical antidepressant treatment (7, 30). The first set, characterized by symptoms of fatigue, lassitude, decreased motivation, motor slowing, and changes in appetite and sleep, developed at early stages of IFN-alpha treatment in almost every patient. In contrast, the second set of symptoms, which included sadness, depressed mood, anhedonia and cognitive alteration, occurred at later stages of treatment in a subpopulation of patients (30 to 50%), suggesting vulnerability factors. This second set of symptoms was prevented by the prophylactic administration of paroxetine, a selective serotonin reuptake inhibitor (SSRI), in contrast to the first set of symptoms that did not respond to the antidepressant (30). Differences between these two symptom dimensions in terms of temporal dynamics and antidepressant responsiveness suggested that they likely involved distinct underlying neurobiological

mechanisms. This assumption was supported by preclinical studies performed in rodent models of inflammation developed to experimentally dissociate sickness behavior (appearing early after the immune stimulation) from protracted depressive-like behaviors (31-34). These models enabled to show that depressive-like symptoms, assessed in behavioral tests modeling despair/resignation, anhedonia, anxiety or measuring cognitive performance, were still present while sickness behavior and increased circulating cytokines levels were not anymore detectable (32-38). Supporting further the implication of distinct underlying mechanisms, neuroanatomical dissociations were found to correlate with the time-course dissociation between lipopolysaccharide (LPS)-induced sickness and depressive-like behaviors in mice (31). Since then, the use of preclinical models together with clinical studies helped starting to decipher the mechanisms differentially involved in the development of inflammation-driven specific symptom dimensions and likely to be common to multiple neuropsychiatric conditions in which increased inflammatory markers have been reported. These studies particularly focused on the potential role of neurobiological systems known to be involved in mood regulation and targeted by inflammatory cytokines (6, 7, 39, 40).

B. Mechanisms differentially involved in the development of inflammation-induced specific symptom dimensions

Among the mechanisms that are likely to underlie the association of inflammation with neuropsychiatric symptoms, one the most relevant refers to the impact of inflammatory factors on neurotransmitter metabolism and function. Consistent with this notion, a large database substantiates the differential contribution of inflammation-induced alterations in monoamine and glutamate systems respectively (through effects on amino-acid metabolism and related enzymatic pathways) in the development of specific neuropsychiatric symptom dimensions.

a) Inflammation-induced alterations in tryptophan metabolism: relevance to serotonin/glutamate functions and related mood, emotional and cognitive symptoms

Peripheral cytokines are able to impact serotonin (5-HT) and glutamate functions through the induction of the enzyme, indoleamine-2,3-dioxygenase (IDO). The activation of IDO by inflammatory factors leads to the transformation of tryptophan (TRP), the essential amino-acid precursor of 5-HT, in kynurenine (KYN) instead of 5-HT, contributing presumably to 5-HT deficit. KYN is then converted into neurotoxic derivatives such as quinolinic acid in microglia at the expense of the neuroprotective compound kynurenic acid in astrocytes (7, 41, 42). In line with this, treatment with IFN-alpha in medically ill patients was found induce significant reductions in circulating levels of TRP together with increases in KYN and in the ratio of KYN/TRP, indicative of augmented IDO activity (43). Interestingly, these alterations correlated with depressive, anxious, and cognitive symptoms (8, 43, 44). Similar findings were reported in elderly subjects with elevated markers of inflammation, where inflammation-associated TRP catabolism correlated with depressive symptoms including pessimistic thoughts, reduced appetite, sleep disturbances and lassitude (45). These findings were corroborated by the observation that elevated KYN/TRP ratio was linked to depressive symptom severity in patients with mastocytosis (46) and by data showing that depressed patients exhibit increased KYN/TRP ratio (47) together with lowered kynurenic acid/quinolinic acid ratio (48-50) correlating with severe anhedonia (48).

IDO-driven degradation of TRP along the KYN pathway leads to the production of neuroactive metabolites, including quinolinic acid, which exerts neurotoxic effects by stimulating glutamate transmission through activation of NMDA receptors, elevation of glutamate release and inhibition of glutamate reuptake by astrocytes (7, 41, 42). Consistent with this, elevated CSF concentrations of KYN and quinolinic acid were reported in patients treated with IFN-alpha and were associated with increased depressive symptoms (51). Similarly, a post-mortem brain analysis of depressed patients showed greater quinolinic acid-microglial cell immunoreactivity within both

ventral and dorsal portions of anterior cingulate cortex (52), known to be involved in the regulation of emotional processes (53, 54). Besides, a recent study using magnetic resonance spectroscopy in IFN-alpha-treated patients indicated that treatment-induced increased glutamate levels in the dorsal anterior cingulate cortex, which is intimately connected to basal ganglia, correlated with reduced motivation (55). Similar findings were found in depressed patients who exhibited increased inflammation correlating with higher levels of glutamate in the basal ganglia that were in turn associated with greater anhedonia and motor retardation (56).

Strong support for a role of inflammation-induced IDO activation and related modulation of 5-HT/glutamate functions in depressive symptoms was also provided by preclinical studies. Rodent models of inflammation have shown that IDO activation, which occurs after the induction of cytokine production in immune-challenged animals (57, 58), coincides with the development of depressive-like symptoms (31, 34, 36, 37, 59, 60). Concomitance between protracted brain IDO expression and depressive-like behaviors was also reported in aged mice (61, 62) and in medical conditions associated with chronic inflammation (63-67). In addition, cytokine-induced IDO activation also paralleled the development of anxiety-like behaviors and/or cognitive alterations in animals treated with cytokine inducers (38, 64, 68-70), as well as in rodent models of chronic inflammatory diseases (67, 71-74). Importantly, pharmacological or genetic inhibition of IDO activation in these inflammatory conditions abolished the induction of emotional and cognitive alterations without impacting sickness behavior (36-38, 59, 64, 67, 71-73), highlighting the causal role of IDO in the induction of these symptom dimensions.

While impaired 5-HT synthesis was initially thought to represent the main pathway by which cytokine-induced IDO activation promotes behavioral alterations, the lack of detectable impact on 5-HT turnover reported in several preclinical studies weakened this hypothesis (59, 61, 70, 75). Nevertheless, it is worth mentioning that these findings do not necessarily discard the involvement of inflammation-related alterations of 5-HT neurotransmission in associated

depressive symptoms. In support of this, cytokines were shown to increase expression of the 5-HT transporter (76), a mechanism that may be responsible for worsened disruptions in 5-HT neurotransmission contributing in turn to depressive symptoms. Mounting evidence rather supports the key role of neurotoxic KYN metabolites (e.g., quinolinic acid, 3-hydroxykynurenine [3-HK]), in the development of inflammation-related depressive symptoms (75, 77, 78). In line with this, direct peripheral administration of KYN or 3-HK in rodents induces depressive-like behaviors, anxiety-like behaviors and/or cognitive impairments in a dose-dependent manner (38, 59, 75, 77, 79, 80). On the contrary, inhibition of the enzymes synthetizing the NMDA receptor agonist quinolinic acid (77, 78), or direct blockade of these glutamate receptors (81) abrogates cytokine-induced depressive-like behaviors. Interestingly, the efficiency of this effect was shown to differ according to symptoms, with behavioral changes modeling anhedonia being less impacted (77). This agrees with a recent study reporting that inflammation-induced impairment of motivation-driven behaviors persists in IDO deficient mice (82). While the dissociation between activation of the KYN pathway and specific depressive symptoms may rely on regional brain differences (75, 77, 78), it may also reflect the involvement of other metabolic pathways and/or neurotransmission systems.

b) Inflammation-induced alterations in tyrosine metabolism: relevance to dopamine function and related symptom dimensions

In addition to their effects on IDO and related monoamine pathways, pro-inflammatory cytokines are able to modulate the activity of GTP-cyclohydrolase I (GCH-I), a key enzyme for tetrahydrobiopterin (BH4) synthesis (83). BH4 is an essential cofactor for aromatic amino acid hydroxylases, including phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), TRP-hydroxylase (TPH) and nitrite oxide synthases (NOS). It is then crucial for the synthesis of noradrenaline, dopamine (DA), 5-HT and nitric oxide from their respective precursors, the

essential amino acids tyrosine, TRP and arginine (84-87). BH4 synthesis results from the sequential action of three complementary enzymes, GCH-I, 6-pyruvoyltetrahydrobiopterin synthase (PTPS) and sepiapterin reductase (SPR) (88). In Human, the induction of GCH-I in macrophages and monocytes is not relayed by the activation of PTPS under inflammatory challenge, leading to accumulation of neopterin, a peripheral early marker of immune activation, at the expense of BH4 (87, 89). Moreover, pro-inflammatory cytokines, such as IFN-gamma, trigger formation of high amounts of reactive oxygen species that can also destroy the oxidation-labile BH4 and then contribute to the substantial reductions in BH4 levels (90). Consistent with this notion, elevated plasma levels of neopterin (43) together with reduced BH4, reflected in increased phenylalanine/tyrosine ratio (91), were reported in patients treated with IFN-alpha and in multiple inflammatory conditions (89).

Due to its crucial role as cofactor in the activity of TH and TPH notably, the oxidation and reduced production of BH4 during inflammatory conditions may lead to significant disruptions in monoamine biosynthesis and neurotransmission (83, 89, 92). In line with this, inflammatory cytokines have been shown to strongly affect DA and DA-relevant neurocircuitry (93-96). Interestingly, IFN-alpha-induced reductions in BH4, as indicated by increased phenylalanine/tyrosine ratio, correlated with increased levels of systemic markers of inflammation together with reduced CSF levels of DA and its metabolite, homovanillic acid (91). In the same study, the oxidized form of BH4, BH2, was also increased in the CSF of IFN-alpha treated patients. Measurements of monoamine levels in murine models of partial deficiencies in BH4 have confirmed its important role in monoamine synthesis (97). Accordingly, reduced levels of 5-HT and DA were described in the brain of *hph-1* mouse, which are genetically deficient for BH4 (98-102). Interestingly, those mice exhibited anxiety and depressive-like behavior when compared to wild-type control mice (101). Similarly, mice deficient in the SPR gene (*Spr-/-*), which catalyzes the final step of BH4 synthesis, displayed reductions in brain BH4 and monoamine levels,

including DA and 5HT, together with disruption in brain maturation, severe growth retardation and locomotor deficits at adulthood (103-105). Interestingly, oral supplementation with tyrosine or BH4 and neurotransmitter precursors improved body weight and motor alterations, and restored phenylalanine metabolism in these animals (103, 106).

Impairments in DA activity and related neurocircuitry have been repeatedly documented during inflammatory conditions. Inflammatory challenges (e.g., IFN-alpha or endotoxin administration, typhoid vaccine) in clinical populations lead to significant alterations in the activity of the basal ganglia and substantia nigra that correlate with symptoms of fatigue, reduced motivation, anhedonia and psychomotor slowing (94, 107-110). Similarly, increased phenylalanine/tyrosine ratio was shown to correlate with reduced motivation, fatigue, and motor symptoms in elderly subjects with low-grade inflammation (45). Moreover, dietary depletion of DA precursors, including phenylalanine and tyrosine, was found to decrease neural activation of the ventral striatum to hedonic reward (111), similar to that observed following administration of IFN-alpha or endotoxin (94, 107). Interestingly, the phenylalanine/tyrosine ratio was shown to be lower in depressed patients who responded to electroconvulsive therapy (112) whereas reduced BH4 levels were found in *postmortem* brains of subjects with a history of severe depression (113, 114).

Animal studies have confirmed the role of inflammatory processes in the occurrence of alterations in DA function and neurocircuitry and their repercussions on the development of DA-related symptoms. Accordingly, nonhuman primates treated with IFN-alpha were found to exhibit lower D2/D3 DA receptor density and reduced striatum DA release in response to amphetamine that correlated with low motivation for food-related rewarding stimulus (115). Interestingly, reduction in DA were restored by L-DOPA administration via reverse *in vivo* microdialysis, suggesting a specific effect of IFN-alpha treatment on impaired DA synthesis (116), consistent with the clinical findings documenting disrupted presynaptic DA function in IFN-alpha-treated patients (94). In line with these data, studies in rodents have indicated that acute peripheral

administration of TNF-alpha induces anhedonia and increases the catabolism of monoamines in the nucleus accumbens (117). Similarly, treatment with IL1-beta or IL6 was found to reduce motivation for food in rats and to significantly lower extracellular DA release in the nucleus accumbens at high dose of IL6 (118, 119).

Administration of BH4 has been tested in depressed patients with contrasting results, inducing either improvement in depressive symptoms (120, 121) or no effect (122). At the preclinical level, peripheral BH4 injection was found to increase hyper-locomotion induced by methamphetamine challenge in mice (123). A pro-locomotor effect of repeated BH4 administration was also reported in a rat model of neonatal serotoninergic lesion (124). More recently, acute peripheral injection of BH4 in mice was shown to enhance amphetamine-stimulated DA release in the nucleus accumbens and to increase motivation (125). However, it remains unclear whether BH4-mediated enhancement of DA release is due to an increase in DA synthesis or to a direct pro-release effect independently of its cofactor action on TH.

c) Inflammation-induced brain imaging abnormalities

Chronic inflammation has been linked to functional brain abnormalities in numerous neuroimaging studies. In particular, inflammatory stimuli were found to disrupt frontal-subcortical loops, involving the anterior cingulate cortex and the basal ganglia. In medically ill patients, treatment with IFN-alpha was found to increase activity of the dorsal anterior cingulate cortex during an attention-demanding task. This activation highly correlated with the number of errors made during the task in IFN-alpha treated patients, albeit task performance of these patients was similar to that measured in control subjects (126). The dorsal anterior cingulate cortex is highly implicated in error detection and conflict monitoring (127-130). Accordingly, overactivation within this cortical area may reflect an aberrant error processing, possibly source of automatic negative thoughts as shown in patients with obsessive-compulsive disorders (126, 131-134).

Increased activity of the anterior cingulate cortex was also found to be part of the response to peer rejection and was considered a predictive marker of the development of depressive symptomatology (135, 136). Interestingly, studies investigating social exclusion and associated negative affect in healthy subjects reported significant associations between greater activity in the dorsal anterior cingulate cortex and insula and increased peripheral concentrations of inflammatory markers in response to acute social stress (137). The activity of the ventral anterior cingulate cortex, which is specifically involved in the regulation of emotional responses (127, 128), is also highly modulated by inflammation. Accordingly, acute inflammatory challenge (typhoid vaccination) in healthy subjects was found to produce an inflammatory response that was associated with mood deterioration, which correlated with increased activity of the subgenual anterior cingulate cortex during the processing and recognition of facial emotions (138).

The basal ganglia were found to represent privileged targets for inflammatory processes. Neuroimaging studies in patients treated with IFN-alpha have contributed to reveal changes in basal ganglia activity, notably in the striatum and globus pallidus, during the first weeks of treatment (108). Interestingly, these brain alterations were associated with the intensity of fatigue experienced by these patients at these early stages of treatment. In another study, lowered activation of the ventral striatum in response to monetary rewards was found to correlate with IFN-alpha-induced reduced motivation, depression and fatigue (94). Midbrain DA neurons projecting to the striatum have been extensively demonstrated to encode a reward prediction error rule and provide information about the predictability of reward, which is essential during reward-directed learning (139-141). An error signal is therefore generated when differences are perceived between reward expectation and reality. Increases in plasma levels of IL-6 after acute stress in healthy volunteers were recently coupled to blunted reward prediction error signals within the ventral striatum during reinforcement learning (142). Interestingly, reduced prediction errors in the striatum and midbrain were documented in depressed patients and this reduction was inversely

correlated with severity of anhedonia (143). Increased levels of hsCRP were also found to be associated with decreased functional connectivity between the medial prefrontal cortex and ventral striatum, which in turn correlated with anhedonia and motor slowing in depressed subjects (96).

Because of their neurotoxic effects, IDO-related KYN derivatives, including quinolinic acid, may also contribute, at least in part, to structural brain abnormalities. In support of this notion, decreased kynurenic acid/quinolinic acid ratio, which correlated with severity of anhedonia (48), was found to be associated with reduced thickness of the pregenual cingulate cortex in a sample of depressed patients (49). In line with this, elevated levels of hsCRP or IL-6 were linked to reduced volume of multiple brain regions, including the prefrontal cortex, amygdala, striatum and hippocampus (144-147), found to be involved in disrupted emotional behaviors and cognitive aspects mediating the expression of neuropsychiatric symptoms (53, 148).

C. Towards the promotion of a phenotype-guided medicine

The discovery that inflammatory processes play a crucial role in the development of various neuropsychiatric symptom dimensions that are common to multiple psychiatric conditions places these processes as prime targets for the implementation of new therapeutic strategies. Inflammatory factors significantly impact the functionality of two distinct enzymatic pathways, IDO and GCH-I, thereby contributing to monoamine deficits contrasting with the excessive production of compounds with neurotoxic properties related to overactivation of the glutamate system (**Figure 1**). Disruptions in these pathways were found to lead to profound structural abnormalities along with significant changes in the functional activity and connectivity of brain circuits regulating cognition, emotion, arousal and motivational aspects, and encompassing key brain regions such as the anterior cingulate cortex, basal ganglia, amygdala and hippocampus. Close relationships were established with specific clinical dimensions ranging from depressive symptoms (sadness, anhedonia, suicidal thoughts) to cognitive (memory/attention/concentration

deficit) and neurovegetative symptoms (fatigue/anergia, abnormal sleep, psychomotor retardation). Noteworthy, the activation of GCH-I and IDO pathways by inflammatory processes, and the related alterations in monoamine and glutamate function, are not exclusive and may share common paths since both monoamines and glutamate are critically involved in basal ganglia function where they are highly interconnected (149-151). In line with this, data obtained in clinical and preclinical models of IFN-alpha-induced neuropsychiatric symptoms indicate that inflammation-induced anhedonia relies on alterations in both DA and glutamate systems (56, 94, 115, 152).

This type of research is particularly relevant to the area of integrative and translational neurosciences interconnecting biomarkers, mainly referring to inflammatory mechanisms, executive function, emotional processing, reward, and behavior-related neurocircuitry, to particular clinical symptom domains. Increasing knowledge on immune-to-brain interactions is expected to facilitate the development and implementation of novel and innovative therapeutic interventions against inflammation targeting, at distinct levels of integration, mechanisms, processes and brain circuits underlying the expression of specific clinical profiles. This will help to prevent or interrupt the cascade of biological events associated with inflammation leading to psychiatric illnesses. Overall, this research approach is a necessary step for the promotion of a precision medicine as a medical procedure intending to better determine "which therapeutics for which patients" (4, 5, 153). Precise characterization of clinical phenotypes based on the patient's inflammatory profile should contribute to further guide decision toward adapted and personalized strategies in everyday practice, therefore enabling to substantially improve poor treatment outcomes in Psychiatry.

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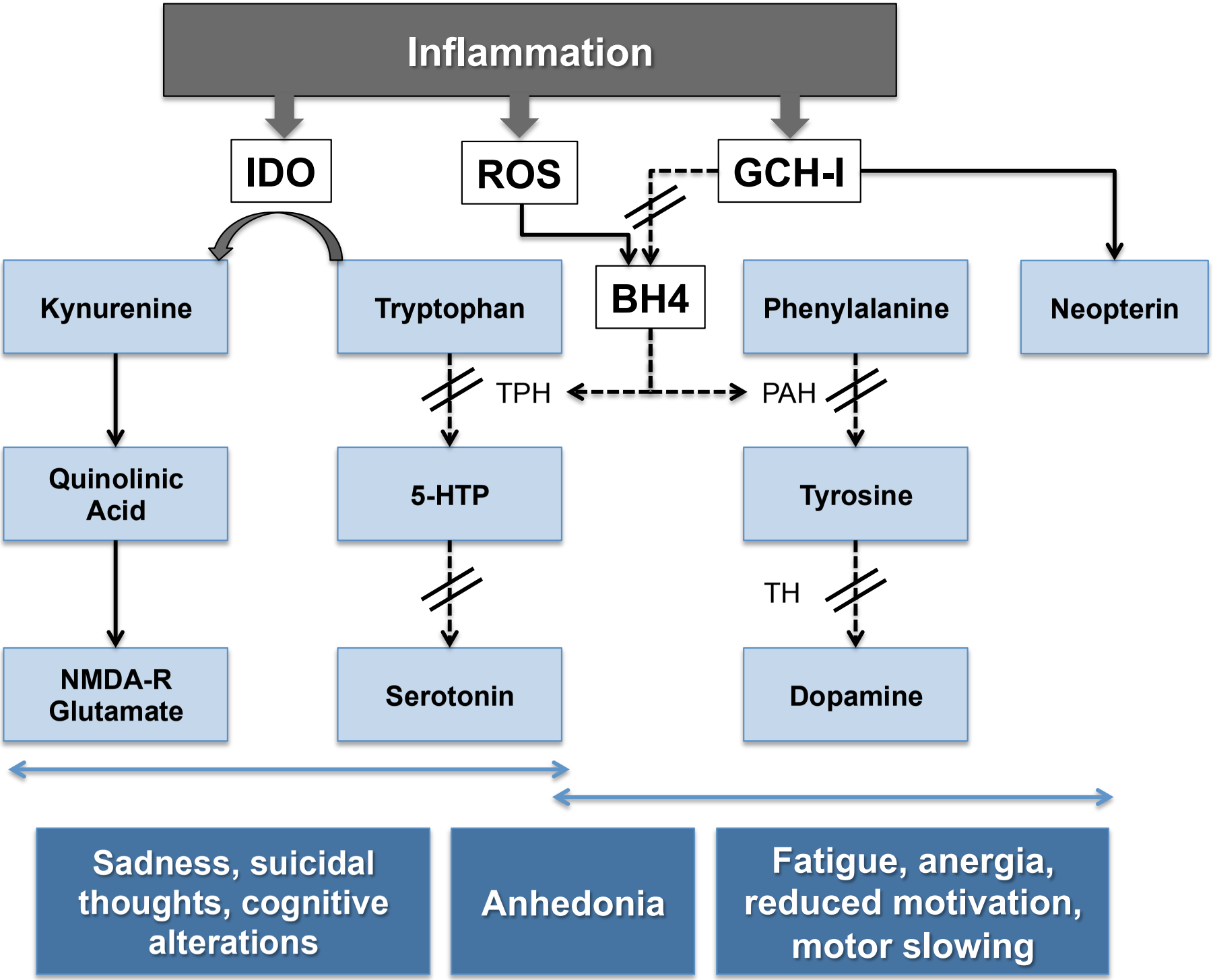
Figure Legend

Figure 1. Inflammation-induced alterations in indoleamine-2,3-dioxygenase (IDO) and GTP-cyclohydrolase 1 (GCH-I) pathways and associations with neuropsychiatric symptom dimensions. Inflammatory factors activate the enzymes IDO and GCH-I that are involved in the biosynthesis of serotonin, dopamine and glutamate. Inflammation-induced IDO activation leads to the degradation of tryptophan, the essential amino acid precursor of serotonin, along the kynurenine pathway, contributing presumably to serotonin deficit. Kynurenine is further degraded in glutamatergic neuroactive compounds, including quinolinic acid that stimulated NMDA receptors (NMDA-R) and promotes oxidative stress. This pathway is believed to contribute to the development of inflammation-related mood and cognitive symptoms, including sadness, suicidal thoughts, cognitive alterations and anhedonia. The activation of GCH-I under inflammatory condition leads to the formation of neopterin to the detriment of tetrahydrobiopterin (BH4), an essential co-factor for phenylalanine hydroxylase (PAH)/tyrosine hydroxylase (TH), tryptophan hydroxylase (TPH) and nitric oxide synthases involved in synthesis of serotonin, dopamine and nitric oxide, respectively. Inflammatory factors also trigger formation of high amounts of reactive oxygen species (ROS) that destroy the oxidation-labile BH4 and then amplify BH4 deficit. Inflammation-driven alterations in GCH-I/BH4 pathway were found to contribute to the development of fatigue, anergia, reduced motivation, motor slowing, and anhedonia.

Abbreviations: BH4: tetrahydrobiopterin; GCH-I: GTP-cyclohydrolase I; 5-HTP: 5-hydroxytryptophan; IDO: indoleamine-2,3-dioxygenase; NMDA-R: NMDA receptors; PAH: phenylalanine hydroxylase; ROS: reactive oxygen species; TH: tyrosine hydroxylase; TPH: tryptophan hydroxylase.


Inflammation
IDO
ROS
GCH-I
Kynurenine
Tryptophan
BH4
Phenylalanine
Neopterin
TPH
PAH
Quinolinic Acid
5-HTP
Tyrosine
TH
NMDA-R Glutamate
Serotonin
Dopamine
Sadness, suicidal thoughts, cognitive alterations
Anhedonia
Fatigue, anergia, reduced motivation, motor slowing