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Review Article

Sickness behaviour and depression: An updated model of peripheral-central immunity interactions

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ABSTRACT

Current research into mood disorders indicates that circulating immune mediators participating in the pathophysiology of chronic somatic disorders have potent influences on brain function. This paradigm has brought to the fore the use of anti-inflammatory therapies as adjunctive to standard antidepressant therapy to improve treatment efficacy, particularly in subjects that do not respond to standard medication. Such new practice requires biomarkers to tailor these new therapies to those most likely to benefit but also validated mechanisms of action describing the interaction between peripheral immunity and brain function to optimize target intervention. These mechanisms are generally studied in preclinical models that try to recapitulate the human disease, MDD, through peripherally induced sickness behaviour. In this proposal paper, after an appraisal of the data in rodent models and their adherence to the data in clinical cohorts, we put forward a modified model of periphery-brain interactions that goes beyond the currently established view of microglia cells as the drivers of depression. Instead, we suggest that, for most patients with mild levels of peripheral inflammation, brain barriers are the primary actors in the pathophysiology of the disease and in treatment resistance. We then highlight data gaps in this proposal and suggest novel lines of research.

1. Introduction

Depression, also known as major depressive disorder (MDD), is a common illness that affects ~5.0 % of the adult population (World Health Organisation, 2021) and is one of the three leading causes of disability worldwide (Global Burden of Disease Study, 2015). 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 (NHS_UK, 2021). 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 (NHS_UK, 2021).

A number of medications used to treat MDD mostly act by increasing monoamine levels in the brain (Delgado, 2000). Treatment efficacy is quite variable and must be tailored to the tolerance of the treatment that also varies substantially (Cipriani et al., 2018). 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 (Rush et al., 2006), and even fewer meeting criteria for both symptomatic and functional remission (Sforzini et al., 2021; Sheehan et al., 2011).

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 circulating mediators as important contributors to its pathophysiology (Miller and Raison, 2016); in particular, elevated markers of peripheral inflammation are associated with treatment resistance (Strawbridge et al., 2015). In this proposal paper 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

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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 in MDD cohorts from 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. At the same time, given the complexity and heterogeneity of the systemic immune response, the plethora of mediators involved and the still partial understanding of brain barriers modulation, the model points to the need of further experimentation to refine the mechanistic understanding of these brain-body interactions in human cohorts.

2. Depression as a disorder of immunity

A significant fraction of MDD patients exhibit elevations in inflammatory cytokines, acute phase proteins, chemokines, adhesion molecules, and inflammatory mediators such as prostaglandins, in peripheral blood (Dantzer et al., 2008; Miller and Raison, 2016). Increased peripheral inflammatory markers in MDD have been consistently replicated in many studies and further documented in recent *meta*-analyses and large studies (Osimo et al., 2019; Osimo et al., 2020; Pitharouli et al., 2021). 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) (Osimo et al., 2019; Osimo et al., 2020; Pitharouli et al., 2021). Interestingly, MDD patients also suffer from disruption in thermoregulation whereas fever, an hallmark of immune response, may be part of the stress response (Oka, 2018; Raison et al., 2014).

From an experimental medicine perspective, acute and chronic[1] administration of cytokines (or cytokine inducers such as lipopolysaccharide [LPS] or vaccination) can cause behavioural symptoms that overlap with those found in major depression (Bonaccorso et al., 2002; Capuron et al., 2000; Harrison et al., 2009; Reichenberg et al., 2001). 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 (Bonaccorso et al., 2002). At the same time, blockade of peripheral inflammation has been shown to reduce depressive symptoms in patients with severe and chronic inflammatory conditions (Abbott et al., 2015; Tyring et al., 2006). However, *meta*-analyses of randomised control trials (RCTs) have demonstrated a mixed picture whereas patients with MDD receiving anti-inflammatory agents have overall demonstrated a very heterogeneous response compared to those receiving placebo suggesting that the identification of subgroups that could benefit from such treatment and a better mechanistic understanding of peripheral-central immunity interactions in these populations might be warranted (Bai et al., 2020; Kohler et al., 2014).

3. 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 LPS (Bluthe et al., 1992), IL-1 (Kent et al., 1992), and the cytokine tumor necrosis factor (TNF)(Bluthe et al., 1991) (please see (Remus and Dantzer, 2016) for a review). The peripheral immune signal is transferred to the brain by separate pathways that are thought to work in parallel (Dantzer, 2018).

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 (Koren et al., 2021). 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 (Koren et al., 2021).

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 (D'Mello et al., 2009; Dantzer, 2009; Dantzer, 2018; Quan and Banks, 2007). Peripheral cytokines also induce the production of prostaglandins by BBB endothelial cells; once in the parenchyma, both prostaglandins and peripheral cytokines stimulate the activation of brain microglia (D'Mello et al., 2009; Dantzer, 2009; Dantzer, 2018; Quan and Banks, 2007). 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 (Miller et al., 2009). Cytokines also have the ability to alter important metabolic pathways, namely the kynurenine and tetrahydrobiopterin (BH4) pathways, which in turn can impair neurotransmission of monoamines, particularly serotonin, glutamate and dopamine (Capuron and Castanon, 2017; Capuron and Miller, 2011; Haroon et al., 2017).

4. 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) (Nestler and Hyman, 2010). Hence, we briefly discuss the evidence of the connection between immunologically-induced sickness behaviour, in humans and in animals, and depression and its treatments.

4.1. Face validity

In rodents, as well as in humans, sickness behaviour demonstrates significant aspects of MDD such as lethargy, anxiety, malaise, loss of appetite, insomnia, hyperalgesia, and failure to concentrate (Stieglitz et al., 2015). 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 (Felger et al., 2020). Subjects with no inflammation generally exhibit CRP concentrations <1 mg/L while those with inflammatory disease have plasma concentrations >10 mg/L (Felger et al., 2020). In the case of human cohorts with MDD, depressed subjects demonstrate mild inflammation, with CRP ~3 mg/L on average (Felger et al., 2020; Stieglitz et al., 2015). Importantly, treatment resistant patients display significantly higher CRP levels (~5 mg/l on average) (Cattaneo et al., 2020; Chamberlain et al., 2019).

While clinical, behavioural and peripheral data on MDD cohorts are abundant and demonstrate good correspondence with models of sickness behaviour, data on central inflammation are rare and more mixed. Increased cytokine levels have been demonstrated into the cerebrospinal

[1] Chronic indicates a condition or treatment lasting months as opposed to days or weeks.

fluid (CSF) of subjects that were suicidal (Levine et al., 1999; Lindqvist et al., 2009) but results in MDD were mixed with 2/3 of the studies reporting reductions or no-change of IL-6 and TNF-α concentrations and the remaining registering moderate increases (Enache et al., 2019).

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 K_d translocator protein (TSPO) (Turkheimer et al., 2015). TSPO-PET has demonstrated high levels of activation of microglia and astrocytes after acute peripheral LPS stimulation in rodents (Vicente-Rodriguez et al., 2021) and human volunteers (Peters van Ton et al., 2021; Sandiego et al., 2015). Note that LPS in humans generates levels of peripheral cytokines that are up to 100 times those detected in MDD cohorts. We have recently used a different peripheral immune challenge with a single injection of IFN-α (Roferon-A 3 million IU/0.5 ml solution for injection) that exhibited quite milder cytokine concentrations (with CRP reaching ~10 mg/L) than the one obtained with LPS but we detected no changes in TSPO in normal volunteers (Nettis et al., 2020) although the subjects clearly exhibited transient sickness behaviour. When considering MDD clinical cohorts, TSPO-PET data have demonstrated increases in signal that, however, are mild and localized particularly in the prefrontal regions (Hannestad et al., 2013; Holmes et al., 2018; Mondelli et al., 2017; Richards et al., 2018; Schubert et al., 2020; Setiawan et al., 2015). In short, clinical data in MDD do demonstrate elevated peripheral immune markers, but data on CNS cytokine are mixed while there is evidence of mild microglial activity; the relationship between TSPO-PET data and peripheral inflammation is described next.

4.2. 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 (Schubert et al., 2020). Lack of correlation could be due to methodological reasons, as TSPO signal in brain is small and difficult to quantify (Turkheimer et al., 2015) as well as not specific for microglia (Betlazar et al., 2020); 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 (Sandiego et al., 2015) and, interestingly, sequential LPS challenges have actually caused a decrease in brain TSPO levels in correspondence of peripheral increases in cytokines (Peters van Ton et al., 2021). Importantly, in our human IFN-α experimental model (Nettis et al., 2020), where cytokines peak at far lower concentrations that are closer to the ones measured in MDD patients, the TSPO-PET signal did not change 24 h after IFN-α, indicating lack of neuroinflammatory response to the peripheral challenge.

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 that is widely used as reviewed in (Varatharaj and Galea, 2017), LPS peripheral challenges in various experimental conditions leads to increased BBB permeability. However clinical evidence on changes of BBB permeability in MDD is scarce and mixed; increased CSF/albumin ratios were found in a sample of elderly women with depression (Gudmundsson et al., 2007) while a *meta*-analysis of VEGF, a plasma marker of BBB permeability, reported inconclusive results (Clark-Raymond and Halaris, 2013). In our IFN-α experimental model, VEGF in serum was actually reduced, indicating loss of permeability instead (Nettis et al., 2020). Very recently, dynamic contrast-enhanced (DCE-) MRI has been used in psychiatric cohorts and detected increased BBB permeability in a subgroup of bipolar patients (Kamintsky et al., 2020). 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 (Wengler et al., 2019a), has shown reduced water permeability (Wengler et al., 2019b).

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 (Rothermundt et al., 2003). 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 bipolar disorder (Ambree et al., 2015). Note that S100β is also expressed in white adipose tissue (adipocytes and adipose tissue macrophages) making the interpretation of variations in S100b circulating levels problematic in cross-sectional studies as it increases in overweight/obese subjects who represent a significant percentage of MDD patients. Interestingly however, in our longitudinal IFN-α experimental model, serum S100β protein did not change significantly (Nettis et al., 2020).

Hence, clinical data do not demonstrate a close relationship between peripheral and central immunity while the state of the BBB in MDD cohorts has yet to be well characterized.

4.3. Predictive validity

There is mixed preliminary evidence that higher levels of peripheral inflammatory markers may 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, did not demonstrate clinical benefit but post-hoc analysis did show that patients with higher levels of C-reactive protein (CRP >5 mg/L) benefited from the drug (Raison et al., 2013). These results led to a later RCT in patients with bipolar depression also using Infliximab as an add-on treatment in a sample enriched a priori on the basis of biochemical (CRP >5 mg/L) and/or phenotypic (e.g. high BMI, triglyceride or cholesterol levels, Diabetes I/II, heavy smoking, high blood pressure, migraine head-aches) where depressive symptoms were also not significantly reduced compared with placebo except for a sub-group with history of childhood trauma (McIntyre et al., 2019). A recent RCT in treatment resistant patients, using minocycline as augmentation therapy over antidepressants, has demonstrated efficacy over placebo only after post-hoc stratification by peripheral immune markers with those with CRP plasma levels >3 mg/L showing the greatest symptomatic improvement (Nettis et al., 2021). 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 (Soczynska et al., 2012).

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 (Borsini et al., 2018; Yirmiya et al., 2015). 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 updated model of peripheral/central immunity interactions that, in our view, better recapitulates that evidence illustrated so far.

5. An updated model of peripheral to central interaction for mild inflammatory states in MDD.

The model is sketched in Box 1, visualized in Fig. 1 and detailed below. As the title of this section suggests, we are concerned with subjects with MDD and mild peripheral inflammation. This range in fact

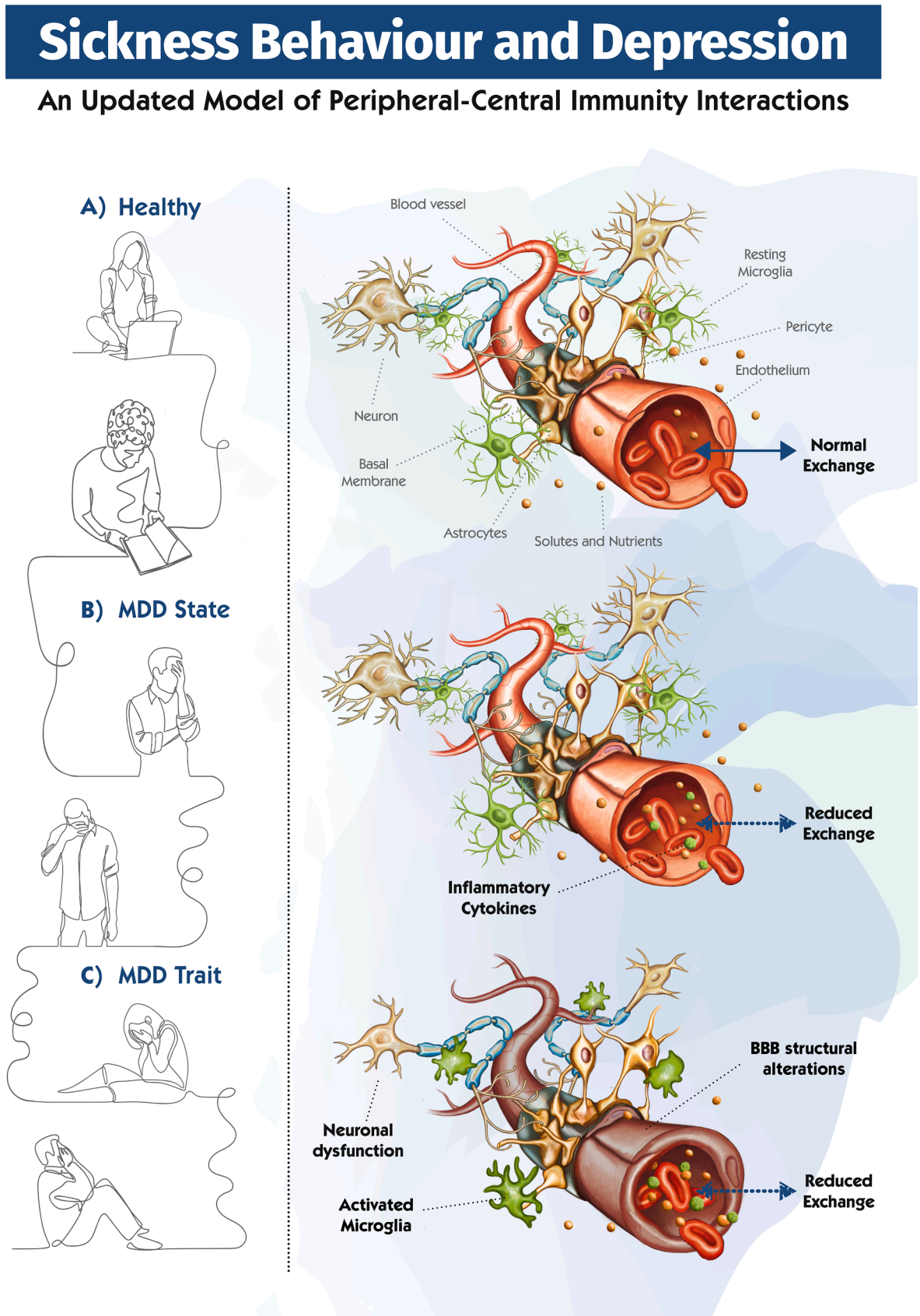

Fig. 1. Graphical representation of the model. In the healthy state, circulating cytokines are null or very low, the permeability of the barriers is normal, microglial cells are in resting state. A temporary increase in circulating cytokines reduces the permeability of the barriers disrupting homeostasis and causing mild sickness behaviour while microglial cells are still in resting state. 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.

should cover a large subgroup of the MDD population, at least those with CRP <10 mg/L, including those with evidence of resistance to standard antidepressant treatment (CRP average 5 mg/L) (Osimo et al., 2020). 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 disruption. Exclusion should also be extended to elderly subjects, where evidence exists of BBB impairment (Popescu et al., 2009).

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 (Turkheimer et al., 2021), the BBB and the blood-CSF barriers (e.g., the choroid plexus, CP). Indeed, the reduction in perfusion rates is substantial, beyond 50 % (Turkheimer et al., 2021).

The CPs are of particular interest in this context as they represent a component of the brain-blood interface more readily measurable in-vivo in clinical populations using standard MRI. The CPs are membranes, simpler than the BBB, made of an endothelial layer, a stroma layer and a layer of epithelial cells called cuboid cells; they control the molecular and immune traffic from the blood into the ventricular spaces and vice versa and produce the CSF (Bitanihirwe et al., 2022). In the clinical literature, volumetric increases of the CP are now considered a robust marker of brain inflammation (Fleischer et al., 2021). We have recently demonstrated increased CP volume in MDD cohorts and its association with reduced CP permeability and increased regional brain inflammation measured with PET (Althubaity et al., 2021). CP enlargement has also been observed in populations of which MDD is a prodrome, such as Alzheimer's disease (Schubert et al., 2019) or accelerated ageing (Alisch et al., 2021), and in psychiatric populations also associated with inflammation, such as schizophrenia (Zhou et al., 2020).

These data are further supported by the elegant results obtained by Carloni et al. (Carloni et al., 2021) 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 whole process resulting in a stress response. The authors note the close similarity between the gut barrier, that also demonstrates an epithelial layer, a stroma and endothelial layer in reverse order, and the anatomy of the CP. Hence, they hypothesize that the CP has a similar role to the gut barrier, e.g. to stop inflammatory messenger to reach the blood from the gut. They also demonstrated that, 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 (Carloni et al., 2021).

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 (Seo et al., 2021) 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 (Cattaneo et al., 2013). The depressive symptoms in the two models were fully rescued by viral expression of p11 in epithelial cells (Seo et al., 2021).

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

The permeability of the barriers is of great importance for brain homeostasis and its reduction is likely to affect a number of metabolic pathways. Endothelial cells in the BBB have a key role in the clearance of extracellular brain glutamate that is found in excess in models of inflammation-associated depression (Dantzer and Walker, 2014). Immune related BBB dysfunction is known to affect CNS drainage pathways, that are now collectively known as the "glymphatic system", hence impeding the clearance of metabolic products (Rustenhoven and Kipnis, 2022). More generally the BBB controls O2 and CO2 diffusion, fluid balance and neuroendocrine and solutes transport (Del Bigio, 2010; Hladky and Barrand, 2016), hence the reduction in permeability is likely to depress brain energetic production (Del Bigio, 2010; Hladky and Barrand, 2016). 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 (Frank et al., 2021).

Note that metabolism and inflammation have strong mechanistic links due to the large energetic cost of immune activity that must be matched by either increases of local ATP production, for example by boosting non-oxidative metabolism (e.g. Warburg effect), or by competitive reduction of tissue activity (Borst et al., 2019; Russell et al., 2019); in fact there is preliminary evidence that both inflammation and metabolic dysfunction contribute jointly to deficits in reward and motor circuits in MDD (Goldsmith et al., 2020). Our proposal does impinge on this relationship but speculates on a reverse loop whereas it is oxidative metabolic stress that elicits neuroinflammation and not *vice-versa*.

3. When inflammation carries on and becomes chronic, brain barriers undergo structural alterations that persist even after peripheral immunity subsides -> depressive trait[2].

While experimentally induced mild peripheral inflammation does not seem to cause microglial activation in humans (Nettis et al., 2020), mild microglial activity is however present in MDD (Schubert et al., 2020). 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 as demonstrated by a significant increase in the volume of the CP in MDD cohorts (Althubaity et al., 2021); this hypothesis is supported by similar observations in patients with relapsing remitting multiple sclerosis with chronic inflammatory profiles (Fleischer et al., 2021; Manouchehri and Stuve, 2021; Ricigliano et al., 2021).

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 and, for this reason, are the most metabolically active (Petanjek et al., 2011); disturbance in energetic homeostasis will then place these tissues under stress with the generation of reactive oxygen species, leading to oxidative damage that will elicits a microglia response (Merelli et al., 2021). In fact, in our data on MDD subjects, CP volume correlated with TSPO-PET signal in prefrontal regions (Althubaity et al., 2021).

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.

(*continued on next page*)

[2] Depressive trait, (also termed depressive personality Klein, D.N., Bessaha, M.L., 2009. Depressive personality disorder. In: Blaney, P.H., Millon, T. (Eds.), Oxford Textbook of `psychopathology. Oxford University Press, New York, pp. 738–751.), here refers to a collection of depressive behaviours or characteristics that persist through time and do not subside once the inflammatory event ceases.

(*continued*)

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

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*.

Note that the main 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. In fact, potentially, microglial activity could have a compensatory, beneficial role in MDD, as 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 (Vichaya et al., 2020).

6. Conclusion

In our view, the model proposed here recapitulates well the vast tapestry of old and new evidence on peripheral and central immunity communication in the context of inflammation-induced depression. The novelty stands in the suggestion of a primary role of the brain barriers as key actors of the relationship between the two immune compartments; where the barriers act as elements of a defence mechanism and are contracted in the presence of peripheral immune reactivity, in order to protect the brain as posited by Carloni et al. (Carloni and Rescigno, 2022); this response disrupts brain homeostasis and affects the energetic balance, inducing depressive symptoms. When this response becomes chronic, the BBB functional changes turn into structural modifications and the tissues of the cortex that are most metabolically active, ultimately, also become chronically stressed and generate a microglia response (da Fonseca et al., 2014).

It is important to stress that the model proposed does not apply across all MDD cohorts but only to those with mildly raised peripheral immunity (CRP <10 mg/L) and excludes those with bipolar disorder, the elderly and those at suicidal risk where the BBB may degenerate; increased BBB permeability has been recently reported in the hippocampus of a post-mortem MDD cohort with a high percentage of suicide (7/16) (Greene et al., 2020) and BBB permeability increase was associated with suicidal risk in an older CSF study across psychiatric cohorts (Niklasson and Agren, 1984).

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. There is very little data on brain barriers permeability in MDD hence the hypotheses proposed here need further testing with either PET or MRI studies. Note that the BBB permeability measures reported here tap into different aspects of BBB transport that spans water diffusion and molecular passive and active transport mechanisms with differential involvements of endothelial cells, gap junctions, pericytes and astrocytes (Bagchi et al., 2019). For example, the tracers used in the PET studies reported above, are mildly lipophilic neutral molecules that get through the endothelial layer of the BBB by endocytosis while the water transport imaged by MRI is thought to generally happen through the gap-junctions. The clinical imaging of CP function and structure also poses some challenges depending on the technique used; in particular, structural CP studies still rely on manual delineation that is cumbersome (Althubaity et al., 2021).

Ultimately, an important part of the mechanistic chain purported here is the effect of brain barriers on homeostasis and metabolism. There are no studies of O2 metabolism in MDD, likely given the complexity of the measurements involved. Hence the hypothesis presented here is speculative but can be tested in the future either using the precise, but logistically cumbersome, triple oxygen PET method (Frackowiak et al., 1980) or novel MRI based methodologies for the mapping of O2 extraction (Blockley et al., 2015).

Given the present lack of data for this part of the proposed model, it is important to purport a potential opposite mechanism whereas microglia alterations could contribute the development of the permeability changes. For example, Haruwaka et al. (Haruwaka et al., 2019) used a peripheral chronic LPS model (1 mg/kg/day for 7 days i.p.) to demonstrate that microglia respond to inflammation by activation and migration towards cerebral vessels before any detectable change in BBB permeability. Although the peripheral immune activation in this model is actually quite severe (an acute challenge can be achieved with half of the daily dose (Vicente-Rodriguez et al., 2021)) and leads to BBB disruption, the initial physical contacts between microglia and endothelial cells protect BBB integrity via expression of the tight-junction protein Claudin-5. Similar stabilization effects of microglia on the BBB in the presence of inflammation have been reported in-vitro (Spampinato et al., 2022).

The model we propose 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 (Turkheimer et al., 2021) – a tighter BBB would then make the entry of all these compounds to the brain less efficient. The mechanism can then be easily tested by combining measures of BBB permeability and CSF sampling after treatment with monoamine-based therapies.

In terms of treatment targets, the model confirms the notion that anti-inflammatory strategies are required to normalize circulating immune messengers. Little is still known about the therapeutic modulation of brain barriers permeability in MDD. However pre-clinical data suggests novel targets on endothelial (e.g., β-catenin 1 signalling pathway) and epithelial cells (e.g., protein p11) may address brain barriers structural and functional abnormalities that may persist even after the normalization of peripheral immunity. In fact, it may also of interest to evaluate the effects of both anti-inflammatory strategies and standard monoamine interventions on brain barrier permeability. It has been reported in the literature that standard antidepressants, such as fluoxetine and imipramine, reduce inflammatory markers and/or increase brain perfusion (Ungvari et al., 1999; Yirmiya et al., 2000). The protein p11 (also known as S100A10) that is known for its role in serotonergic signalling and the regulation of gene transcription (Svenningsson et al., 2013) has a key role in the regulation of epithelial function. Lastly, the efficacy of electroconvulsive therapy has been accrued, at least in part, to its associated increases in BBB permeability (Andrade and Bolwig, 2014; Bolwig et al., 1977).

The fact that reduction in brain barriers' perfusion is associated with distant stressful events, such as child abuse (Turkheimer et al., 2021), also opens 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 neuronal stress, with microglia activation possibly a coincidental epiphenomenon or even a protective mechanism, rather than the primary culprit. The hypothesis is based on a small number of experimental and cohort studies hence further replication is also warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Data availability

No data was used for the research described in the article.

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