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Sickness Behaviour and Depression: An Updated Model of Peripheral-Central Immunity Interactions.

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Abstract

Current lines of research into mood disorders indicate that immune mediators participating in the pathophysiology of chronic somatic disorders have potent influences on brain functions, even when these mediators are produced in peripheral tissues. Elevated levels of circulating immune molecules have been consistently associated with depressive symptoms in a number of clinical populations and experimental models, to the extent that major depressive disorder (MDD) is now seen, at least in part, as a disorder of immunity. This paradigm has brought to the fore the use of anti-inflammatory therapies as adjunctive to standard antidepressant therapy with the hope to improve treatment efficacy, particularly in those cohorts that do not respond well to standard medication. Such new practice requires the availability of biomarkers to tailor these new therapies to those most likely to benefit but also clear mechanisms of action describing the interaction between peripheral immunity and brain function. These mechanisms are generally studied in preclinical models that try to recapitulate the human disease through peripherally induced sickness behaviour as the model for immune-induced MDD. After an appraisal of the data in rodent models and their adherence to the data in clinical cohorts, we propose a modified model of periphery-brain interaction that goes beyond the currently established view of interaction between peripheral cytokines and microglia cells as the driver of depression. Instead, we suggest that brain barriers are primary actors in the communication between body and brain and, as a consequence, in the pathophysiology of the disease. This model suggests novel biomarkers, novel targets for therapies as well as a novel mechanism for resistance to standard treatments.

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Introduction

Depression, also known as major depressive disorder (MDD), is an illness that is common as it affects ~ 5.0% of the adult population (1) and is one of the three leading causes of disability worldwide (2). To be diagnosed with MDD one should experience depressive episodes characterized by depressed mood (sadness, irritability, emptiness) or anhedonia (loss of pleasure or interest in activities), for most of the day, nearly every day, for at least two weeks (3). Other symptoms may also be present such as poor concentration, feelings of guilt or low self-worth, hopelessness about the future, disrupted sleep, changes in appetite or weight, tiredness, and thoughts about dying or suicide (3).

A number of medications used to treat MDD mostly act by increasing monoamine levels in the brain (4). Treatment efficacy is quite variable and must be tailored to the tolerance of the treatment that also varies substantially (5). Frequently however, even with multiple medication exposures, pharmacological treatments fail to improve MDD symptoms with as many as one third of individuals not achieving full symptomatic remission (6), and even fewer meeting criteria for both symptomatic and functional remission (7, 8).

The pressing need for better treatments has translated into the search for novel mechanisms of MDD, with a substantial amount of data pointing to the inflammatory response as an important contributor to its pathophysiology (9); in particular, elevated markers of peripheral inflammation are associated with treatment resistance (10). In this manuscript we will first outline the current view on the role of peripheral immunity in MDD, and review the relevant associative and causal data in clinical cohorts and in preclinical models. Since insights into the mechanistic links between peripheral and brain immunity have been gathered in preclinical models of sickness behaviour, we review the potential problems in the translation of these models into MDD cohorts. We then propose a different model for brain-immunity interactions that, in our view, accommodates better all hitherto available data as well as novel data obtained via functional and structural imaging in MDD cohorts, including both magnetic resonance imaging (MRI) and positron emission tomography (PET). This model predicts testable mechanisms for treatment resistance, and points to both state (e.g., functional) and trait (e.g., structural) biomarkers of immune-related MDD as well as to novel targets for pharmacological intervention.

Depression as a Disorder of Immunity

MDD patients exhibit all the cardinal features of inflammation, with elevations in inflammatory cytokines, acute phase proteins, chemokines, adhesion molecules, and inflammatory mediators such as prostaglandins, in peripheral blood (9, 11). Increased

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peripheral inflammatory markers in MDD have been consistently replicated in many studies and further documented in recent meta-analyses and large studies (12-14). Most reliable markers of inflammation in MDD relate to the acute phase protein CRP (C-reactive protein) and cytokines of the innate immune response (TNF-α, IL-6, IL-12, IL-18) (12-14).

From an experimental medicine perspective, acute and chronic administration of cytokines (or cytokine inducers such as lipopolysaccharide [LPS] or vaccination) can cause behavioural symptoms that overlap with those found in major depression (15-18). For example, 20% to 50% of patients receiving chronic IFN-alpha therapy for the treatment of infectious diseases or cancer develop clinically significant depression which can respond to antidepressants (15). At the same time, blockade of peripheral inflammation has been shown to reduce depressive symptoms in patients with severe and chronic inflammatory conditions (19, 20). Importantly, meta-analyses of randomised control trials (RCTs) have confirmed that patients with MDD receiving anti-inflammatory agents have responded better to antidepressant treatment, with higher remission rates than those receiving placebo (21, 22).

Mechanisms of Peripheral-Central Immunity Interactions in MDD

The mechanisms of peripheral to central immunity communication in depression have been elegantly dissected by work on sickness behaviour in rodents elicited by the cytokine inducer, lipopolysaccharide (LPS) (23), IL-1 (24), and the cytokine, tumor necrosis factor (TNF)(25) (please see (26) for a review). The peripheral immune signal is transferred to the brain by separate pathways that are thought to work in parallel (27).

Firstly, local inflammation generates a neural message that is relayed to the brain by afferent nerves as part of the nervous system activity that regulates immune function; such system is in fact quite sophisticated so much so that the brain can store and retrieve specific immune responses that can be transmitted peripherally once the pathogenic process is recognized (28). Indeed, using cell activation markers, Koren and colleagues were able to determine neuronal clusters associated with the immune response to two different peripheral immune challenges; activation of these clusters replicated the immune response to the previous inflammatory conditions (28).

Secondly, the neural message from the periphery is accompanied by either a slower diffusion of cytokines into the parenchyma through the fenestrations of the blood-brain barrier (BBB) in the circumventricular organs, or by overspill through active BBB transport or increased BBB permeability (27, 29-31). Peripheral cytokines also induce the production of prostaglandins by BBB endothelial cells; once in the parenchyma, both prostaglandins and

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peripheral cytokines stimulate the activation of brain microglia (27, 29-31). Microglia then start an inflammatory cascade which results in cytokine and glutamate release, oxidative stress and decline in neurotrophic support, ultimately disrupting neural activity and plasticity (32).

Sickness Behaviour Models: Validity and Translation in MDD

Sickness behaviour is a coordinated set of adaptive behavioural changes that develop in ill individuals during the course of an infection, with the aim of promoting energy conservation and reallocation to facilitate immune activation. Experimentally inducing sickness behaviour in animals by agents affecting the immune system has contributed to much of the current understanding about the link between peripheral and central immunity. However animal models need to be established based on the three basic constructs of face validity (phenotype similar to humans who have the illness), construct validity (mechanisms that result in human pathology are recapitulated by the model), and predictive validity (sensitivity to interventions that are effective for the disease or condition in humans) (33). Hence, we briefly discuss the evidence of the connection between immunologically-induced sickness behaviour, in humans and in animals, and depression and its treatments

Face Validity

In rodents, as well as in humans, sickness behaviour recapitulates well the significant aspects of MDD such as lethargy, anxiety, malaise, loss of appetite, sleepiness, hyperalgesia, and failure to concentrate (34). Face validity is further supported by the observation that patients with sickness behaviour also demonstrate peripheral inflammatory profiles that are consistently similar with those with MDD. We use here as a biomarker of reference CRP, an acute phase reactant produced by the liver in response to innate immune cytokines such as IL-6 and TNF-α, that is a reproducible and stable marker of peripheral inflammation as it does not exhibit daily variations (35). Subjects with no inflammation generally exhibit CRP concentrations <1 mg/L while those with inflammatory disease have plasma concentrations >10 mg/L (35). In the case of human cohorts with MDD, depressed subjects demonstrate mild inflammation, with CRP in the 1-3mg/L range (34, 35). Importantly, treatment resistant patients display significantly higher CRP levels (~ 5 mg/l on average) (36, 37).

While clinical behavioural and peripheral data are abundant and demonstrate good correspondence with sickness behaviour, data on central inflammation are rare and more mixed. Increased cytokine levels have been demonstrated into the cerebrospinal fluid (CSF) of subjects that were suicidal (38, 39) but results in MDD were mixed with 2/3 of the studies

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reporting reductions or no-change of IL-6 and TNF-α concentrations and the remaining registering moderate increases (40).

Data have also been collected on brain microglia activity that can be measured *in-vivo* using positron emission tomography (PET) and ligands targeting the 18 Kd translocator protein (TSPO) (41). TSPO-PET has demonstrated high levels of activation of microglia and astrocytes after acute peripheral LPS stimulation in rodents (42) and human volunteers (43, 44) but we detected no changes in TSPO in normal volunteers after a single peripheral injection of IFN-α (45), even in the presence of increased peripheral inflammation and transient sickness behaviour. Note that LPS in humans generates levels of peripheral cytokines that are up to 100 times those detected in the IFN-α experiment, where CRP already reaches levels up to 10 mg/L. In MDD cohorts, TSPO-PET data have demonstrated increases in signal that, however, are mild and localized particularly in the prefrontal regions (46-51)

Construct Validity

A key aspect of the construct validity of sickness behaviour as a model for MDD is the relationship between peripheral and central immunity; all rodent models described in the previous section predict that in depressed patients there should be a strong correlation between peripheral cytokines and microglial activity. While clinical data confirm that, as mentioned above, activated central immunity can be present in MDD (e.g., TSPO-PET signal is raised in the brain of MDD cohorts), microglial activity is not proven as a state as no PET imaging study has reported a correlation between peripheral cytokines and brain TSPO in MDD (46). Lack of correlation could be due to methodological reasons, as TSPO signal in brain is small and difficult to quantify (41) as well as not specific for microglia (42)(52); however correlations between plasma cytokines and brain TSPO have not been found also in human models of acute sickness behaviour after LPS challenge, large peripheral and central surges in signal notwithstanding (43) and, interestingly, sequential LPS challenges have actually caused a decrease in brain TSPO levels in correspondence of peripheral increases in cytokines (44). Importantly, in the human IFN-α experimental model (45), where cytokines peak at far lower concentrations that are closer to the ones measured in MDD patients, no microglial activity is detected.

A second important question regards a central element of the chain of events that connects peripheral immunity to microglial cells, that is the BBB. In the model of peripheral-to-CNS communication proposed by D'Mello et al., (31) and widely used afterwards as reviewed in (53), LPS peripheral challenges in various experimental conditions lead to "leakages" in BBB

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with consequent passage of immune mediators and immune cells; this straightforward mechanism is easily testable. However clinical evidence on BBB leakage in MDD is scarce and mixed; increased CSF/albumin ratios were found in a sample of elderly women with depression (54) while a meta-analysis of VEGF, a plasma marker of BBB permeability, reported inconclusive results (55). In our IFN-α experimental model, VEGF in serum was actually reduced, indicating loss of permeability instead (45). Very recently, dynamic contrast-enhanced (DCE-) magnetic resonance imaging (MRI) has been used in psychiatric cohorts and detected increased BBB permeability in a sub-group of bipolar patients (56). However, the only study that investigated BBB integrity in patients with MDD, using the recently developed Intrinsic Diffusivity Encoding of Arterial Labelled Spins (IDEALS) MRI technique (57), has shown reduced water permeability (58).

An interesting marker of BBB damage is S100β, a protein that is predominantly located in the cytoplasm and nucleus of astrocytes and cannot pass the BBB, but if the BBB is disrupted, can pass from CSF to serum (59). A review of studies in MDD reported elevated S100β levels but only in patients with acute episodes in MDD and manic and depressive episodes in BD (60). In our aforementioned IFN-α experimental model, serum S100β protein did not change significantly (45).

Predictive validity

There is very good preliminary evidence that higher levels of peripheral inflammatory markers predict efficacy of anti-inflammatory treatments in MDD. An RCT in patients with treatment resistant depression with add-on treatment with Infliximab, an antibody acting as TNF-α antagonist, found that only patients with higher levels of C-reactive protein (CRP > 5 mg/L) benefited from the drug (61). A recent RCT in treatment resistant patients, using minocycline as augmentation therapy over antidepressants, has demonstrated efficacy over placebo only in those with CRP plasma levels > 3mg/L (62). Minocycline is a tetracycline antibiotic with broad anti-inflammatory properties both in the periphery and in the CNS as it has good penetration through the BBB (63).

Given that antibodies do not cross the BBB and minocycline does but also has peripheral activity, it is unclear so far whether anti-inflammatory treatments acting centrally possess better efficacy profile. Hence a better understanding of the mechanisms by which peripheral inflammation acts on brain function may suggest more targeted and efficacious therapeutic paradigms. For example, microglia activity modifiers (e.g., suppressors or stimulating), have been proposed as antidepressants (64, 65). With this in mind, in the following section we build on our recent published data using PET and MRI data in order to formulate an

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updated model of peripheral/central immunity interactions that, in our view, better recapitulates that evidence illustrated so far.

An Updated Model of Peripheral to Central Interaction for Mild Inflammatory States in MDD.

The model is sketched in Box 1, visualized in Figure 1 and detailed below. As the title of this section suggests, we are concerned with subjects with MDD and mild peripheral inflammation, e.g., CRP< 10 mg/L. This range in fact should cover most of the MDD population (average CRP ~ 3mg/L) including those with evidence of resistance to standard antidepressant treatment (average 5mg/L) (14). This grouping excludes very acute cases, subjects at suicidal risk, patients with bipolar disorder, as well as instances of medically-induced sickness behaviour, where the evidence so far suggests that a cytokine storm is in progress and/or there is evidence of BBB disfunction and leakage. Exclusion should also be extended to elderly subjects, where evidence exists of BBB impairment (66). In the majority of subjects with MDD and mild peripheral inflammation, we will argue that a "tighter" BBB, rather than a "leakier" BBB, is driven by the peripheral inflammation.

1. *Short-lived inflammatory states, via circulating cytokines, cause the* ***reduction*** *of permeability of the brain barriers.*

We have recently shown that both in MDD subjects and in experimentally induced mild sickness behaviour there is a very strong negative correlation between plasma CRP and the permeability of the two main blood brain barriers (67), the BBB and the blood-CSF barrier (e.g., the choroid plexus, CP). This relationship indicates that inflammation in depression is associated with a "tighter", not a leakier, BBB. Indeed, the reduction in perfusion rates is substantial, beyond 50% (67).

These data are further supported by the elegant results obtained by Carloni et al. (68) in a murine model of experimental colitis whereas the cytokines released in the blood stream by gut inflammation cause the closure of the CP and stop the passage of bigger molecules to the CSF. The authors note the close similarity between the gut barrier, that demonstrates an epithelial layer, a stroma and endothelial layer, and the anatomy of the CP, that demonstrates an endothelial layer, a stromal space and epithelial (cuboid) cells. Hence, they hypothesize that the CP has a similar role to the gut barrier; the latter is enabled to stop inflammatory messenger to reach the blood from the gut. In the brain, the observed "closure" of the barriers, enacted by action of the β-catenin 1 signalling pathway on the endothelial tight junctions, acts as a similar defence mechanism against circulating cytokines entering the CSF (68).

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The third brain barrier, the epithelial layer that separates the ventricles from the parenchyma, has also demonstrated reduction in permeability in a model of MDD. Seo and colleagues (69) have very recently demonstrated perfusion reduction of the epithelial barrier in two mouse models of depression, as well as loss of p11, a key epithelial protein that is characteristically reduced in the plasma of MDD patients (70). The depressive symptoms in the two models were fully rescued by viral expression of p11 in epithelial cells (69). In our IFN-α human experimental model we were not able to determine the permeability of the ventricle epithelial barrier due to limitations of the radiotracer (67).

2. *Barriers' closure disrupts transport of solutes in and out of the brain and reduce brain activity –> depressive state*

Given the importance of the barriers for brain metabolism (e.g., O2 and CO2 diffusion), fluid balance, neuroendocrine and solutes transport, the reduction in perfusion is likely to affect homeostasis and will depress brain energetic output (71, 72). In fact, a recent pooled analysis of cohort studies on the association between systemic inflammation and individual symptoms of depression has found that CRP concentrations are most strongly associated with physical (loss of energy) and cognitive (anhedonia) depressive symptoms, and least associated with emotional depressive symptoms (73). This hypothesis is further supported by the use of a genetic model of endothelial junction closure of the CP that demonstrated anxiety-like behaviour and short memory loss (68).

3. *When inflammation carries on and becomes chronic, brain barriers undergo structural alterations that persist even after peripheral immunity subsides -> depressive trait*

While experimentally induced mild peripheral inflammation does not seem to cause microglial activation in humans (45), mild neuroinflammation is however present in MDD (46). We speculated that peripheral inflammation, when chronic as in some MDD subjects, would cause structural changes to the brain barriers achieving the chronicization of the barriers' impairment. To test this hypothesis, we measured brain barriers thickness by focusing on the one structure that is clearly visible and measurable on T1 MRI imaging, the CP, and demonstrated a clear increase in the volume of the CP in MDD cohorts (74).

4. *Disrupted homeostasis due to persistent inflammation elicits microglial reactivity -> central immunity activation*

Persistent disturbance of homeostasis affects brain activity and in particular the neotenic regions, such as prefrontal cortex, that in the adult cortex still retain high synaptic density

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and, for this reason, are the most metabolically active (75); disturbance in energetic homeostasis will then place these tissues under stress and elicit a microglia response. In fact, in our data on MDD subjects, CP volume correlated with TSPO-PET signal in prefrontal regions (74).

The key role of the CP volume as a marker of brain inflammation has also been recently confirmed in a different immune disorder, multiple sclerosis, in both preclinical models and clinical populations (76, 77). Note that the implication of these observations is that microglial activity is not a primary cause of depressive symptoms but a secondary effect of the closing of the barriers and disturbed homeostasis. The secondary, and potentially beneficial role of neuroinflammation in MDD, is in fact supported by recent data on sickness behaviour in rats and mice depleted of microglia where LPS-induced sickness was not abrogated, rather it was exacerbated (78).

Box 1: Sketch of Novel Model for Brain-Immunity Interactions for Mild inflammatory states.

Step 1: Short-lived inflammatory states, via circulating cytokines, cause the reduction of permeability of the brain barriers.

Step 2: Barriers closure disrupt transport of solutes in and out of the brain and reduce brain activity –> *depressive state*

Step 3: When inflammation carries on and becomes chronic, brain barriers undergo structural alterations that persist even after peripheral immunity subsides -> *depressive trait*

Step 4: Disrupted homeostasis due to persistent inflammation elicits microglial reactivity -> *central immunity activation*

Conclusion

In our view, the model proposed here recapitulates well the vast tapestry of old and new evidence on peripheral and central immunity communication. The novelty stands in the suggestion of a primary role of the brain barriers as key actors of the communication between the two immune compartments; barriers that, as elements of a defence mechanisms, we posit are contracted in the presence of peripheral immune reactivity, in order to protect the brain; this response disrupts brain homeostasis and affects the energetic balance, inducing depressive symptoms. However, when this response becomes chronic, the BBB functional changes turn into structural modifications and the tissues of the cortex that are most metabolically active become stressed. Microenvironmental and BBB changes, ultimately, generate a microglia response (79).

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The model purports two new key imaging markers of peripheral-to central immunity effects; the first is the brain barriers' permeability that is a state marker while, the second one, CP volume is a trait marker. Interestingly, the use of these markers has been already extended to populations of which MDD is a prodrome, such as Alzheimer's disease (80) or accelerated ageing (81), and to psychiatric populations also associated with inflammation, such as schizophrenia (82).

It also suggests a mechanism for treatment resistance, as antidepressants have very similar molecular weight and lipophilicity to the same radiotracers that have demonstrated reduced transfer from plasma to brain (67) - a tighter BBB would then make the entry of all these compounds to the brain less efficient.

In terms of treatment targets, the model confirms the notion that anti-inflammatory strategies are required to normalize circulating immune messengers; however pre-clinical data also suggests novel targets on endothelial (e.g., β-catenin 1 signalling pathway) and epithelial cells (e.g., protein p11) to address brain barriers structural and functional abnormalities that may persist even after the normalization of peripheral immunity. In fact, it may also be valuable to evaluate the effects of standard monoamine interventions on brain barrier permeability. For example, we have noted above the important role of the multifunctional protein p11 (also known as S100A10) in the regulation of epithelial function; however p11 is better known for its role in serotonergic signalling and the regulation of gene transcription (83). β-catenin, on the other hand, has been previously implicated in behavioural resilience via its action on D2 dopamine spiny interneurons in the nucleus accumbens (84). Interestingly, the efficacy of electroconvulsive therapy has been accrued, at least in part, to its associated increases in BBB permeability (85, 86)

The fact that reduction in brain barriers' perfusion is associated with distant stressful events, such as child abuse (67), opens also the possibility of using these biomarkers for the study of traits acquired during neurodevelopment as well as offers potential therapeutic strategies for their treatment.

In conclusion, we believe that the classic model of microglia activation induced by peripheral inflammation and leading to depression via glutamatergic and neurotoxic signals is insufficient to explain all available evidence, and should instead be expanded to include an intermediate step where peripheral inflammation leads to the tightening of BBB permeability as a defence mechanism, which, over weeks or months, causes depression via

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neuronal stress, with microglia activation possibly a coincidental epiphenomenon or even a protective mechanism, rather than the primary culprit.

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Sickness Behaviour and Depression

An Updated Model of Peripheral-Central Immunity Interactions

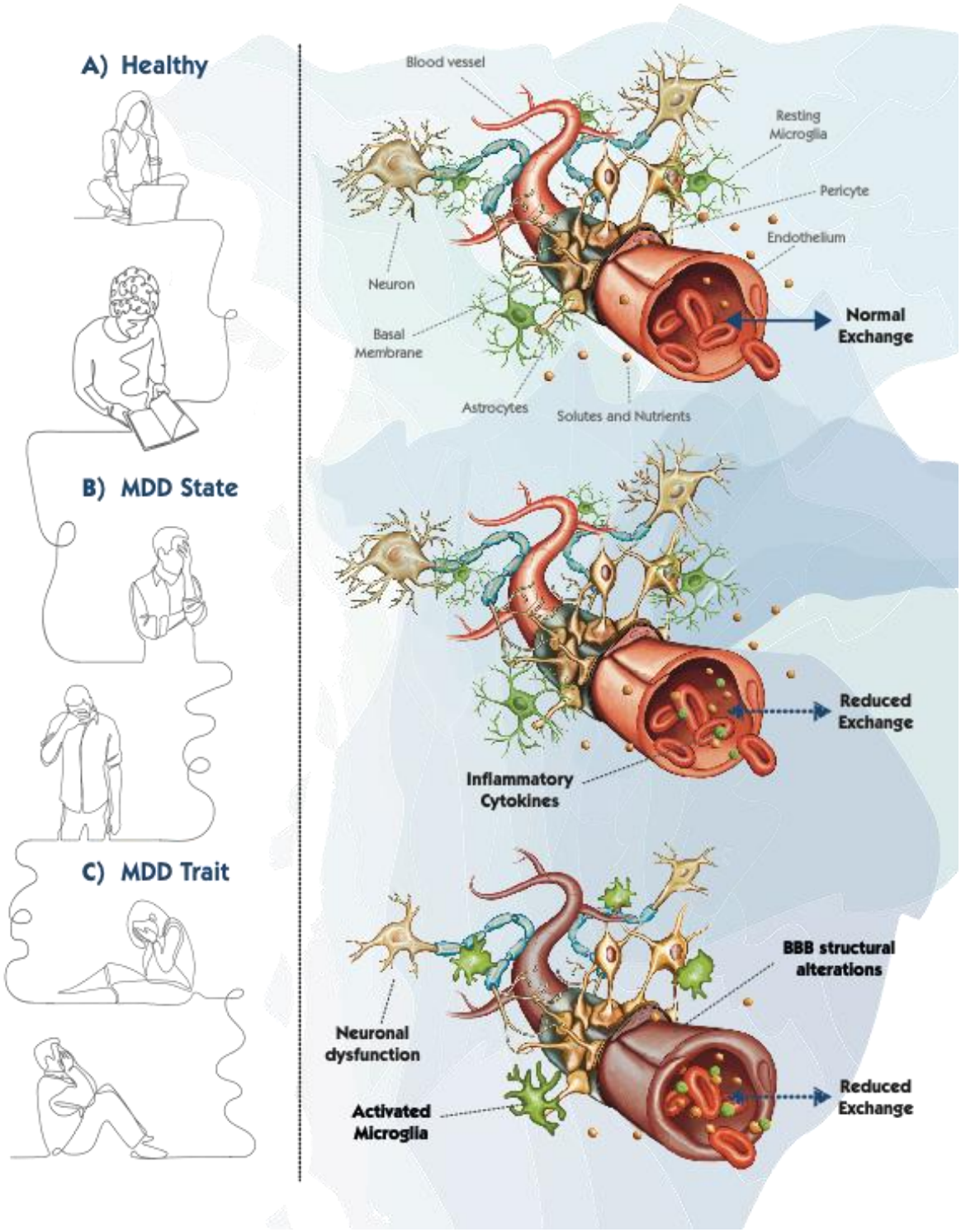

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Figure Legends

Figure 1.

Graphical representation of the model.

A. In the healthy state, circulating cytokines are null or very low, the permeability of the barriers is normal, microglial cells are in resting state.
B. A temporary increase in circulating cytokines reduces the permeability of the barriers disrupting homeostasis and causing mild sickness behaviour while microglial cells are still in resting state.
C. When inflammation persists and becomes chronic, the functional changes in the barriers become structural and depressive behaviour is accompanied by microglial activity that reacts to the persistent perturbation of solute concentrations and of the BBB.

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 doi:10.20944/preprints202203.0062.v1

References

1. World Health Organisation W (2021): Depression: fact sheet. Geneva.
2. Global Burden of Disease Study C (2015): Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 386:743-800.
3. NHS_UK (2021): Symptoms - Clinical depression.
4. Delgado PL (2000): Depression: the case for a monoamine deficiency. *J Clin Psychiatry*. 61 Suppl 6:7-11.
5. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. (2018): Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 391:1357-1366.
6. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. (2006): Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 163:1905-1917.
7. Sheehan DV, Harnett-Sheehan K, Spann ME, Thompson HF, Prakash A (2011): Assessing remission in major depressive disorder and generalized anxiety disorder clinical trials with the discan metric of the Sheehan disability scale. *Int Clin Psychopharmacol*. 26:75-83.
8. Sforzini L, Worrell C, Kose M, Anderson IM, Aouizerate B, Arolt V, et al. (2021): A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. *Mol Psychiatry*.
9. Miller AH, Raison CL (2016): The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 16:22-34.
10. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ (2015): Inflammation and clinical response to treatment in depression: A meta-analysis. *Eur Neuropsychopharmacol*. 25:1532-1543.
11. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008): From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 9:46-56.
12. Pitharouli MC, Hagenaars SP, Glanville KP, Coleman JRI, Hotopf M, Lewis CM, et al. (2021): Elevated C-Reactive Protein in Patients With Depression, Independent of Genetic, Health, and Psychosocial Factors: Results From the UK Biobank. *Am J Psychiatry*. 178:522-529.
13. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM (2019): Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol Med*. 49:1958-1970.
14. Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD (2020): Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain Behav Immun*. 87:901-909.
15. Bonaccorso S, Marino V, Puzella A, Pasquini M, Biondi M, Artini M, et al. (2002): Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J Clin Psychopharmacol*. 22:86-90.
16. Capuron L, Ravaud A, Dantzer R (2000): Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon alfa-2b therapy. *J Clin Oncol*. 18:2143-2151.
17. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD (2009): Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol Psychiatry*. 66:407-414.

18. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. (2001): Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 58:445-452.
19. Abbott R, Whear R, Nikolaou V, Bethel A, Coon JT, Stein K, et al. (2015): Tumour necrosis factor-alpha inhibitor therapy in chronic physical illness: A systematic review and meta-analysis of the effect on depression and anxiety. *J Psychosom Res*. 79:175-184.
20. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. (2006): Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet*. 367:29-35.
21. Bai S, Guo W, Feng Y, Deng H, Li G, Nie H, et al. (2020): Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. *J Neurol Neurosurg Psychiatry*. 91:21-32.
22. Kohler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, et al. (2014): Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*. 71:1381-1391.
23. Bluthe RM, Dantzer R, Kelley KW (1992): Effects of interleukin-1 receptor antagonist on the behavioral effects of lipopolysaccharide in rat. *Brain Res*. 573:318-320.
24. Kent S, Bluthe RM, Dantzer R, Hardwick AJ, Kelley KW, Rothwell NJ, et al. (1992): Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin 1. *Proc Natl Acad Sci U S A*. 89:9117-9120.
25. Bluthe RM, Dantzer R, Kelley KW (1991): Interleukin-1 mediates behavioural but not metabolic effects of tumor necrosis factor alpha in mice. *Eur J Pharmacol*. 209:281-283.
26. Remus JL, Dantzer R (2016): Inflammation Models of Depression in Rodents: Relevance to Psychotropic Drug Discovery. *Int J Neuropsychopharmacol*. 19.
27. Dantzer R (2018): Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa. *Physiol Rev*. 98:477-504.
28. Koren T, Yifa R, Amer M, Krot M, Boshnak N, Ben-Shaanan TL, et al. (2021): Insular cortex neurons encode and retrieve specific immune responses. *Cell*. 184:5902-5915 e5917.
29. Quan N, Banks WA (2007): Brain-immune communication pathways. *Brain Behav Immun*. 21:727-735.
30. Dantzer R (2009): Cytokine, sickness behavior, and depression. *Immunol Allergy Clin North Am*. 29:247-264.
31. D'Mello C, Le T, Swain MG (2009): Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. *J Neurosci*. 29:2089-2102.
32. Miller AH, Maletic V, Raison CL (2009): Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 65:732-741.
33. Nestler EJ, Hyman SE (2010): Animal models of neuropsychiatric disorders. *Nat Neurosci*. 13:1161-1169.
34. Stieglitz J, Trumble BC, Thompson ME, Blackwell AD, Kaplan H, Gurven M (2015): Depression as sickness behavior? A test of the host defense hypothesis in a high pathogen population. *Brain Behav Immun*. 49:130-139.
35. Felger JC, Haroon E, Patel TA, Goldsmith DR, Wommack EC, Woolwine BJ, et al. (2020): What does plasma CRP tell us about peripheral and central inflammation in depression? *Mol Psychiatry*. 25:1301-1311.

36. Cattaneo A, Ferrari C, Turner L, Mariani N, Enache D, Hastings C, et al. (2020): Whole-blood expression of inflammasome- and glucocorticoid-related mRNAs correctly separates treatment-resistant depressed patients from drug-free and responsive patients in the BIODEP study. *Transl Psychiatry*. 10:232.
37. Chamberlain SR, Cavanagh J, de Boer P, Mondelli V, Jones DNC, Drevets WC, et al. (2019): Treatment-resistant depression and peripheral C-reactive protein. *Br J Psychiatry*. 214:11-19.
38. Levine J, Barak Y, Chengappa KN, Rapoport A, Rebey M, Barak V (1999): Cerebrospinal cytokine levels in patients with acute depression. *Neuropsychobiology*. 40:171-176.
39. Lindqvist D, Janelidze S, Hagell P, Erhardt S, Samuelsson M, Minthon L, et al. (2009): Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol Psychiatry*. 66:287-292.
40. Enache D, Pariante CM, Mondelli V (2019): Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. *Brain Behav Immun*. 81:24-40.
41. Turkheimer FE, Rizzo G, Bloomfield PS, Howes O, Zanotti-Fregonara P, Bertoldo A, et al. (2015): The methodology of TSPO imaging with positron emission tomography. *Biochem Soc Trans*. 43:586-592.
42. Vicente-Rodriguez M, Singh N, Turkheimer F, Peris-Yague A, Randall K, Veronese M, et al. (2021): Resolving the cellular specificity of TSPO imaging in a rat model of peripherally-induced neuroinflammation. *Brain Behav Immun*. 96:154-167.
43. Sandiego CM, Gallezot JD, Pittman B, Nabulsi N, Lim K, Lin SF, et al. (2015): Imaging robust microglial activation after lipopolysaccharide administration in humans with PET. *Proc Natl Acad Sci U S A*. 112:12468-12473.
44. Peters van Ton AM, Leijte GP, Franssen GM, Bruse N, Booij J, Doorduin J, et al. (2021): Human in vivo neuroimaging to detect reprogramming of the cerebral immune response following repeated systemic inflammation. *Brain Behav Immun*. 95:321-329.
45. Nettis MA, Veronese M, Nikkheslat N, Mariani N, Lombardo G, Sforzini L, et al. (2020): PET imaging shows no changes in TSPO brain density after IFN-alpha immune challenge in healthy human volunteers. *Transl Psychiatry*. 10:89.
46. Schubert J, Veronese M, Fryer TD, Manavaki R, Kitzbichler MG, Nettis M, et al. (2020): A modest increase in 11C-PK11195-PET TSPO binding in depression is not associated with serum C-reactive protein or body mass index.2020.2006.2004.20099556.
47. Hannestad J, DellaGioia N, Gallezot JD, Lim K, Nabulsi N, Esterlis I, et al. (2013): The neuroinflammation marker translocator protein is not elevated in individuals with mild-to-moderate depression: a [(1)(1)C]PBR28 PET study. *Brain Behav Immun*. 33:131-138.
48. Richards EM, Zanotti-Fregonara P, Fujita M, Newman L, Farmer C, Ballard ED, et al. (2018): PET radioligand binding to translocator protein (TSPO) is increased in unmedicated depressed subjects. *EJNMMI Res*. 8:57.
49. Holmes SE, Hinz R, Conen S, Gregory CJ, Matthews JC, Anton-Rodriguez JM, et al. (2018): Elevated Translocator Protein in Anterior Cingulate in Major Depression and a Role for Inflammation in Suicidal Thinking: A Positron Emission Tomography Study. *Biol Psychiatry*. 83:61-69.
50. Setiawan E, Wilson AA, Mizrahi R, Rusjan PM, Miler L, Rajkowska G, et al. (2015): Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry*. 72:268-275.

51. Mondelli V, Vernon AC, Turkheimer F, Dazzan P, Pariante CM (2017): Brain microglia in psychiatric disorders. *Lancet Psychiatry*. 4:563-572.
52. Betlazar C, Middleton RJ, Banati R, Liu GJ (2020): The Translocator Protein (TSPO) in Mitochondrial Bioenergetics and Immune Processes. *Cells*. 9.
53. Varatharaj A, Galea I (2017): The blood-brain barrier in systemic inflammation. *Brain Behav Immun*. 60:1-12.
54. Gudmundsson P, Skoog I, Waern M, Blennow K, Palsson S, Rosengren L, et al. (2007): The relationship between cerebrospinal fluid biomarkers and depression in elderly women. *Am J Geriatr Psychiatry*. 15:832-838.
55. Clark-Raymond A, Halaris A (2013): VEGF and depression: a comprehensive assessment of clinical data. *J Psychiatr Res*. 47:1080-1087.
56. Kamintsky L, Cairns KA, Veksler R, Bowen C, Beyea SD, Friedman A, et al. (2020): Blood-brain barrier imaging as a potential biomarker for bipolar disorder progression. *Neuroimage Clin*. 26:102049.
57. Wengler K, Bangiyev L, Canli T, Duong TQ, Schweitzer ME, He X (2019): 3D MRI of whole-brain water permeability with intrinsic diffusivity encoding of arterial labeled spin (IDEALS). *Neuroimage*. 189:401-414.
58. Wengler K, Chen K, Canli T, DeLorenzo C, Schweitzer ME, He X (2019): Abnormal Blood-Brain Barrier Water Permeability in Major Depressive Disorder. *ISRM 27th*. Montreal, QC, Canada.
59. Rothermundt M, Peters M, Prehn JH, Arolt V (2003): S100B in brain damage and neurodegeneration. *Microsc Res Tech*. 60:614-632.
60. Ambree O, Bergink V, Grosse L, Alferink J, Drexhage HA, Rothermundt M, et al. (2015): S100B Serum Levels Predict Treatment Response in Patients with Melancholic Depression. *Int J Neuropsychopharmacol*. 19:pyv103.
61. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. (2013): A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry*. 70:31-41.
62. Nettis MA, Lombardo G, Hastings C, Zajkowska Z, Mariani N, Nikkheslat N, et al. (2021): Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial. *Neuropsychopharmacology*. 46:939-948.
63. Soczynska JK, Mansur RB, Brietzke E, Swardfager W, Kennedy SH, Woldeyohannes HO, et al. (2012): Novel therapeutic targets in depression: minocycline as a candidate treatment. *Behav Brain Res*. 235:302-317.
64. Yirmiya R, Rimmerman N, Reshef R (2015): Depression as a microglial disease. *Trends Neurosci*. 38:637-658.
65. Borsini A, Cattaneo A, Malpighi C, Thuret S, Harrison NA, Consortium MRCI, et al. (2018): Interferon-Alpha Reduces Human Hippocampal Neurogenesis and Increases Apoptosis via Activation of Distinct STAT1-Dependent Mechanisms. *Int J Neuropsychopharmacol*. 21:187-200.
66. Popescu BO, Toescu EC, Popescu LM, Bajenaru O, Muresanu DF, Schultzberg M, et al. (2009): Blood-brain barrier alterations in ageing and dementia. *J Neurol Sci*. 283:99-106.
67. Turkheimer FE, Althubaity N, Schubert J, Nettis MA, Cousins O, Dima D, et al. (2021): Increased serum peripheral C-reactive protein is associated with reduced brain barriers permeability of TSPO radioligands in healthy volunteers and depressed patients: implications for inflammation and depression. *Brain Behav Immun*. 91:487-497.

68. Carloni S, Bertocchi A, Mancinelli S, Bellini M, Erreni M, Borreca A, et al. (2021): Identification of a choroid plexus vascular barrier closing during intestinal inflammation. *Science*. 374:439-448.
69. Seo JS, Mantas I, Svenningsson P, Greengard P (2021): Ependymal cells-CSF flow regulates stress-induced depression. *Mol Psychiatry*.
70. Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, et al. (2013): Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology*. 38:377-385.
71. Hladky SB, Barrand MA (2016): Fluid and ion transfer across the blood-brain and blood-cerebrospinal fluid barriers; a comparative account of mechanisms and roles. *Fluids Barriers CNS*. 13:19.
72. Del Bigio MR (2010): Ependymal cells: biology and pathology. *Acta Neuropathol*. 119:55-73.
73. Frank P, Jokela M, Batty GD, Cadar D, Steptoe A, Kivimaki M (2021): Association Between Systemic Inflammation and Individual Symptoms of Depression: A Pooled Analysis of 15 Population-Based Cohort Studies. *Am J Psychiatry*. 178:1107-1118.
74. Althubaity N, Schubert J, Martins D, Yousaf T, Nettis MA, Mondelli V, et al. (2021): Choroid plexus enlargement is associated with neuroinflammation and reduction of blood brain barrier permeability in depression. *Neuroimage Clin*. 33:102926.
75. Petanjek Z, Judas M, Simic G, Rasin MR, Uylings HB, Rakic P, et al. (2011): Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc Natl Acad Sci U S A*. 108:13281-13286.
76. Fleischer V, Gonzalez-Escamilla G, Ciolac D, Albrecht P, Kury P, Gruchot J, et al. (2021): Translational value of choroid plexus imaging for tracking neuroinflammation in mice and humans. *Proc Natl Acad Sci U S A*. 118.
77. Ricigliano VAG, Morena E, Colombi A, Tonietto M, Hamzaoui M, Poirion E, et al. (2021): Choroid Plexus Enlargement in Inflammatory Multiple Sclerosis: 3.0-T MRI and Translocator Protein PET Evaluation. *Radiology*. 301:166-177.
78. Vichaya EG, Malik S, Sominsky L, Ford BG, Spencer SJ, Dantzer R (2020): Microglia depletion fails to abrogate inflammation-induced sickness in mice and rats. *J Neuroinflammation*. 17:172.
79. da Fonseca AC, Matias D, Garcia C, Amaral R, Geraldo LH, Freitas C, et al. (2014): The impact of microglial activation on blood-brain barrier in brain diseases. *Front Cell Neurosci*. 8:362.
80. Schubert JJ, Veronese M, Marchitelli L, Bodini B, Tonietto M, Stankoff B, et al. (2019): Dynamic (11)C-PiB PET Shows Cerebrospinal Fluid Flow Alterations in Alzheimer Disease and Multiple Sclerosis. *J Nucl Med*. 60:1452-1460.
81. Alisch JSR, Kiely M, Triebswetter C, Alsameen MH, Gong Z, Khattar N, et al. (2021): Characterization of Age-Related Differences in the Human Choroid Plexus Volume, Microstructural Integrity, and Blood Perfusion Using Multiparameter Magnetic Resonance Imaging. *Front Aging Neurosci*. 13:734992.
82. Zhou YF, Huang JC, Zhang P, Fan FM, Chen S, Fan HZ, et al. (2020): Choroid Plexus Enlargement and Allostatic Load in Schizophrenia. *Schizophr Bull*. 46:722-731.
83. Svenningsson P, Kim Y, Warner-Schmidt J, Oh YS, Greengard P (2013): p11 and its role in depression and therapeutic responses to antidepressants. *Nat Rev Neurosci*. 14:673-680.
84. Dias C, Feng J, Sun H, Shao NY, Mazei-Robison MS, Damez-Werno D, et al. (2014): beta-catenin mediates stress resilience through Dicer1/microRNA regulation. *Nature*. 516:51-55.

85. Andrade C, Bolwig TG (2014): Electroconvulsive therapy, hypertensive surge, blood-brain barrier breach, and amnesia: exploring the evidence for a connection. *J ECT*. 30:160-164.
86. Bolwig TG, Hertz MM, Paulson OB, Spotoft H, Rafaelsen OJ (1977): The permeability of the blood-brain barrier during electrically induced seizures in man. *Eur J Clin Invest*. 7:87-93.