Received: 29 June 2023 | Accepted: 23 August 2023

DOI: 10.1002/prp2.1136

REVIEW

Autocrine positive feedback of tumor necrosis factor from activated microglia proposed to be of widespread relevance in chronic neurological disease

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Abstract

Over a decade's experience of post-stroke rehabilitation by administering the specific anti-TNF biological, etanercept, by the novel perispinal route, is consistent with a wide range of chronically diminished neurological function having been caused by persistent excessive cerebral levels of TNF. We propose that this TNF persistence, and cerebral disease chronicity, largely arises from a positive autocrine feedback loop of this cytokine, allowing the persistence of microglial activation caused by the excess TNF that these cells produce. It appears that many of these observations have never been exploited to construct a broad understanding and treatment of certain chronic, yet reversible, neurological illnesses. We propose that this treatment allows these chronically activated microglia to revert to their normal quiescent state, rather than simply neutralizing the direct harmful effects of this cytokine after its release from microglia. Logically, this also applies to the chronic cerebral aspects of various other neurological conditions characterized by activated microglia. These include long COVID, Lyme disease, post-stroke syndromes, traumatic brain injury, chronic traumatic encephalopathy, post-chemotherapy, post-irradiation cerebral dysfunction, cerebral palsy, fetal alcohol syndrome, hepatic encephalopathy, the antinociceptive state of morphine tolerance, and neurogenic pain. In addition, certain psychiatric states, in isolation or as sequelae of infectious diseases such as Lyme disease and long COVID, are candidates for being understood through this approach and treated accordingly. Perispinal etanercept provides the prospect of being able to treat various chronic central nervous system illnesses, whether they are of infectious or non-infectious origin, through reversing excess TNF generation by microglia.

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APOE4, Apolipoprotein E4; CCL11, C-C motif chemokine 11; EEG, electroencephalogram; NF-κB, nuclear factor kappa B; PET, positron emission tomography; TLR4, TOLL receptor 4; TNF, tumour necrosis factor; TNFR1, TNF receptor 1; WAIS-111, Wechsler Adult Intelligence Scale 3rd edition; WMS-111, Wechsler Memory Scale 3rd edition.

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KEYWORDS
activated microglia, autocrine feedback loop, endometriosis pain, long COVID, post-stroke, psychiatric states, TNF

1 | INTRODUCTION

Our interest in differential persistence of TNF in the brain and elsewhere arose 16 years ago through a report that post-lipopolysaccharide (LPS)-induced TNF generation in the mouse persists in the CSF for very much longer (at least 10 months) than in the serum (all gone in 6 h)[1] after intraperitoneal injection of LPS. This is consistent with an earlier report by Kuno[2] of a positive feedback loop existing in the activation of microglia by the TNF that these cells generate. In short, Kuno and co-authors argued that an autocrine loop, driven by TNF, prolongs the activation of the microglia that generate this same cytokine. This has also been expressed functionally by demonstrating, in a rabbit model, that usual systemic endotoxin tolerance, as expressed in terms of reduced TNF generation, does not occur in the CSF-containing subarachnoid space.[3] From this background, we discuss cerebral disease states in which microglia may remain chronically activated and are kept in this state by the very TNF they are generating.

In our view, applying the above seminal work of Kuno and co-workers to the existence of an autocrine positive feedback loop of microglial activation mediated by TNF-TNFR1 signaling illuminates much about chronic cerebral conditions. In other words, by blocking TNFR1 signaling with an antibody that suppressed most of LPS-induced TNF release into the culture supernatants, these authors demonstrated that LPS-induced, microglia-derived TNF further stimulates TNF production via TNFR1 activation in an autocrine manner. Subsequent findings[4] indicate that the N-glycosylation of TNFR1 plays an important role in this process. This implies that the pathogenesis of conditions in which microglia are routinely confirmed to be activated will demonstrate chronically increased TNF levels in the cerebrospinal fluid. Thus, neutralizing the TNF that is perpetuating this activation with a specific anti-TNF biological, such as etanercept, administered perispinally[5] so it reaches where it is required, can be expected to long-term deactivate these microglia. Chronic cerebral dysfunction would be accordingly terminated. As discussed throughout this review, this additional information on the relationship between microglia and TNF[2] has potentially wide relevance to the pathogenesis and treatment in a surprising number of neurodegenerative states (Figure 1). In addition, it accords with the outcome of the impressively large number of off-label post-stroke treatments accumulating since 2011.[5,6] The logic of funding large random controlled trials (RCTs) is correspondingly strengthened.

TNF is the most conspicuous cytokine in the literature, and specific anti-TNF biologicals are the largest aggregate source of income for the pharmaceutical industry. In low concentrations, TNF is an essential signaling molecule in physiology across much of non-botanical biology, whereas its excessive generation is central to our understanding of much human disease. Not surprisingly, therefore, the advent of anti-TNF biologicals has led to their widespread successful therapeutic use by neutralizing excess TNF generation in a number of chronic non-cerebral conditions. Here we discuss the scientific rationale for extending this principle to the brain, with specific anti-TNF biologicals and their biosimilars being equally efficacious in the CNS as elsewhere. However, routine intra-cerebrovascular administration of any large molecule is clinically impractical, and forms of anti-TNF biologicals small enough to pass through the blood–brain barrier (BBB) are not yet developed.

From our interest in the wide relevance of TNF in the normal and dysfunctional brain,[7] about a decade ago we contributed a background to the roles of microglia in neurodegenerative diseases.[8] This included the roles of cytokines such as TNF generated by these cells in normal synaptic function. Ample evidence[9,10] also exists that microglia directly influence neural networks. Here we review aspects of these interactions, focusing on the influence of activated microglia in disease, and the functions and interactions of the cytokines that mediate many of these effects. We particularly consider how non-infectious (post-stroke syndromes, traumatic brain injury) or infectious conditions (Lyme disease, COVID-19) can lead to very similar cerebral outcomes that often become chronic, with life-changing consequences. Exposure to danger-associated molecular patterns (DAMPs), from either damaged tissue or endogenous cellular material not normally released or from external sources or to pathogen-origin molecular patterns (PAMPs) on the surface of infectious organisms acting as agonists mainly for Toll-like receptors, generate essentially identical harmful cerebral outcomes. This occurs through their shared ability to induce secreted proinflammatory cytokines, which cause disease when generated in excess. We have previously[11] discussed the work of those who constructed these remarkably useful concepts.[12,13]

2 | PERISPINAL ADMINISTRATION

An alternative route of administration, termed perispinal,[6] is discussed here regarding employing etanercept, one of the specific anti-TNF biologicals. As reviewed,[5] this route of cerebral venous drainage via the cerebrospinal venous system, or Batson's Plexus,[14] has no valves. It has had, since its discovery well over a century and a half ago, an intermittent and interesting history in medical advances. Its potential as a route of administration inadvertently began in 1994 when researchers in aviation medicine were exploring an animal model of the effects of gravity and body position on pilots of high-performance aircraft.[15] This involved restraining anesthetized rabbits on a tilt board and rotating them to a head-down position. This considerably increased CSF levels of the plasma protein albumin within 5 minutes. The authors noted, in passing, that as well as aiding their particular field, their data had implications for getting large molecular weight molecules into the brain for chemotherapeutic purposes. It so happens that etanercept has a similar molecular weight

to that of albumin – hence the mild tilting at the end of the perispinal procedure. However, rheumatoid arthritis, Crohn's disease, and psoriasis have been transformed by neutralizing soluble TNF with specific anti-TNF biologicals administered systemically, treatment of chronic neurological states of clinical importance are yet to gain substantially from this developing body of knowledge, despite being proposed[6] and used widely by the same author in case studies of post-stroke patients, as discussed.[16–19]

3 | NORMAL HOMEOSTATIC CEREBRAL FUNCTIONS OF TNF

The important functional, and cytokine, overlap between the brain and the innate immune system is reinforced in comprehensive reviews such as that by Yirmiya.[20] As Tchessalova and co-authors noted,[21] the naïve homeostatic baseline is not the absence of neuroimmune signaling or activity. Instead, these mediators physiologically interact with neurons and thus regulate neural function and synaptic plasticity. Indeed, as nicely portrayed,[22] the mediators of innate immunity are, as unlikely as it seems, also routinely utilized for finely sculpting the circuitry of the normal CNS. In particular, TNF, the keystone of much innate immunity, is also involved in normal neurotransmission via modulating excitatory inputs,[23] trafficking of AMPA receptors,[24] homeostatic synaptic scaling,[25] synaptic glutamate levels,[26] and long-term potentiation.[27] As discussed in Section 4.1, TNF also controls induction of C-C motif chemokine Ligand 11 (CCL11).[28] TNF also regulates neuronal type-1 inositol trisphosphate receptors (IP3R), which are central to neuronal Ca^{++} homeostasis, and thus, the ionic signaling cascades on which normal function of neurons depends.[29] Appropriate levels of this key cytokine also maintain normal background levels of neurogenesis.[30] Moreover, normal mitochondrial function, presumably in neurons as much as elsewhere,[31] depends on physiological levels of TNF, as does regulation of the neurotransmitter, orexin.[32] As reviewed,[33] orexin then controls an impressively varied list of phenomena, including sleep, motor control, focused effort, appetite, and water intake. Consequential distinctive clinical outcomes are to be expected through homeostasis being lost by the high local TNF generation by local high PAMP and DAMP activity. Unfortunately, it is rarely noted in the neuroinflammatory disease literature that these normal, particularly synaptic, physiological functions of TNF,[23–27] homeostatically controlled in health, are clearly vulnerable to inappropriate and harmful distortion during neuroinflammation.

4 | BRIEF SUMMARIES OF TWO EXAMPLES OF PAMP-DRIVEN MICROGLIAL ACTIVATION

The following two syndromes exhibit prolonged activation of microglia by infectious agents, and associated chronic excess of cerebral TNF, with an associated distortion of homeostasis and function loss. Detailed clinical consequences of chronically activated microglia inevitably depend on the degree and anatomical distribution of this activation.

4.1 | Involvement of the TNF-induced cytokine cascade in cerebral long COVID-19

We proposed last year[34] that TNF, which initiates this cascade, is pivotal to understanding the chronic cerebral consequences of not just long COVID but also of similar systemic infections, such as Lyme disease, caused by a tick-borne spirochaete, *Borrelia burgdorferi*. These PAMP-driven alterations in brain function were noted to be the same, in mechanism as well as nature, as the syndromes observed after DAMP-induced events such as stroke and post-traumatic brain injury induced by excess activity of the same cytokine pathways. All four cerebral functional alterations, two post-DAMP and two post-PAMP, were discussed in the same terms, i.e., all being initiated by TNF cascade cytokines generated chronically and excessively from chronically activated microglia.[34] The physiological homeostasis that these cascade-related cytokines normally control is therefore placed in jeopardy. As discussed earlier, such homeostasis is required for normal physiological neurotransmission via modulating excitatory inputs,[23] trafficking of AMPA receptors,[24] synaptic scaling,[25] and long-term potentiation.[27] Among the basic cerebral physiological foundations that can be expected to perform poorly in the face of chronically excessive levels of cerebral TNF is neurogenesis.[30] Not surprisingly, the principles involved can also explain the nature of post-sepsis neurological dysfunction.[35]

Two recent publications in cell respectively generated[36] and commented upon[37] data that, apparently unwittingly, add further to our knowledge of the role of the TNF cascade in understanding COVID disease, particularly neurological long COVID. They both relate the consequences of increased circulating levels of CCL11 – a synonym for eotaxin, a chemokine, being central to understanding these conditions. Neither group commented that this places CCL11 firmly within the TNF cascade, as evidenced by its induction by TNF[28] and its in vivo reduction by etanercept.[38] TNF has been observed to be involved in controlling neurogenesis since 2006,[39] and the case has been made[34] for significantly reducing its concentration in COVID brains with etanercept. The specific anti-TNF biological, etanercept, had already been reported to reduce TNF, IL-1β, and IL-6 mRNA as well as TNF itself.[40] Hence, the reduction by etanercept of a cytokine further down the cascade, such as CCL11, is to be expected.

4.2 | Chronic cerebral aspects of Lyme disease

The acute phase of Lyme disease, with its influenza-like symptoms, malaise, headache, fever, myalgia, radicular pain, paresthesia,

fatigue, and a subjective sense of clouded thinking, is evidently consistent with the excess TNF generation. The notion to search for sequestered forms, or fragments, of this spirochaete for their long-term antigenic activity[41] that can induce a persistent, neurological stage, and the link, or otherwise, between this and the acute disease phase, is the focus of some controversy. Accordingly, literatures on two separate clinical entities, post-treatment Lyme disease (when pathogen can no longer be detected) and chronic Lyme disease (when possible, pathogen remnants are recorded) exist side by side, unresolved.[42] This conundrum continues to the present day and still generates the controversies commented on over 15 years ago.[43]

In our view, the researchers whose approach is most likely to advance our understanding of chronic cerebral Lyme disease are those making parallels with chronic inflammation,[44,45] a shorthand term for the prolonged effects of a chronically upregulated, TNF-induced, cytokine cascade. We reason that the chronic microglial activation discussed throughout this Review in conditions that include long COVID-19 and the syndromes seen in survivors of stroke and traumatic brain injury provide useful background material for understanding persistent Lyme disease. As in these other conditions, we argue here that the normal homeostatic cerebral functions of TNF in synaptic function, and thus connectivity across the brain, are chronically overwhelmed, as reflected in the observed functional changes.[34] In short, these changes are much more likely to arise from chronic TNF generation by chronically activated microglia, rather than *B. burgdorferi* remnants chronically acting as perpetual PAMPs. Thus, we see chronic Lyme disease and post-treatment Lyme disease as a single functional entity, not unlike the cerebral aspects of long COVID. Significantly more activated microglia are identified in post-treatment Lyme disease patients than in controls[46] by employing 11C-PK11195 labeling, the same marker used to enumerate these cells in post-stroke syndromes[47] and traumatic brain injury (TBI).[48]

In essence, we make the case for the activity of a TNF-positive feedback loop continuing to keep microglia in post-treatment Lyme disease activated, with this being performed, as we have noted earlier, by the very TNF their activated state generates. Predictably, therefore, removing this excess TNF by administering perispinal etanercept can be expected, through deactivating these microglia, to be useful for treating persistence of the neurological symptoms' characteristic of this condition. Examples of such syndromes that are plausible additional targets are discussed in the next Section.

5 | EXAMPLES OF CEREBRAL DISEASE-ASSOCIATED DAMP-DRIVEN MICROGLIAL ACTIVATION

5.1 | Post-stroke syndromes

As discussed earlier,[34] post-stroke syndromes are consistent with the presence of excess cerebral TNF as a component of neuroinflammation. Confirmation from basic models continues to accumulate,[49] with 11C-PK11195, a well-established PET marker of in vivo microglial activation, being employed on such patients.[47] The same technique has been also been used to establish the dynamics of the same changes along affected nerve tracts,[50] including in chronically affected patients.[51] Others[52] have discussed the possibility of clinical implementation of this imaging to assess stroke-associated neuroinflammation with the potential to provide image-guided diagnosis and treatment. These authors also summarized the results from associated clinical studies evaluating the efficacy of anti-inflammatory interventions in stroke. This is reflected in much, and continuing, off-label clinical experience with perispinal etanecept[16,17] as well as a modestly sized, public donation-funded, RCT.[53]

5.2 | Traumatic brain injury and chronic traumatic encephalopathy

Researchers investigating the same concepts with TBI patients[48] have observed increased whole-brain binding of 11C-PK11195 6 months after the damaging event. As has been noted,[54] the concept of sustained neuroinflammation after brain or spinal cord trauma, a relationship known since the 1950s, is well supported by these and similar studies that demonstrate extensive microglial and astroglial activation in chronic traumatic inflammatory encephalopathy. Others[55] have examined these aspects of microglial activation in a rat TBI model and found increased numbers of ionized calcium-binding adapter molecule 1-positive cells, as well as active inflammation (e.g., increased levels of TNF, IL-1β, and IL-6). All these changes were shown to be significantly reduced by intrathecal etanercept treatment. It has subsequently been demonstrated in an experimental model[56] that, in the absence of microglia, neurons do not undergo TBI-induced changes in gene transcription or structure. Moreover, microglial elimination prevented TBI-induced cognitive changes 30 days post-injury. This is consistent with mediators secreted by microglia having a critical role in disrupting neuronal homeostasis after TBI, particularly at subacute and chronic timepoints. Predictably, these principles have been extended to chronic traumatic encephalopathy (CTE) in head-contact sports injuries.[57] This condition has also gained attention through its recently recognized high incidence in young children, in whom mild trauma has been reported to have a previously unsuspected link to persistent behavioral and learning difficulties.[58]

5.3 | Post-chemotherapy and post-irradiation cerebral dysfunction

For some years now, the MRI and PET scanning literatures have indicated altered functional and metabolic changes in the post-chemotherapy brain. Subsequently[59] it was argued that TNF was likely to be central to post-chemotherapy cerebral dysfunction. Impaired cognitive function has been found to be widespread,

and to encompass a lower capacity for attention, mental flexibility, speed of information processing, visual memory, and motor function.[60] Affected sites include the frontal cortex, cerebellum, and basal ganglia.[61] More recently, it has been argued at length[62] that chemotherapy-induced microglial activation, a circumstance in which excess TNF is generated within the brain, is central to the dysregulation of cerebral function that often follows. These changes are more pronounced in APOE4$^+$ individuals receiving chemotherapy.[63] This association is to be expected, since this genotype is a known marker for higher levels of TNF induction. For example, when bacterial LPS, the TLR4 agonist that is the prototype TNF inducer, is administered intravenously to APOE4$^+$ and APOE4$^-$ volunteers, much higher levels of TNF are generated in the APOE4$^+$ group.[64] The same pattern of events can also rationalize post-irradiation cerebral dysfunction, given that irradiation induces microglial activation,[65] and selective inhibition of microglia-mediated neuroinflammation has been reported to mitigate radiation-induced cognitive impairment in tumor patients.[66]

5.4 | Cerebral palsy

After decades of research activity on this condition, a path through to persistent microglial activation arose from the laboratories of Olaf Dummann[67] and Pierre Gressens.[68] This made the field much more intelligible, and indeed intriguing, to a wider audience of researchers. Within a decade, Galinsky[69] had further extended the fetal sheep model of cerebral palsy developed by others[70] by steering it towards the microglial activation ideas outlined above. In brief, late preterm fetal sheep were infused with LPS, the prototype TNF inducer, with and without etanercept. Etanercept delayed the rise in circulating IL-6, prolonged the increase in IL-10, and attenuated EEG suppression, hypotension, and tachycardia after bolus injection of LPS. It also normalized LPS-induced gliosis, and the increase in TNF-positive cells, as well as proliferation of oligodendrocytes.

Subsequently, this group subjected chronically instrumented pre-term fetal sheep to 25 minutes of hypoxia-ischemia induced by complete umbilical cord occlusion, followed by intracerebroventricular infusion of etanercept.[71] This treatment markedly attenuated cystic white matter injury on the side of the intracerebroventricular infusion, with partial contralateral protection. Three weeks later, histology sections showed that etanercept had improved oligodendrocyte maturation and labeling of myelin proteins in the temporal and parietal lobes. As the authors noted, the inference of these outcomes is that delayed TNF blockade may be a viable approach to reducing the risk of cystic and diffuse white matter injury and potentially cerebral palsy after preterm birth, and after an unexpectedly favorable therapeutic window. Reflecting on their data,[72] this group proposed that the tertiary phase of injury might be different than previously thought, with a surprisingly wide window of opportunity 1 to 2 weeks after hypoxic–ischemic injury to prevent delayed cystic lesions, further reducing the risk of cerebral palsy after preterm birth.

5.5 | Fetal alcohol syndrome

Another field of research following a similar pattern concerns fetal alcohol syndrome, a consequence of ethanol exposure to the fetus during pregnancy. In human studies on chronic heavy alcohol-user mothers, TNF, IL-1α, and IL-1β levels have been reported to be persistently increased in maternal and cord serum, and in cultured cells.[73] These disorders can persist, leading to lifelong disabilities, with resultant dysfunctional behavior and cognition. Microglial activation, associated with high TNF levels, is also recorded.[74] Alcohol consumed during gestation has recently been shown to prejudice brain development by reducing the synthesis and release of neurotrophic factors and neuroinflammatory markers into the plasma of pre-pubertal children with fetal alcohol syndrome.[75] Significantly more microglia were also present in the hypothalamus in alcohol-fed adult rats,[76] and these cells showed more TNF and IL-6 expression in response to LPS than did the same cells from normal rats. In 2020, others[77] reported that mice receiving prenatal and lactational alcohol exposure demonstrated increased expression of IL-6 and TNF in the hippocampus and frontal cortex, and microglial activation in the dentate gyrus. Therefore, it is not surprising that elimination of TLR4 abolishes the effects of ethanol on the innate and the adaptive inflammatory response induced by ethanol treatments in macrophages.[78] Treatment with curcumin (diferuloylmethane), a component of turmeric (*Curcuma longa*), which is inexpensive and somewhat reduces TNF,[79] is reported to reduce these alcohol-induced mouse memory deficits.[77] Clearly, this condition has many parallels, in both pathogenesis and potential therapy, with the rest of this group of chronic neurogenic disease states.

5.6 | The antinociceptive state in morphine-tolerant rats

As well-reviewed by Eidson et al[80] and earlier authors, the acquisition of morphine tolerance is best explained nowadays in terms of activation in neuroinflammatory cells, such as microglia, and ensuing changes in inflammatory cytokine generation. In keeping with this, studies exist on etanercept preserving the antinociceptive state in morphine-tolerant rats[40] and therefore being predicted to extend the effectiveness of opioids in clinical pain management. A key step here, as described throughout this publication, is microglial activation being suppressed by etanercept. As discussed above in the context of cerebral palsy in sheep,[69] etanercept reduced post-LPS gliosis in the white matter of fetal lambs. Here again, therefore, long-term microglial activation, consistent with the positive feedback loop described by Kuno,[2] can reasonably be incriminated in morphine tolerance.

5.7 | Hepatic encephalopathy

Research in a mouse model, designed to understand more about the mechanism of hepatic encephalopathy, a serious neuropsychiatric

complication of liver failure, unearthed the same general conclusion as above. Namely, that microglial activation, assessed by OX-42 immunoreactivity, was attenuated by etanercept,[81] again implicating Kuno's positive feedback loop[2] and therefore a plausible application of perispinal etanercept.[6]

6 | PSYCHIATRIC CONSEQUENCES OF ANY EXCESSIVE CEREBRAL INCREASE IN TNF

Ignatowski et al[82] appear to have been the first, in 1996, to awaken an interest in cerebral functional changes, whether behavioral, affective, or cognitive, being mediated by cytokines such as TNF. Many subsequent publications are consistent with this. For example, in 2006 Paterson et al[83] demonstrated, using pro- and anti-psychotic drugs in a rat model, and in human autopsy brain, that levels of TNF in relevant brain regions were altered in ways consistent with a causal TNF link. Indeed, as discussed later in this Section, it is increasingly acknowledged that the cerebral functional loss discussed above in terms of excess TNF, however induced, be it a PAMP (long COVID[84] or post-treatment Lyme disease[85]) or a DAMP (post-stroke[86] or TBI[87]), is associated with an increased incidence of the more common psychiatric conditions. Whatever the trigger, the literature of psychiatric disorders, such as clinical depression, or major depression disorder (MDD), schizophrenia,[88] and bipolar states,[89] is increasingly consistent with this association.

For example, it has been reported, after employing [(11)C]PBR28 binding,[88] that microglial activation is elevated in the frontal and temporal lobes of patients with schizophrenia. Microglial activation at these sites was also present in those with subclinical symptoms of a high risk of psychosis and was related to at-risk symptom severity. Others have more recently reported that infliximab improved cognitive function in patients with bipolar depression.[90] This was found to be mediated via secondary changes in leptin, a mediator closely associated with TNF in many ways.[91] As reported,[92] several specific anti-TNF biologicals, as well as minocycline, a semi-synthetic second-generation tetracycline that attenuates TNF production, have been demonstrated to be a useful adjunct treatment for MDD, schizophrenia, and bipolar disorder. This is consistent with a recent extensive study of microglial activation in MDD[93] and also a report of co-expression networks in brains of patients with psychiatric disorders.[94] In brief, this genome-wide association study revealed that transcripts closely related to innate immunity gene activity interacted closely with transcripts of genes associated with CNS systems.

6.1 | Lyme disease and psychiatric disorders

A considerable literature on Lyme disease, a multi-systemic illness, demonstrates that it can exhibit late-onset neuropsychiatric changes after the pathogen, *B. burgdorferi*, is no longer present. These changes can persist for months or years and have been described as compromising neuropsychological performance, as shown by the WAIS-III and WMS-III mental tests.[95] Detailed descriptions of what has been documented in neuropsychiatric Lyme disease are widely available.[96]

6.2 | Long COVID and psychiatric disorders

Given their similar presentations – flu-like symptoms of fever, chills, sweats, malaise, myalgia and arthralgia, neurological dysfunction, all consistent with excess TNF generation in both of these conditions – diagnostic confusion between post-treatment Lyme disease and long COVID-19 is to be expected. Hence, a potential delay for an accurate diagnosis is a real possibility.[97] Predictably, therefore, long-term consequences of post-treatment Lyme disease and long COVID-19 also have similarities. For instance, long COVID appears to share with what could be termed long Lyme disease the increased frequency of the MDD and other common psychiatric disorders.[84,85] Our reasoning here is entirely consistent with the outcome of recent studies[98] that focused on the details of the PAMP activity of certain structural proteins of SARS-CoV-2 in this same context. Their conclusions also plausibly apply to the psychiatric disorders recorded in Lyme disease, above.[95]

It also warrants noting that CCL11, a chemokine inducted by TNF[28] and reduced in vivo by etanercept,[38] has recently been noted to be a marker for long COVID neurological disorders.[36,37] This provides further evidence of the same principles applying across these PAMP/DAMP-induced neurological disorders and the common psychiatric disorders. Notably, this chemokine has also been reported to be increased in schizophrenia, bipolar disorder, and MDD, often correlating with the severity of psychopathological and cognitive parameters.[99]

7 | CHRONIC NEUROGENIC PAIN AS A CONSEQUENCE OF INCREASED CEREBRAL TNF

For over 20 years, the involvement of cytokines released from glial cells to mediate pain has been a topic of basic and clinical research.[100–106] Milligan and Watson warrant particular acknowledgment.[107] Indeed, a few years earlier this group had demonstrated that intrathecal minocycline, a selective inhibitor of microglial activation, attenuates mechanical allodynia in a rat model.[108] The effect was slight, but this agent is a much weaker TNF inhibitor than present-day specific biosimilars. Typically, these studies have been directed at post-stroke pain, but the literature on TNF-associated neurogenic pain extends to essentially all of the disease states discussed in this review: TBI,[109] Lyme disease, long COVID (discussed in Section 6.2), cerebral palsy,[110] fetal alcohol syndrome,[111] and hepatic encephalopathy.[112] The term Chronic Regional Pain Syndrome[113] is used generically in this context. It can also include spinal cord injury, as outlined in the next paragraph.

7.1 | Spinal cord injury as an example of chronic neurogenic pain

Examples consistent with the practical application of this evidence for a positive feedback phenomenon, with anti-TNF reversing microglial cell activation, and thus long-term excess cerebral TNF generation, are readily available in the pain literature. For example, 4 years after – albeit not noting – Kuno's study,[2] Marchand et al[114] investigated, in a rat model, the cause of the neuropathic pain that affects some 70% of patients with spinal cord injury. They reported that etanercept treatment soon after injury reduced pain, as assessed by reduction of mechanical allodynia for at least a month. It also reduced OX-42 immunostaining, an indicator of spinal microglial cell activation. In the same publication, minocycline, an established but less potent anti-TNF inhibitor, also significantly reduced microglial OX-42 expression, i.e., activation.

7.2 | The chronic pain of endometriosis

For some time, the severe pain that can accompany endometriosis has been associated with excess local TNF levels. Apart from assaying for this key cytokine, this has been implicated from evidence for triggering of Toll-like receptor 4 being essential to pain generation,[103,115] Relevant downstream signaling pathway activity has also been reported.[116] The hallmark chronicity of this condition is consistent with the finding, discussed throughout this review,[2] of the TNF generated by activated microglia keeping these cells activated. Moreover, much evidence exists for microglial activation in this condition – particularly in experimental models, where it is very widespread.[117] It is also discussed in patient research.[118,119] Should microglial activation become accepted as a key phenomenon in human endometriosis pain, an interest in perispinal administration of anti-TNF therapy, as for post-stroke pain,[17,53] is likely to be compelling.

8 | THERAPEUTIC IMPLICATIONS

In summary, the case is made here that much shared neurological chronicity arises largely from the positive feedback loop described by Kuno[2] causing the persistence of the activation of microglia by the TNF that these cells generate.

Since all of the conditions listed above – post-stroke syndromes, traumatic brain injury and chronic traumatic encephalopathy, post-chemotherapy and post-irradiation cerebral dysfunction, cerebral palsy, fetal alcohol syndrome, morphine tolerance, neurogenic pain and hepatic encephalopathy – exhibit chronic microglial activation, we proposed that, when further explored, they will be widely regarded, by the reasoning outlined above, to warrant consideration as candidates for treatment with a single dose of perispinal etanercept. This is directed at the excess TNF that, from Kuno's study,[2] is keeping the microglia chronically activated, rather have it overwhelmed normal cerebral function (see Section 3), although this is plausibly influenced. In summary, lowering this excess cerebral TNF by introducing a specific anti-TNF agent perispinally appears to be a logical routine procedure to reverse much of the function loss caused by this persistent, TNF-maintained, and TNF generating, microglial activation in a range of chronic neurological conditions.

In future, these outcomes may well be achieved by potent specific anti-TNF agents small enough to pass the blood–brain barrier. Until then, open-mindedly encouraging large RCTs of delivery of etanercept, or similar activity large molecule specific biologicals, through the perispinal route shows promise of improving many lives, across a range of neurological conditions.

Another agent proving to be instructive in this context is Fingolimod, an orally administered fungal derivative.[120] Its relevant useful activities include protecting against injury in a post-stroke syndrome model of brain ischemia, which is associated with reduced activation of NF-κB signaling pathways, leading to significant improvement associated with reduced levels of inflammatory cytokines.[121] Moreover, illness mitigation by Fingolimod in a mouse model of Gulf War Syndrome, a condition with unremitting central nervous system function loss, is associated with reduced activity of inflammatory signaling pathways and, notably in the present context, decreased activation of microglia.[122]

9 | RATIONALIZING A SINGLE ETANERCEPT INJECTION GENERATING A CONTINUING THERAPEUTIC EFFECT

Reported outcomes after a single off-label perispinal treatment of post-stroke syndromes are commonly characterized by remarkably long-term neurological improvement. This very simply obtained measurement of duration has now been reported for over a decade for very many such patients, from the first set of case reports in 2011.[16] Given the short in vivo half-life of etanercept,[123] this long-term improvement is decidedly counterintuitive, given the typical weekly requirement for this class of therapy when neutralizing the harmful effects of TNF in rheumatoid arthritis.[124] It seems that Tobinick's initial 2011 proposal[16] for a mechanism, quoting a capacity of increased etanercept to reduce microglial activation,[125] and therefore the continuous production of TNF by these cells, may require being taken more seriously than it has been to date. Importantly, as discussed above, cerebral TNF evidently has a propensity to maintain its own production by keeping microglia, the main cerebral cells that produce it, in the activated state necessary for its continuous generation. Namely, as Kuno and co-authors subsequently established,[2] an autocrine-positive feedback loop exists whereby TNF can prolong the activation of the cerebral microglia that generate it. Indeed, 5 years ago we quoted and explained Kuno's data in an Editorial[126] in order to address neurologists' skepticism of possible longevity of the effect of etanercept in post-stroke syndromes.

Accordingly, using perispinal administration of etanercept, another TNF-specific biosimilar, or indeed a smaller equally specific

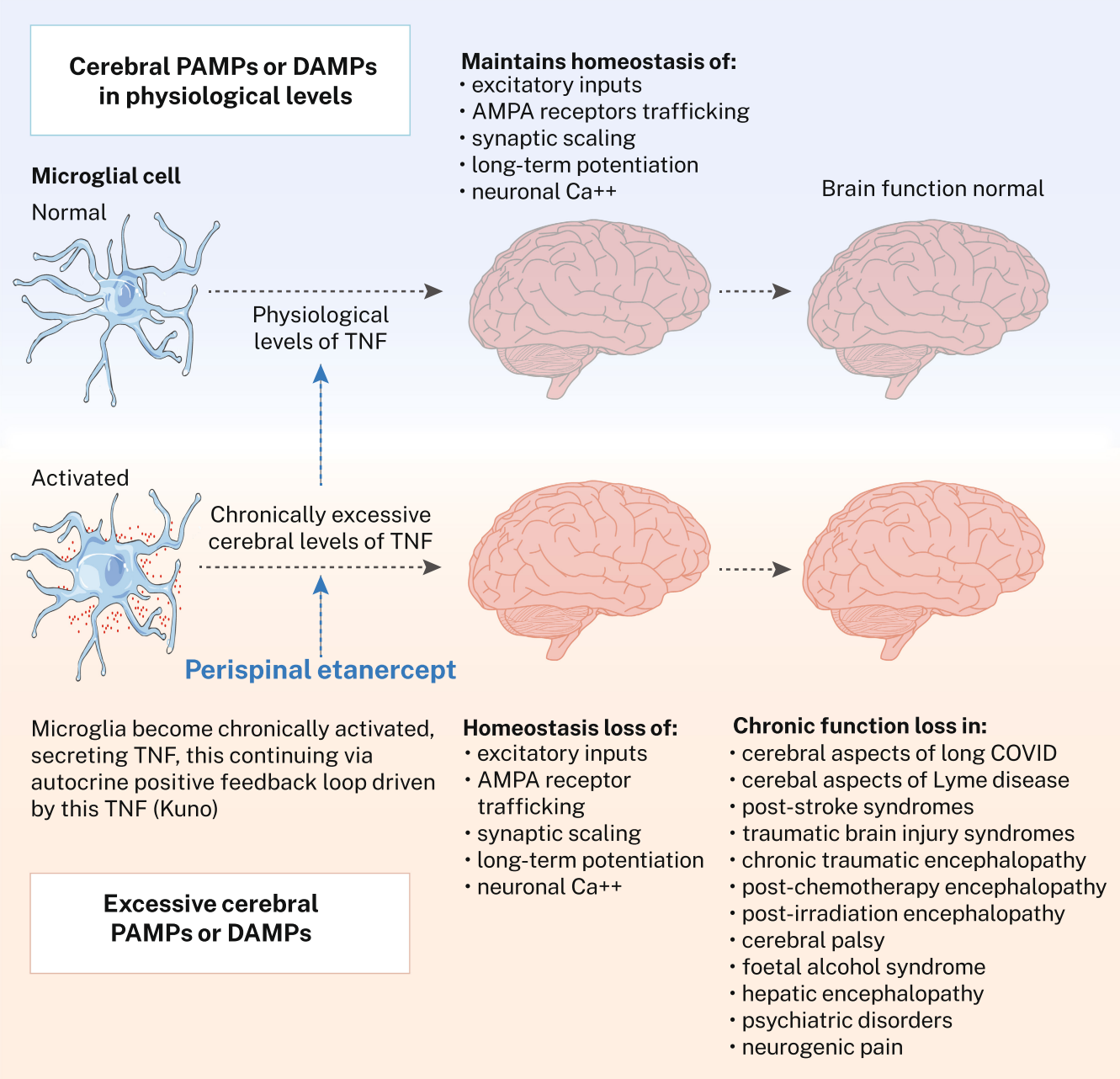

FIGURE 1 The proposed consequences of, and how to ameliorate, chronically activated microglia. An illustration of the rationale for the long-term effectiveness of a single anti-TNF perispinal treatment through activated microglia reverting to the normal quiescent state, rather than simply neutralizing the direct harmful effects of this cytokine. The recorded presence of chronically activated microglia across a range of neurodegenerative states thus indicates the predictability of the usefulness of anti-TNF administration so that it reaches the CSF.

agent by other routes, to remove the excess TNF initiating this positive feedback can be expected to prevent activated microglia continuing to generate and releasing excess TNF, thus rationalizing a long-term therapeutic effect from a single dose.

10 | CONCLUSIONS

Rewards for performing large perispinal etanercept RCTs are very likely not restricted to post-stroke syndromes, for which most experience exists. Its usefulness plausibly extends to the chronic cerebral aspects of long COVID, post-treatment Lyme disease, cerebral palsy, TBI and chronic traumatic encephalopathy, post-chemotherapy and irradiation cerebral dysfunction, fetal alcohol syndrome, the antinociceptive state in morphine-tolerance, hepatic encephalopathy, spinal cord injury, certain psychiatric states, and chronic neurogenic pain in a number of conditions. On a wider canvas, these concepts also link influenza and herpesvirus to the risk of various neurodegenerative diseases later in life. These pathogens both have documented PAMP activity,

and these neurodegenerative states all possess a literature on microglia being chronically activated. This combination provides the long-term potential to overwhelm the normal homeostatic control mechanisms such as synaptic plasticity and scaling. Included here is control over the neuronal type-1 inositol trisphosphate receptors (IP3R),[29] which are central to neuronal Ca^{++} homeostasis and thus to the ionic signaling cascades on which normal function of neurons depend.

In conclusion, the observations of Kuno et al[2] warrant being taken into consideration when understanding and treating a wide array of chronic dysfunctional neurological states.

AUTHOR CONTRIBUTIONS

Ian A. Clark contributed his cytokine, PAMP and DAMP, infectious disease, cerebral pathophysiology expertise, and wrote the draft of the text. **Bryce Vissel** contributed his wider basic central nervous system background. Both authors approved the final manuscript.

ACKNOWLEDGMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Open access publishing facilitated by Australian National University, as part of the Wiley - Australian National University agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

Neither author has any conflict of interest regarding the contents of this manuscript. Because of the commentary nature of this article, no novel data is available, nor patient or animal ethics involved.

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How to cite this article: Clark IA, Vissel B. Autocrine positive feedback of tumor necrosis factor from activated microglia proposed to be of widespread relevance in chronic neurological disease. *Pharmacol Res Perspect*. 2023;11:e01136. doi:10.1002/prp2.1136