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Brain microglia in psychiatric disorders

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Abstract

The role of immune activation in psychiatric disorders has attracted considerable attention over the last two decades, contributing to the rise of a new era for psychiatry. Microglia, the macrophages of the brain, are progressively becoming the main focus of the research in this field. Here we critically review the literature on microglia activation across different psychiatric disorders, including both post-mortem and in vivo studies in humans and experimental studies in animals. We find that, while microglia activation is present across psychiatric disorders, there is no association with specific diagnostic categories. Moreover, the findings from these studies highlight that not all psychiatric patients have microglial activation. Hence, the questions arise on what is causing neuroinflammation in these cohorts and what are its implications. We discuss psychosocial stress as one of the main factors determining microglia activation in patients, and explore the relevance of these findings for future treatment strategies.

Key words: microglia, depression, psychosis, bipolar disorder, neuroinflammation, stress.
1. Introduction

The role of immune activation in development of psychiatric symptoms was first hypothesised almost a century ago. Although over the past few decades strong evidence has clearly demonstrated increased levels of peripheral inflammatory biomarkers in both patients with psychosis or affective disorders, it remains still unclear whether this peripheral immune activation is associated with immune activation in the brain, and ultimately if this is a causal or secondary pathological mechanism in these disorders. In the last decade, studies investigating the innate immune response in the central nervous system (CNS) have started to emerge, focussing in particular on the activation of microglia, which act as resident macrophages of the CNS. The aim of this review is to summarize and critically discuss studies investigating central immune activation across psychiatric disorders. Throughout the manuscript, we will use the term “neuroinflammation” to define activation of immune cells in the CNS; therefore in this context, our use of the term “neuroinflammation” would not include the attraction/recruitment processes of other cells into the CNS as traditionally intended when using term “inflammation”.

2. Phenotype and function of microglia

Microglia are the resident macrophages of the CNS and represent 5-10% of total CNS cells. One of the main recognized functions of microglia is to provide the brain first line of “self-defence” from tissue damage and infection, including pathogen recognition, phagocytosis and antigen presentation. On top of this important function, microglia also regulate a wider series of processes needed for CNS development and homeostasis, including control of cell number and formation and refinement of neural circuits.

In the healthy brain, microglia are located relatively uniformly throughout the parenchyma. The morphology of microglia has been suggested to reflect their functional capacity. Specifically, in a healthy brain, microglia tend to be in a quiescent state and present a downregulated phenotype.
displayed by a ramified shape with short, fine, highly motile processes, which allow an increased surface area for tissue surveillance. When an insult occurs (injury, inflammation), microglia morphology changes over time with shortening and and extensive branching of processes, hypertrophy of the cell body and the release of different inflammatory mediators, including cytokines. Classically, this is referred to as microglial activation.  

Recently the field has tried to move beyond this and differentiate sub-types of reactive microglial phenotypes, depending on the nature of the immune-related signals that they are exposed to. Specifically, previous studies have described an M1 phenotype, induced by molecules like lipopolysaccharide (LPS), which releases pro-inflammatory mediators; and an M2 phenotype, induced by anti-inflammatory molecules (e.g. interleukin (IL)-4), which releases major anti-inflammatory cytokines to antagonize the pro-inflammatory responses. Following this differentiation, activated microglia could therefore be either cytotoxic or neuroprotective; therefore, although brain pathology is usually associated with activation of microglia, it remains unclear if, in the context of psychiatric disorders, this activation is beneficial or detrimental. Indeed, it is also debated if this represents real inflammation, or simply a homeostatic, adaptive function. More recently, with the increased body of research on microglia, the classification of M1 and M2 has been challenged. This is due, on one hand, to the fact that the M1/M2 classification has been developed mainly from the study of peripheral macrophages rather than microglia, and secondly to the fact that the definition of the M1/M2 phenotype has been developed from the exposure of microglial cells to stimuli in vitro, while the M1 and M2 states consistently fail to emerge as isolated phenomena in vivo. The microglial M1/M2 classification is therefore gradually disappearing, while it has more recently suggested that the microglia phenotype may vary along a continuum.

A further important methodological point is that this morphological analysis alone is often used to report on glial activation state. In other words, whilst microglia undergo cytoskeletal
rearrangements that alter their morphology as described above, these morphological changes may not accurately represent an “active” inflammatory profile. In particular, in contrast to macrophages, a recent study could not identify morphologic differences between M1 and M2 adult human microglia. Moreover, a previous study in mice following peripheral LPS injection found a correlation between elevation in cytokine expression from microglia and active sickness behavior, however this preceded any alteration in microglia morphology. In fact, morphological alterations in microglia following LPS were delayed and only evident during the resolution/recovery phase of the immune response to LPS.

3. **Evidence of microglia activation in psychiatric disorders**

Over the past years increasing evidence has supported the role of activated microglia in the development of psychiatric disorders. However, some of the most interesting data have come from animal models of depression. Here we review first the evidence from post-mortem studies and then data from *in vivo* positron emission tomography (PET) studies. We will then summarise indirect *in vivo* neuroimaging evidence of central immune activation, tested using magnetic resonance imaging (MRI) techniques.

3.1 **Immunohistochemistry/Post-mortem studies**

A recent meta-analysis of post-mortem studies in schizophrenia has identified a total of 22 studies investigating microglia. Eleven of these studies found increased levels of microglia markers, while 3 studies reported a decrease; 8 studies did not detect any difference. Most of the studies focussed on immunostaining or gene expression of HLA-antigens, since induction of major histocompatibility complex class II in microglia is considered a sensitive marker of neuroinflammation in histological studies. It has been suggested that inconsistencies across the studies may be partially due to the heterogeneity in study design, from the type of brain region analysed to the markers measured and of course to the stage of the disorder. Furthermore, although few studies considered the effect of
death by suicide on their measurements, many of the studies included in this meta-analysis did not report these data. Suicide has been linked to increased neuroinflammation (as described more in detail below) and the lack of this information is an important limitation in the interpretation of these data.

A recent study has provided the first evidence of increased microglial activation in post-mortem brain samples from middle-aged depressed people who died by suicide. 12 Previously, Steiner et al 13 found increased cerebral grey matter HLA-DR-immunoreactive microglial densities in people who died by suicide; however, this was not specific for patients with depression as the study included patients suffering from schizophrenia or affective disorders. More recently, Schnieder and colleagues 14 investigated markers of neuroinflammation, including density of microglia, in post-mortem brains of patients with affective disorders, schizophrenia and subjects with no psychiatric diagnosis. The authors did not find an effect of psychiatric diagnosis but found a significant effect of suicide on density of perivascular cells in the dorsal white matter. According to the authors, the findings, which seem to be more specific for suicide than for a psychiatric diagnosis, support the stress/diathesis model of suicide: according to this model, an acute stress could activate an immune response in the brain that may put an individual at higher risk for suicide. 14 Finally, one post-mortem study using next generation sequencing to quantify neuroimmune mRNA expression showed an increase in inflammatory response pathways in the dorsolateral prefrontal cortex of patients with schizophrenia compared with healthy controls, 15 which was present in approximately 40% of patients with schizophrenia.

3.2 *PET/In vivo studies*

Increased activation of microglia *in vivo* can now be investigated with PET using radioligands for the 18kD translocator-protein (TSPO). TSPO is a five-membrane domain protein localized mainly in the outer mitochondrial membrane of steroid-synthesizing cells, including those in the central nervous
system, endothelial and glial cells in particular. One of its main functions is the transport of the substrate cholesterol into mitochondria, a prerequisite for steroid synthesis. Peripheral LPS injection in human primates has been shown to increase TSPO expression in a uniform manner across the brain. Elevation in TSPO levels is associated with microglial activation and is robustly associated withIonised calcium adaptor binding protein -1 (Iba1) positive cells in pre-clinical model as well as histological markers of brain activation in human post-mortem tissue.

\[^{11}C\]-(R) PK11195 is one of the main radiotracers that have been used to study brain TSPO expression in vivo. However, given the increasing interest in studying neuroinflammation in vivo, a number of second-generation TSPO radiotracers have been developed with increased affinity and possibly improved signal-to-noise ratio. The studies below should be interpreted in the light of major methodological problems affecting the quantification of TSPO density using PET: first, the affinity of second-generation radiotracers for the TSPO depends on the recently discovered rs6971 nucleotide polymorphism in the TSPO gene (rs6971); and, second, quantification is further hampered by the cellular heterogeneity of TSPO in brain tissue (that is present in microglia, astrocytes but also endothelium), the presence of TSPO (and its variability) in blood cells, and the high affinity of TSPO radioligands for plasma proteins, and particularly for proteins upregulated during peripheral inflammatory events. Thus, peripheral inflammation is likely to increase the retention of these radiotracers in plasma thus reducing brain uptake. Currently there are no analytical methods sensitive enough to correct for these effects, which may result in the underestimation of TSPO density in the diseased cohorts.

A summary of the TSPO-PET studies conducted until now in patients with psychosis, depression or bipolar disorder is reported in Table 1.
To date, three studies have been published investigating microglia activity using TSPO-PET brain imaging in patients with depression. Two of these studies reported increased TSPO expression in depression and one found no difference. The negative study investigated brain TSPO expression in patients with mild-to-moderate depression and low peripheral inflammation (defined as blood C reactive protein (CRP) levels below 5mg/l); in contrast, the two studies reporting increased TSPO expression in patients with depression focussed on patients exhibiting more severe depression or significantly higher peripheral inflammation. The only study so far published in patients with bipolar disorder showed an increase in $[^{11}\text{C}]$PK11195 binding in the right hippocampus of patients with bipolar disorder. Most patients were euthymic at time of the imaging.

To date, nine studies have been published investigating microglia activity using TSPO-PET brain imaging in patients with psychosis, with three studies finding an increase in TSPO binding, one finding an increase in medicated patients but not in drug-naïve patients, and the other five not finding significant differences between patients and matched controls. Some of the inconsistencies across the studies could be partly be explained by the above-mentioned methodological problems when using second-generation radiotracers. In particular, while $[^{11}\text{C}]$PK11195 quantification uses only brain data and seeks to quantify microglial activity using as an inflammation-free tissue in the parenchyma detected by automatic computing methods, the quantification of second generation tracers, like $[^{18}\text{F}]$FEPPA, uses both plasma and brain radioactive concentrations. In our view, TSPO reductions could thus be due to the anomalous retention of the tracer in blood due to increased plasma protein binding caused by peripheral immunity, as previously mentioned, that is not accounted for in the quantification.

In agreement with this view, in the study by Bloomfield et al, the data showing an increase in patients with schizophrenia, obtained using plasma radioactivity as input for quantification, became evident only when data were further normalized to the whole brain uptake. However, in other
studies the findings remained negative even after the distribution volume was corrected for the whole brain grey matter TSPO binding; highlighting that the discrepancies across studies may not all be ascribed to methodological differences.

The most recently published study reported no differences in $[^{11}C]$PK11195 binding between antipsychotic-free patients and controls but found increased $[^{11}C]$PK11195 binding in medicated patients with schizophrenia compared with controls, perhaps suggestive of a possible effect of antipsychotics on TSPO expression. Another possible interpretation of the increased TSPO binding in the medicated patients by Holmes et al, is that the increased TSPO binding denotes a condition of treatment-resistance, since the medicated group of patients in this study was significantly symptomatic despite treatment with antipsychotic.

3.3 **Anatomical and Diffusion MRI correlates of microglia activation**

Contrary to PET, MRI methods lack specificity to detect microglia activation. They can be used however to provide indirect measures of neuroinflammation, such as blood-brain barrier breakdown, interstitial microenvironment changes, cellular infiltration and gliotic reaction.

The interpretation of the $T_2$ relaxation time signal has been taken by some as providing indirect evidence of neuroinflammation. This is because $T_2$-weighted images are sensitive to molecular motion and to interactions between neighbouring molecules. As such, they provide high contrast for cerebrospinal fluid, which has application in pathologies characterised by water accumulated within tissue. However, the $T_2$ signal could be increased by other molecular changes that occur in tissue composition and in iron, hence the exact interpretation of its contrast remains uncertain.

Some studies have used Magnetisation Transfer Imaging and provided values for Magnetisation Transfer Ratio (MTR), which should be sensitive to changes in the water content of tissue due to
inflammation. However, the fact that MTR might also reflect demyelination complicates evidence generated in studies of psychiatric disorders.

Diffusion Tensor Imaging (DTI) is another approach used to investigate white matter microstructure. However, the two main measures provided by DTI, Fractional Anisotropy and Mean Diffusivity, are not specific, and can reflect alterations in myelination, fibre organisation or membrane permeability. However, more recently, free-water fraction Diffusion Tensor Imaging has been proposed to better reflect the presence of neuroinflammation in white matter.

While there have been some functional MRI studies of models of inflammation-induced depression, we did not identify any anatomical MRI or DTI study that have used the measures described above to evaluate the presence of neuroinflammation in patients with depression or bipolar disorder. A few neuroimaging studies have evaluated T2 signal in MRI scans of relatively small samples of patients with schizophrenia. These studies have mostly found an increase of the T2 signal in these patients, particularly in the frontal and temporal cortex white matter. These findings are suggestive of neuroinflammation; however, as mentioned above, increase in T2 signal could reflect other type of changes in tissue composition.

Magnetization Transfer Imaging studies have reported conflicting findings. Some have reported significantly higher MTR in the uncinate, arcuate, and inferior frontal occipital fasciculi of patients with schizophrenia in comparison to healthy controls, and interpreted as evidence of neuroinflammation. However, others have found decreased MTR in various areas, including frontal and temporal regions, and in the uncinate and superior occipitofrontal fasciculi, cingulum bundle, corpus callosum, internal capsule, and fornix, in patients with schizophrenia compared with healthy controls, and no evidence of MTR differences in the thalamus.
Studies that have used free water DTI have shown evidence that supports the presence of neuroinflammation already at the time of the first episode of schizophrenia. For example, Pasternak et al. found that most of the differences at first episode of schizophrenia were explained by an increase in extracellular volume in grey and white matter.\(^{52}\) The same group found a smaller abnormal increase in the volume of the extracellular space in chronic schizophrenia, suggesting a less extensive neuroinflammatory response in this later stage.\(^{53}\) Still, in patients with chronic schizophrenia, the presence of active symptomatology (delusions) has been associated with extracellular free-water in the left cingulum bundle, again suggestive of neuroinflammation in the more acute illness states.\(^{54}\)

In conclusion, MRI offers enormous potential for the \textit{in vivo} study of neuroinflammation, and it has several advantages: is largely available; it does not require the use of radio-active ligands and is therefore safer for repeated scanning studies; and is considerably less expensive. The ongoing development of new MRI techniques will eventually help dissecting the various components of the neuroinflammatory processes that have become increasingly implicated in the pathophysiology of psychiatric disorders.

4. Limitations of clinical studies

Human post-mortem and \textit{in vivo} imaging studies of patients with psychiatric disorders have some important limitations. The majority of the post-mortem studies have been conducted on tissue from patients with heterogeneous clinical presentations, often with a long duration of illness and decades of antipsychotic exposure, as well as other potential confounders, such as age-related incidental lesions. Therefore, it is hard to definitively distinguish drug-related changes from those related to disease.\(^{55}\) Clearly, clinical imaging findings using either PET or MRI offer different information from post-mortem neuropathology assessment, and do not provide information on the phenotype of microglia \textit{in vivo} following antipsychotic treatment.\(^{56}\)
Perhaps most critically, other risk factors for psychosis or depression may be hypothesised to drive the changes in neuroinflammation and microglia, but these cannot be easily tested in clinical studies. Of these, psychosocial stressors are a well described and documented risk factor for psychiatric disorders, and neuroinflammation, and in particular elevated microglial activity, has been proposed to mediate this association. This raises the question of whether the putative microglial activation and inflammation seen in the brains of these patients is linked to the neurobiology of their illness or to the effects of stress and other confounders, including alcohol, cigarette smoking, lifestyle and other environmental factors.

5. Microglia in animal models of stress

Unpacking this idea mechanistically is difficult in patient populations. Whilst rodent models cannot recapitulate all features of human psychiatric disorders, they allow invasive studies to probe the neurobiology associated with specific genetic or environmental risk factors linked to psychiatric disorders. This can also of course be applied to elucidate the effects of other potential confounders, such as exposure to antipsychotic medication.

In this context, much more is known about the effects of stress on microglia from animal studies that use a wide range of different psychosocial stressors (see panel 2). In the context of microglial activation following stress exposure, Calcia et al. observe that in the rodent hippocampus, at least eleven published studies report increases in the expression of the microglia/macrophage cell surface marker Iba1, albeit over a wide range of magnitudes, depending on the type and duration of the exposure to stress. In the prefrontal cortex, at least ten published studies have also reported that exposure to diverse psychosocial stressors resulted in elevated Iba-1 levels. Under stress conditions, microglia activation has been also reported in other brain areas such as the nucleus
accumbens, amygdala and paraventricular nucleus. One may therefore conclude that, at least in rodents, exposure to psychosocial stressors has an impact on central Iba1+ microglia in brain regions relevant to the neurobiology of psychiatric disorders.

To focus exclusively on stress exposure alone as an inducer of microglial activation in animals may however be considered too reductionist. In fact, a wide range of factors relevant or implicated in psychiatric disorders, including repeated exposure of animals to noxious insults or direct pro-inflammatory stimuli such as repeated exposure to infectious pathogens or perinatal malnutrition can induce central microglial activation.

Focussing exclusively on the morphology and/or number of microglia is only partially, or sometimes poorly, linked to the true functional state of these cells following exposure to the stressors listed above. It is therefore difficult to establish the precise nature of these microglial changes and their clinical implications. For example, whether they represent inflammation or homeostatic changes and if these are beneficial, or adverse, or even epiphenomenon. Perhaps most relevant for the clinical studies described herein, it is currently unclear how exposure to stress or other immune-stimuli in animals corresponds to changes in TSPO within microglia in vivo. A very recent study in an infection-mediated neurodevelopmental mouse model shows that behavioural abnormalities relevant to schizophrenia and increased pro-inflammatory cytokine expression are associated with decreased TSPO levels in the prefrontal cortex. In the same study, TSPO protein levels were instead strongly increased in a mouse model of acute neurodegeneration and reactive gliosis induced by intrahippocampal injection of kainic acid. These findings suggest the need to quantify cytokines and other inflammatory biomarkers, microglial number, morphology and transcriptional phenotype and determine how these relate to changes in TSPO following stress.
Of note, TSPO is not a typical immune-related target, but it is a mitochondrial protein generally activated under conditions of mitochondrial stress. In brain, TSPO is mostly expressed by microglia and cells on the vasculature (e.g., endothelial cells and perivascular macrophages) but is not expressed in neurons. Hence, cellular mechanisms of mitochondrial regulation as a consequence of environmental stress are only active on these cells. From a molecular perspective, the presence of TSPO up-regulation in patients with psychiatric disorders could then well indicate stress as the driving mechanism of microglial activation, not only through peripheral inflammation but also through mitochondria-related mechanisms, more than disease per se.

6. Discussion

Increasing evidence point towards an activation of microglia in patients with psychiatric disorders; however, this activation is not consistently reported across all patients and interestingly appears not to be specific for any particular diagnostic category. Some of the post-mortem studies have shown that increased density of activated microglia, or increased density of perivascular cells, is associated with suicide rather than a specific psychiatric diagnosis. These findings suggest that neuroinflammation, and more specifically activation of microglia, may a play role in more severe states of these disorders. This may not be specific for patients at higher risk for suicide but could involve a more general lack of response to traditional psychotropic medications. Indeed, although direct evidence about microglia activation is lacking, we and others have shown that peripheral immune activation from blood samples has been associated with poor treatment response both in patients with depression and in patients with psychosis. PET studies in patients with depression also found increased TSPO binding mainly in patients at the more severe end of the clinical spectrum rather than in those patients with mild-to-moderate depression. One suggestion is that the presence of microglia activation marks a more severe, more untreatable end of the spectrum of psychiatric disorders.
Why are microglia activated in some but not all patients with psychiatric disorders?

To understand why some, but not all, patients with psychiatric disorders show an activation of microglia, we need to understand what physiologically leads to microglia activation. Microglia usually activates in presence of harmful stimuli. These harmful stimuli can be represented not only by inflammatory stimuli, such as an infection, but also by psychosocial stressors. As previously mentioned, psychosocial stress is one of the main risk factors for development and relapse of psychiatric disorders. As discussed above, various preclinical studies have shown that psychosocial stressors lead to an activation of microglia across different brain regions. 66

Although there is no direct evidence in humans that stress leads to activation of microglia, our recent meta-analysis of clinical studies has shown that experience of childhood traumatic events is associated with higher blood levels of inflammatory markers in adulthood. 61 These observations support the hypothesis that microglia activation may represent a marker of stress rather than of the mental health problem. In this context, the activation of microglia would work as mediating mechanism between the stressful event and the development/increased severity/difficult-to-treat psychiatric condition (Figure 1).

Notwithstanding the clear evidence of increased peripheral inflammation in psychiatric disorders, the link between peripheral inflammation and microglia activation remains still elusive. A recent study, using LPS injection in humans in vivo, has demonstrated that peripheral immune activation is associated with robust microglia activation measured through TSPO binding, 75 supporting the idea that the presence of peripheral immune activation in our patients may mirror a central immune activation. However, changes in peripheral immune-related proteins may confound these results, as discussed above; moreover, whether the peripheral immune activation precedes the central immune activation or vice-versa in our patients is still unclear. Of note, few studies that have tried to assess correlations between central (TSPO binding) and peripheral measures of inflammation have
so far not reported positive results. A recent review by Weber et al, discuss more in detail the evidence of a bidirectional communication between CNS and peripheral immune system in response to stress and how this contributes to an increase in neuroinflammation. More specifically, the activation of the sympathetic nervous system in response to stress appears to contribute to a shift in hematopoiesis and a generation of new monocytes which appear less mature and more inflammatory than “homeostatic” monocytes and that are actively recruited to the brain promoting neuroinflammation. In this context a further question also arises; is the degree of peripheral immune activation relevant to central inflammation? The recent evidence that only patients with peripheral inflammation above a specific threshold do not respond to antidepressants and antipsychotics and respond to anti-inflammatory treatment indicates that the degree of peripheral immune activation is important for detection of microglia activation.

Implications for treatment

Given the growing evidence of the role of microglia activation in psychiatric disorders, it is not surprising that both academia and industry have shown increasing interest in identifying and developing drugs that inhibit microglia activation.

One of the main drugs proposed to have an effect in reducing microglia activation is Minocycline. Minocycline is a broad-spectrum tetracycline antibiotic with a broad anti-inflammatory action. A number of studies have shown that Minocycline reduces microglia activation following stress or immune stimulation. In a study using chronic stress in rats, Minocycline prevents both microglia activation and the depressive behaviour induced by chronic stress. This unique ability of Minocycline to reduce microglia activation could be due to its broader spectrum of anti-inflammatory actions; indeed, a recent critical review has challenged the suggestion that Minocycline is a “selective microglia inhibitor” as this drug affects also peripheral immune cells as
well as astrocytes, oligodendrocytes and neurons. Clinical trials using minocycline in patients with schizophrenia or depression are showing some promising but not consistent results. The lack of consistent results could be due to the lack of stratification of patients in these trials. Indeed, we have mentioned that microglia activation appears to be present only in a proportion of patients, and recent trials testing anti-inflammatory treatments in depression have shown these to be effective only in patients with increased baseline inflammation, further suggesting that only patients presenting microglia activation may benefit from drugs that specifically target microglia (Figure 1).

It is however worth pointing out that the impact of existing psychotropic medications on the immune system also requires more detailed exploration, particularly given the suggestions that antipsychotics influence microglial activation in rodents and potentially in patients with schizophrenia. Again, whether these effects are beneficial or detrimental remain to be explored fully in rodent model systems, although we are actively pursuing this question.

7. Conclusions

Although the role of immune activation in development of psychiatric disorders was suggested already almost a century ago, the renewed interest in this area has generated considerable amount of data mainly over the past two decades. The emerging evidence of a role of microglia activation across different psychiatric disorders is contributing to developing a new era for psychiatry.

Although microglia activation may not be a marker for specific diagnostic category, it is important to note that it may be a consequence of excessive exposure to stress in these patients and that it may play a role in identifying more severe/treatment-resistant patients, and as a target for novel pharmacological interventions. Whilst these hypotheses deserve further investigation, the development of novel treatments targeting microglia instils a new hope for modern psychiatry.
8. **Legend to Figure 1:**

Proposed model of psychosocial stress increasing microglia activation in subsample of patients with psychiatric disorders across diagnostic categories, possibly through increased peripheral inflammation. The model proposes that those patients with increased microglia activation represent the more severe end of the spectrum and include those patients more resistant to current treatment. Anti-inflammatory treatment targeting microglia activation could specifically be more effective in those patients who present increased microglia activation.

9. **Authors and Contributors**

All authors contributed to literature search, data synthesis, discussion of the data, and writing of the manuscript.

10. **Declaration of Interests**

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12. References


