Immunological perturbations, psychiatric disorders and associated therapeutics: a new era for psychiatry?

Abstract

The three main theories explaining major mental illness, namely mood disorders, psychoses and dementias, have been partially discredited. Alongside this, there are emerging links between perturbations of the immune system and the onset and phenotypic features of these disorders. This article outlines the alternative pathophysiology and suggests potential treatments which could improve disease burden and avoid the need for psychotropic medication, with their associated side effects and relapse following withdrawal.

Key words: COVID-19; Gut microbiome; Microglial activation; Oligomer clearance; Synaptic pruning

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Introduction

Most consultations and treatment in clinical psychiatry relate to three major syndromes: mood disorders, neurodevelopmental conditions (including the major psychotic conditions) and neurodegenerative dementias. Pathophysiological explanations have been based on presumed neurochemical imbalances in the brain. However, as a result of the less than full effectiveness of neurochemical inhibitors and enhancers in clinical practice, researchers have been questioning the validity of the neurochemical theory of psychiatric disorders.

An analysis of pooled data suggested that major mood disorders are not associated with deficits of serotonin production or distribution (Moncrieff et al, 2022); the basis of the monoamine hypothesis of mood disorders. Furthermore, the dopamine hypothesis of schizophrenia – symptoms are caused by excess dopamine production – appears to be overly simplistic, as inactivity of the pre-frontal cortex appears to lead dopamine to be diverted to the striatum thus causing the positive symptoms (Kindler et al, 2018). Finally, Alzheimer's type dementia does not appear to be the result of a deficit of acetylcholine (the cholinergic hypothesis) or excess production of amyloid beta (the amyloid hypothesis), rather the result of inadequate clearance of misfolded proteins in general (Morris et al, 2014), with secondary effects on neurochemicals including acetylcholine.

Following improvements in ligand-linked neuroimaging, researchers are investigating neuroimmunity including neuronal pruning, activity of the glymphatic system and effects of cytokines. It is hoped that the results of these studies will lead to new treatments, replacing the neurochemical enhancers and inhibitors currently used to treat patients with psychiatric conditions.

Major depression

Major depression is linked with excess microglial activity in the pre-frontal cortex (Rial et al, 2016), secondary to stress-induced excess cortisol production or as a result of systemic inflammation caused by physical disease including infections and autoimmune conditions. Consistent with this, a variety of non-steroidal anti-inflammatory drugs has been used successfully to treat resistant depression (Feltes et al, 2017). Selective serotonin-reuptake inhibitors, atypical antipsychotics and psychedelic agents such as ketamine and psilocybin have anti-inflammatory properties, which might explain their antidepressant effects and their effectiveness in intractable depression (Davis et al, 2021).

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Observations that a single course of antibiotics increased the risk of mood disorders twofold lead to interest in dysfunction of the gut microbiota in relation to mood disorders (Prichett et al, 2022). Similar concerns have been expressed about long-term exposure to dietary glyphosate, which disrupts tight junctions between endothelial cells, resulting in harmful bacteria (*Escherichia coli*, Clostridia) entering the subendothelial lamina propria. This leads to production of T-17 inflammatory cells, which migrate to the brain parenchyma causing excess microglial activity. Conversely, a healthy gut microbiota stimulates the development of T-reg (regulator) cells which modifies inflammation in the body and brain. These findings have led to use of probiotic species (eg *Lactobacillus*) and faecal transplantation (via ingested capsules from a suitable donor) to reverse mood disorders (Koppenol et al, 2022); with this study showing a significant reduction in severity of depressive and anxiety symptoms 4 weeks after faecal transplantation in group of 49 patients receiving treatment for *Clostridioides difficile* infection.

The gut microbiome also communicates with the brain via the vagus nerve and the hypothalamic–pituitary–adrenal axis. The vagus nerve traverses the gut, the heart and the brain (Breit et al, 2018) with bidirectional transfer of impulses. A healthy gut microbiota can produce vagal impulses which modulate the neural network of the heart as well as those of the limbic system. Electrical stimulation of the vagus nerve has been used for the adjunctive treatment of atypical depression. Furthermore, excess activation of the hypothalamic–pituitary–adrenal axis as a result of unremitting stress can affect the gut with inflammation of the immune compartment (Farzi et al, 2018).

Psychoses, autism and attention deficit hyperactivity disorder

Synaptic pruning via microglial scavenger cells allows the brain to 'fine tune' neuronal circuits and maintain plasticity. Microglia, in their usual neuroprotective manifestation, use cytoplasmic projections to check surrounding synapses. Chemokines generate 'find me' and 'eat me' signals to transform microglia to a phagocytic phenotype. Furthermore, replicating neurones produce a chemokine called fractalkine which binds to the microglial receptor CX3CR1 causing microglial phagocytosis of selected synapses (Jones et al, 2010). Astrocytes also secrete transforming growth factor beta to help microglia prune synapses via the complement cascade (C1q, C4, C2 and C3). Microglia can also be activated (specifically in the pre-frontal cortex) by systemic inflammatory cytokines such as interleukin 6 in the presence of acute stress. In healthy adults not facing acute stress, there is genomic blockade of CX3CR1 to reduce microglial activation, promoting neurogenesis and synaptic growth (Tirone et al, 2013). A healthy brain maintains a balance between synaptic pruning and synaptic proliferation.

Typically, there are three 'seasons' of synaptic pruning within a person's lifetime (Lieberman et al, 2019). From birth until 2 years of age, a whole brain prune occurs to develop sensory–motor circuitry. A further spell typically occurs between the ages of 11 and 15 years, to integrate motor and emotional responses. The onset and duration of these spells is genetically directed. A further spell of more selective pruning occurs in early adulthood (18–25 years), predominantly involving the pre-frontal cortex, to develop executive function. This appears to be mainly directed by life events, for example leaving home or starting work.

It has been hypothesised that variations in timing and degree of neuronal pruning can occur, resulting in neurodevelopmental disorders (de Silva, 2018; Sakai, 2020; Germann et al, 2021). Markedly limited pruning appears to be linked with autism, and attention deficit hyperactivity disorder appears to be linked to reduced rate velocity of pruning (without major seasonal variation), with full pruning achieved by adulthood. Schizophrenia, bipolar disorder and schizoaffective disorder appear to be associated with excessive pruning during the usual seasons, predominantly affecting pre-frontal areas in people with schizophrenia (active in executive functioning), and bilateral anterior and subgenual cingulate cortices in people with bipolar disorder (areas related to mood awareness). Threatening life events appear to 'reignite' pruning in people with these conditions outwith the typical seasons.

Evidence for this hypothesis involves longitudinal magnetic resonance imaging scanning of adolescents presenting with schizophrenia compared to siblings and healthy controls (Thompson et al, 2001). Over a 5-year period, a fourfold excess loss of grey matter was

Table 1. Evidence for influence of synaptic pruning on psychiatric conditions

Condition	Pruning changes	References	Strength of evidence
Schizophrenia	Excess pruning of pre-frontal cortex	Thompson et al (2001), Hakobyan et al (2005), Bloomfield et al (2016)	Strong (as a result of serial scanning over time of high risk people and first-degree relatives)
Bipolar disorder	Selective excess pruning (cingulate–thalamic–cerebellar axis)	Singh et al (2012), Strakowski et al (2012)	Moderate (some longitudinal and serial scanning)
Attention deficit hyperactivity disorder	Slowed brain maturation and ?synaptic pruning	Shaw et al (2007), Vaidya (2012), Walker et al (2012)	Weak (confounding caused by stimulant medication exposure, symptom variation, lack of serial scanning)
Autism	Lack of synaptic pruning, leading to excess white matter insulation	Courchesne and Pierce (2005), Tang et al (2014)	Weak (confounding caused by sex, IQ, lack of serial scanning, small numbers of subjects)

seen in adolescents with schizophrenia compared to controls, with their siblings showing a similar loss which thereafter returned to volumes of healthy controls. A positron emission tomography study has shown evidence of excess microglial activation in people with schizophrenia compared to control subjects (Bloomfield et al, 2016). Immunological studies in people with schizophrenia have shown alterations in the complement cascade, with excess activity of C1, C3 and C4 and reduced activity of C2 compared to controls (Hakobyan et al, 2005).

Imaging suggests that levels of synaptic pruning are lower in people with attention deficit hyperactivity disorder than those in people with schizophrenia, with evidence of slower maturation of the frontal and pre-frontal areas (Shaw et al, 2007). In people with autism, diffusion tensor imaging has shown limited long track connections between the different brain lobes alongside excessive local connections. Reduced overall microglial activation has also been observed (Walker et al, 2012) (Table 1).

Treatments being considered to reduce excess pruning include minocycline, which reduces microglial activation. This is currently used in people with psychosis as augmentation of usual antipsychotic medication (Krynicki et al, 2021). Alternatively, increasing neurogenesis to treat damage caused by excess pruning could be undertaken by increasing the expression of brain-derived neurotropic factor via exercise and sleep hygiene, or in future, using epigenetic modification. In vivo maturation of stem cells harvested from bone marrow to T-reg cells can provide neuroprotective potential (Machhi et al, 2020).

Dementias

If it were possible to prompt microglia to clear misfolded oligomers from the brain parenchyma it might be possible to prevent the development of dementia (Sweeney et al, 2017). Each type of dementia is characterised by the presence of different oligomers; amyloid beta (Aβ) in Alzheimer's disease, alpha synuclein in Parkinson's dementia and a combination of tau and DP-43 in frontotemporal dementia.

Around 25 years ago, Aβ antigens were administered to people with Alzheimer's disease to produce antibodies. This showed clearance of amyloid from the brain parenchyma but deposition in the glymphatic system, that caused meningoencephalitis in some people (Boche et al, 2008). Vaccine development had subsequently languished until the development of mRNA technology. A combined Aβ and tau antigenic vaccine has been produced that is currently undergoing human trials. Monoclonal antibodies are being used to 'mark' amyloid for immune clearance; the latest being lecanemab for slowing cognitive decline in people with early Alzheimer's disease (van Dyck et al, 2023).

Another option uses the non-specific effects of repurposed vaccines to improve the performance of microglia. It has been suggested that bacillus Calmette–Guérin (BCG) boosters can improve the phagocytic function of microglia in clearing oligomers (de Silva, 2020), probably through 'trained immunity' involving epigenetic modification (Chen et al, 2023). BCG boosters have shown reductions in the rate of conversion to clinical Alzheimer's disease;

a serendipitous finding in a trial to treat bladder cancer (Weinberg et al, 2023). A prospective trial of the BCG booster is currently underway in a group of older adults, looking at effects on biomarkers for Alzheimer's disease (https://www.clinicaltrials.gov/study/NCT04507126).

COVID-19

There are emerging concerns about neuropsychiatric features of 'long COVID' (symptoms lasting over 6 months after the initial infection). A retrospective 2-year follow-up study of over 1.5 million people diagnosed with clinical COVID-19 showed significant increases over baseline incidence of new onset psychoses, seizures and dementias (Taquet et al, 2022). There was also an excess of subjective 'brain fog' among post COVID-19 subjects. Neuroimaging studies have shown loss of whole brain volume in subjects infected with SARS-CoV-2 (Douaud et al, 2022). Furthermore, reduced numbers of T-reg cells are observed, alongside increased levels of inflammatory cytokines compared to non-infected subjects (Dhawan et al, 2023).

Future research directions

The major confounder in terms of future research is the lack of consistency and specificity between psychiatric diagnoses, cluster analytic findings and genome-wide association studies (Hyman, 2010). Efforts to remedy this are ongoing, with successive iterations of psychiatric classification systems. There is a plethora of findings on the link between immune perturbation, specifically changes in microglial function, and the major psychiatric disorders, but these are often based on single studies with small sample sizes. Meta-analyses and studies with larger sample sizes are needed. Clinically, comparison of the effect sizes of novel immunological therapies with those of traditional psychotropics would be helpful, for example use of psychedelics vs combination antidepressants in people with resistant depression.

Naturalistic ('real world') treatment trials, for example using faecal transplants or psychedelics such as ketamine to treat resistant depression, anxiety and compulsions, need to be scaled up. The key question for neurodevelopmental disorders is how to modulate synaptic pruning, although this is still in vitro research. In vivo electromagnetic stimulation could also affect microglial function (Lennikov et al, 2022).

The non-specific benefits of repurposed vaccines like BCG for slowing manifestations of cognitive impairment before the onset of dementia needs to be investigated further, as these vaccines also have a good safety record. Novel vaccines using mRNA technology may be effective in treating the early manifestations of cognitive decline predementia in people at high risk, for example, as signalled by their ApoE allele profile (Husain et al, 2021), and comorbid cardiometabolic risk.

Conclusions

Pathophysiological explanations of psychiatric disorders are moving away from neurochemical imbalances towards ideas emanating from neuroimmunology, with emerging imaging and clinical findings justifying this move. Therapeutic implications include manipulating the strength of the brain immune processes such as modifying microglial activity, reducing the expression of cytokines in the brain, influencing T regulator (T reg) cell migration to the brain, and improving the gut microbiota using faecal transplantation to influence the gut-heart-brain vagal nerve activity. However, emerging immune based therapies will initially be used as adjuncts to 'conventional' psychiatric treatments pending more robust, replicated findings.

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Conflicts of interest

The author declares that there are no conflicts of interest.

Key points

- Inflammatory activity of microglia in the pre-frontal cortex appears to be linked with major depression, with anti-inflammatory agents (including ketamine and non-steroidal anti-inflammatory drugs) and microglial modulators (such as minocycline) showing promise as adjuncts in treatment.
- Perturbations of the usual synaptic pruning periods have been shown in serial structural imaging to precede onset of major psychoses and bipolar disorder, with autism and attention-deficit hyperactivity disorder associated with reduced synaptic pruning.
- Polyvalent vaccines have been shown to reduce the rate of conversion to Alzheimer's and associated dementias, probably by 'trained innate immunity' via epigenetic means.
- There is concern that people who experience clinical COVID-19 are more likely to have long-term cognitive consequences, alongside an increased incidence of psychoses, seizures and subjective 'brain fog'.

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