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Review Article

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Neuroinflammation as a Mechanism in Long COVID

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ABSTRACT

Long COVID is recognized as a chronic post-viral condition characterized by fatigue, cognitive impairment, mood changes, and other neuropsychiatric symptoms that go beyond the acute phase of COVID-19. More research is now suggesting that neuroinflammation processes, involving microglial reactivity, altered cytokine signaling, and increased permeability of the blood-brain barrier, may contribute to the persistence of these symptoms. This paper provides a critical review of four recent empirical studies that directly examined neuroinflammatory mechanisms in individuals with long COVID using functional neuroimaging, biomarker analysis, and structural MRI measures. Across studies, converging evidence shows persistent central and peripheral immune activation linked to deficits in memory, attention, and mood regulation. Despite promising findings, the literature is limited by small sample sizes, inconsistent diagnostic criteria, and primarily cross-sectional designs, which limit conclusions about causality. Differences in imaging techniques and biomarker measurement approaches hinder direct comparison and synthesis of results. Future research should prioritize longitudinal, multimodal designs that integrate neuroimaging with immune and behavioral markers to clarify the trajectory and clinical relevance of neuroinflammation in long COVID. Overall, the evidence suggests that neuroinflammation plays a significant role in long COVID related cognitive and mood disturbances and emphasizes the need for biologically guided and consistent clinical approaches.

Introduction

The aftermath of the COVID-19 pandemic has revealed an increase of individuals who continue to experience lingering symptoms well after recovery from the acute infection. Commonly referred to as long COVID or post-acute sequelae of COVID-19 (PASC), this condition affects a significant proportion of individuals recovering from infection, with estimates ranging from 10% to 30% of those infected [1]. These individuals often report fatigue, difficulty concentrating, slowed information processing, sleep disturbance, and mood changes that persist for months or even years [2]. The wide range of cognitive, emotional, and physical symptoms associated with long COVID has made it difficult for researchers and clinicians to identify a single underlying biological mechanism.

While explanations such as viral persistence, immune dysregulation, and vascular injury have been considered, current evidence supports neuroinflammation as a possible explanation for the neurological and psychological symptoms in long COVID [3]. Neuroinflammation involves activation of the brain's innate immune cells, primarily microglia and astrocytes, leading to the release of proinflammatory cytokines that disrupt neural signaling, neuroplasticity, and neurotransmitter regulation [4]. These inflammatory responses can disrupt brain regions involved in mood regulation and cognitive processing, such as the prefrontal cortex and hippocampus, potentially contributing to symptoms like depression, anxiety, and brain fog [6].

Emerging research supports the presence of persistent immune activation in individuals with long COVID, even months after recovery from the acute illness. Neuroimaging research has demonstrated increased binding of the translocator protein (TSPO), an indicator of microglial activation, while biomarker studies report ongoing elevations in cytokines [4,7]. These findings indicated that neuroinflammatory activity may help explain how acute COVID-19 infection leads to lasting cognitive and emotional difficulties.

Despite this evidence, the current literature remains limited by methodological variability, small sample size, and inconsistent case definitions of long COVID. Few studies have used longitudinal designs or multimodal approaches to establish causality or track the persistence of neuroinflammatory changes over time [8]. These shortcomings point to the need for a systematic evaluation of current research on neuroinflammation as a factor in the cognitive and emotional consequences of long

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COVID. The purpose of this review is to critically evaluate recent empirical studies investigating neuroinflammatory mechanisms in long COVID using neuroimaging, biomarker, and structural brain methodologies. This review aims to integrate key findings, critically examine methodological issues, and identify future avenues of research that can support more biologically grounded understanding and clinical care.

Conceptual Background

Definition and Mechanisms of Neuroinflammation

Neuroinflammation refers to immune activation within the central nervous system (CNS), driven primarily by microglia and astrocytes, the brains immune cells [8]. When activated by infection, injury, or systemic inflammation, these cells release proinflammatory signals that can disrupt synaptic communication, impair neuroplasticity, and change normal patterns of neuronal activity [4,7]. Persistent or dysregulated activation of these pathways interferes with neuroplasticity, neurotransmitter balance, and the brain's energy regulation [3].

The blood-brain barrier (BBB) plays an important role in regulating communication between the peripheral immune system and the CNS. During periods of inflammation, the BBB permeability may increase, allowing cytokines and immune cells to enter neural tissue and increase neuroinflammatory signaling [7]. This breakdown in regulation creates a feedback loop between peripheral and central immune activity, maintaining inflammation long after the initial immune trigger has resolved. Continuous neuroinflammation can change levels of important neurotransmitters such as serotonin and dopamine, which are important for mood and motivation and can impair brain regions involved in memory and executive functioning [8]. These mechanisms provide a biological basis for understanding the persistent cognitive and emotional symptoms observed in long COVID.

Evidence from Other Post-Viral and Neuroimmune Conditions

Research on other post-viral syndromes offers valuable insight into how prolonged immune activation can lead to persistent neurological and cognitive symptoms, offering insight into the biological mechanisms now being observed in long COVID. For example, individuals recovering from Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) often showed ongoing fatigue, memory problems, and mood changes months after the illness resolved [9]. Neuroimaging studies on these populations showed white matter abnormalities and reductions in gray matter volume that were consistent with inflammatory injury [9].

Similar patterns have been documented following Epstein-Barr virus (EBV) infection, where patients experience prolonged cognitive slowing, issues with concentration, and low mood [10]. These lingering symptoms have been associated with ongoing immune activation and changes in brain regions involved in attention and memory [3,10]. Neuroinflammatory effects have also been reported after severe influenza, particularly in cases involving significant systemic inflammation. Studies show that some patients experience continued cognitive difficulties and emotional dysregulation following recovery, which are thought to reflect persistent immune signaling affecting neural pathways [8]. These findings across SARS, MERS, EBV, and influenza show that viral infections can trigger prolonged neuroimmune responses that disrupt brain structure and function. Observing these same neuroimmune disruptions in other post-viral conditions supports long COVID as part of a broader pattern of persistent cognitive and emotional effects following significant infection.

Long COVID as a Neuroimmune Syndrome

Long COVID can be understood as a condition in which ongoing immune activity affects the brain in ways that interfere with thinking, mood, and overall cognitive functioning. COVID-19 may influence the brain through more than one pathway. Some research suggests that the virus may affect the nervous system directly, particularly through areas connected to smell, while other research points to indirect effects caused by widespread inflammation in the body [11]. When the body's immune response remains active for an extended period, it can disrupt normal communication between the immune system and the brain, creating conditions that support continued inflammation in neural tissue. This kind of persistent immune activity can influence how brain cells communicate and how brain regions involved in attention, memory, and emotion function day to day [8]. Evidence showing ongoing activation of immune-related cells in the brain, along with studied reporting elevated inflammatory markers in the bloodstream, provides a biologically possible explanation for symptoms such as brain fog, irritability, and increased anxiety [4]. These symptoms can fluctuate or worsen with stress, a pattern that aligns with research suggesting that prolonged immune activation may sensitize certain neural pathways over time [12].

These findings support the idea that long COVID involves lingering immune-related changes in the brain that disrupt cognitive and emotional functioning. This view helps explain why symptoms can continue for months and points to the importance of exploring how persistent immune activity influences the brain.

Critical Review of Empirical Studies

PET Evidence of Microglial Activation in Long COVID

A research study conducted by Braga et al. examined whether individuals with long COVID show signs of ongoing neuroinflammation in the brain [5]. The researchers focused on people experiencing persistent depressive and cognitive symptoms following COVID-19, a presentation they refer to as COVID-DC. To explore whether neuroinflammation might be contributing to these symptoms, the study used a PET imaging tracer that binds to a translocator protein (TSPO), an indicator of microglial activation. PET scans were used to measure TSPO levels in several brain regions involved in motivation, emotion regulation, and cognitive processing, including the ventral striatum, dorsal putamen, anterior cingulate cortex, prefrontal cortex, and hippocampus [5].

The study included twenty individuals with COVID-DC and twenty healthy adults who were similar in age and sex. All participants completed neuropsychological assessments in addition to the PET scan, allowing Braga et al. to link brain changes with symptom patterns [5]. Results showed significantly higher TSPO levels in COVID-DC group compared to healthy

controls. The largest elevations were found in the ventral striatum and dorsal putamen, which are brain regions involved in motivation, reward processing, and motor speed [5]. These imaging findings were consistent with the symptom profile described by participants, who endorsed challenges with low motivation, reduced energy, anhedonia, and slower motor functioning.

The study also found a relationship between imaging results and behavior. Higher TSPO levels in the dorsal putamen were associated with slower performance on a finger-tapping task [5]. This association suggests that the neuroinflammatory activity seen on PET imaging may have a meaningful effect on everyday cognitive and motor functioning in people with long COVID [5]. These results provide evidence of neuroinflammation in individuals experiencing ongoing depressive and cognitive symptoms months after infection.

Methodological Strengthens and Limitations

The study offers important insights; however, several limitations exist. Although the study included individuals with long COVID, the sample represented only those experiencing depressive and cognitive symptoms, which limits the extent to which these findings apply to the broader long COVID population. The cross-sectional design also makes it difficult to determine whether the neuroinflammation observed contributed to the symptoms or developed in response to them. Additionally, TSPO binding could vary across individuals due to genetic differences, and although standard procedures were used, the study provided limited details about how these differences were handled. Symptom measurements were primarily based on self-report, which may overlook subtle cognitive difficulties. In addition, self-report measures carry the risk of overreporting, which could influence symptom severity scores.

Even with these limitations, the study makes a meaningful contribution by showing measurable signs of neuroinflammation in people who continue to experience depressive and cognitive symptoms after COVID-19. The areas of the brain with the highest TSPO are closely tied to motivation, reward, and motor speed [5]. This overlap between the PET findings and the self-reported symptoms, strengthens the idea that inflammation may be playing a role is slowed thinking, reduced motivation, and decreased energy that many individuals describe after COVID. The study also found a relationship between higher TSPO levels and slower performance on a finger-tapping task, suggesting that these inflammatory changes may have real-world behavioral effects rather than being just an imaging finding [5].

Braga et al. points out that prolonged immune activation of the brain's support cells, referred to as gliosis, could eventually be a target for treatment [5]. At the same time, they explain that this response is complicated because gliosis can sometimes protect the brain and sometimes contribute to symptoms [5]. It remains unclear exactly how gliosis fits into long COVID, and additional research is needed to fully understand its impact.

Overall, Braga et al. offers support for neuroinflammation as a possible contributing mechanism in long COVID [5]. Their research helps build a foundation for future studies and shows the need for larger, longitudinal research that can track these brain changes over time and clarify how they relate to symptom patterns. As one of the first studied to use PET imaging in this population, it shows both the potential value of neuroimaging and the need for more rigorous and comprehensive approaches going forward.

Peripheral Cytokine Markers and Cognitive Symptoms in Long COVID

A research study conducted by Damiano et al. examined whether individuals with long COVID show ongoing immune system changes that relate to cognitive difficulties [4]. The researchers were particularly interested whether blood-based inflammatory markers, such as cytokines and chemokines, were elevated months after the initial infection and if those markers were connected to cognitive symptoms, such slowed thinking or mental fatigue. To explore this question, they included individuals with long COVID, people who had recovered without lingering symptoms, and a group of healthy controls. The researchers measured inflammatory markers in each group and then looked at how those markers corresponded with scores on attention, processing speed, and memory tasks.

The study included 127 adults: 66 with long COVID, 25 who had recovered without persistent symptoms, and 36 healthy controls. All participants completed a cognitive battery that assessed attention, memory, processing speed, and mental fatigue. Blood samples were analyzed for a broad panel of inflammatory markers, including cytokines involved in immune activation and cell signaling. This design allowed the researchers to look not only at whether inflammation was elevated, but also whether these biological markers were meaningfully linked to cognitive complaints [4].

Across several analyses, individuals with long COVID showed higher levels of specific inflammatory markers compared to both recovered participants and healthy controls [4]. Although the patten varied across markers, the strongest differences involved cytokines related to immune activation and cell recruitment, suggesting that a portion of the immune system remained more active in those with long COVID [4]. These elevations were present months after the initial illness, reinforcing the idea of prolonged immune dysregulation rather than a short-term post-infection response.

In addition, higher levels of certain inflammatory markers were associated with slower processing speed, reduced attention, and greater self-reported cognitive fatigue. These relationships suggest that elevated immune activity may contribute to the kind of brain fog frequently described in long COVID [4]. The study also found that those with the highest inflammatory markers tended to perform more poorly on tasks requiring sustained attention and mental effort, indicating a connection between immune activation and cognitive performance [4].

Methodological Strengths and Limitations

While this study offers important insight into the biological mechanisms of cognitive symptoms in long COVID, several methodological limitations should be considered. The three comparison groups were not equal in size, with the long COVID

group being much larger than the recovered group, which may influence group differences. In addition, cytokine expression could vary based on factors like stress, sleep, or time of day, which are difficult to fully control even with standardized blood collection procedures [13]. The study was also cross sectional, with all data gathered during a single visit. This makes it difficult to tell if inflammation played a role in causing the cognitive difficulties or if people who were already struggling simply showed higher inflammatory markers that day.

Symptom ratings also relied on self-reports, which could be influenced by mood, health concerns, or general fatigue and could lead to either underreporting or overreporting. Another limitation is that the study assessed inflammation only through blood samples. While these markers are helpful for identifying ongoing immune activity, they do not show whether the same processes are happening in the brain [14]. Inflammation in the body and inflammation in the brain can be related, but they don't always move together, and the study did not include any direct measure of what is happening in neural tissue [14]. As a result, it is hard to know whether the elevated cytokines found in this sample actually signal neuroinflammation or whether they reflect a more general immune response.

Even with its limitations, this study offers useful insight into how lingering immune activation might related to the cognitive complaints many people describe after COVID-19. One of the most meaningful components of the study is that the elevated inflammatory markers were not only different from the control groups, but were also tied to specific cognitive patterns, particularly slower processing speed and difficulty sustaining attention [4]. These connections give some biological context to the brain fog complaints that are commonly reported in long COVID and help move the conversation beyond symptoms alone.

Another strength of the study is that the inflammation elevations were present months after the initial infection, which supports the idea that long COVID is not simply a prolonged recovery period. Instead, it may reflect an ongoing immune process that continues long after the acute illness. This perspective helps explain why some individuals experience cognitive slowing or mental fatigue even when their initial illness was mild [4].

The researchers point out that identifying reliable inflammatory markers could eventually help clinicians better track long COVID or identify subgroups that respond differently to treatment [4]. While much more work is needed before these markers can be used clinically, this study provides an early step toward understanding how immune activity and cognitive functioning might fit together.

Overall, Damiano et al. contributes a different but complementary piece to the growing picture of long COVID [4]. Instead of examining inflammation in the brain directly, they show that systemic immune changes may still have meaningful cognitive effects. Their work shows why it is important to consider long COVID from several biological angles. Longer term research will be important for understanding how these immune shifts relate to symptom changes as time goes on.

PET Evidence of Neuroinflammation in Long COVID

A research study conducted by VanElzakker et al., examined whether individuals with long COVID show signs of ongoing inflammation, and if these brain changes relate to markers of vascular dysfunction [6]. Using a PET imaging approach that detects glial activation, the researchers compared 12 adults with long COVID to 43 healthy adults. The long COVID participants had been experiencing symptoms for about 20 months and were never hospitalized during their infection. By focusing on people who were never hospitalized during their acute infection, the study reduces the chance that the findings are due to complications from severe illness and instead reflect changes more specific to long COVID [6].

The results showed a noticeable pattern of elevated PET signal in the long COVID group, suggesting higher levels of glial activation throughout the brain [6]. This means that the brain's support and immune cells appeared more active than expected nearly two years after the initial infection. The increased PET signals were found across several regions, including the cingulate cortex, thalamus, basal ganglia, precentral gyrus, and corpus callosum [6]. These regions play important roles in attention, emotional regulation, motor functioning, sensory processing, and communication between the two hemispheres for the brain.

Seeing this patten across such a wide area is meaningful because it ties directly to the symptoms many people with long COVID describe, such as slowed thinking, reduced mental clarity, fatigue, and trouble concentrating. The cingulate cortex and thalamus are especially involved in sustaining attention and managing emotional responses, while the basal ganglia and precentral gyrus contribute to movement, motivation, and energy levels [6]. The corpus callosum supports communication across brain regions, which is important for efficient processing and problem solving [6]. When these areas show signs of increased immune related activity, it becomes easier to understand why individuals might have difficulty with tasks that require sustained focus, multitasking, or mental effort.

Another important aspect of the study is that the elevated PET signal was not limited to one isolated region of the brain but appeared across multiple interconnected systems. This suggested that long COVID might not affect a single cognitive function but instead disrupts broader brain networks that support daily functioning [6]. Because these regions are involved in such fundamental processes, even small disturbances could have noticeable effects on thinking, mood, and fatigue. Overall, this pattern of elevated PET signal across multiple brain regions helps clarify why people with long COVID often experience different cognitive and emotional symptoms and points to ongoing inflammation in the brain as one possible reason for these challenges.

A helpful aspect of this study is that the researchers collected blood samples right before the brain scans, which allowed them to look at how the imaging results aligned with biological markers in the bloodstream. They found that people who showed the higher PET signal in the brain, also had higher levels of certain vascular related proteins in their blood [6]. The proteins they found are often elevated when there is inflammation or stress in the vascular system [6]. This pattern is important

because it suggests that what is happening in the brain and what is happening in the body may be connected. Instead of showing neuroinflammation on its own, the findings point to a broader process that involved both immune activity in the brain and signals of vascular strain in the bloodstream. This gives a more complete picture of long COVID by showing that the condition may involve multiple biological systems working together, rather than a single isolated mechanism. The fact that individuals who had the strongest PET signal also reported more difficulties with fatigue, concentration, and mental clarity adds context to the biological findings. Although these symptoms were based on self-report rather than formal cognitive testing, the consistency between subjective experiences and biological markers suggests that these complaints may reflect underlying physiological changes rather than being purely subjective [6].

Methodological Strengths and Limitations

Although this study provides important evidence of neuroinflammation in long COVID, several methodological issues should be considered. The sample size was small, with only 12 people in the long COVID group. While PET imaging studies often include small samples due to cost, this limits how confidently the findings can be generalized to the broader long COVID population. The samples were also mostly female, which makes it difficult to know if these findings apply equally to men. Another limitation is that the study only captured data at one point in time and cannot show when these brain changes began or how they shift as symptoms continue. A longitudinal design would be helpful to understand if the neuroinflammatory patterns seen on PET imaging remain stable, worsen, or improve over time. Another limitation is that the study did not include any objective cognitive testing. All symptom information was based on self-report, which limits the ability to track how closely the PET findings related to daily cognitive functioning. Without objective cognitive testing, it is difficult to know how closely the PET abnormalities align with actual performance in daily cognitive tasks.

In addition, the correlations between the PET signal and vascular related markers are interesting but do not show which process is driving the other. These findings suggest a possible link between neuroinflammation and vascular stress, but the direction and nature of that relationship remain unclear. Since participants were scanned at the same research site using the same equipment, it is unclear whether these results would look similar in other samples or at different imaging centers.

Overall, this study helps broaden the understanding of long COVID by showing that neuroinflammation and vascular stress may be occurring together rather than as separate processes. What makes these findings especially meaningful is that they were observed in people who were never hospitalized and had relatively mild acute infections yet continued to experience symptoms nearly two years later. This reinforces the idea that persistent cognitive and emotional difficulties can have a biological basis in individuals without severe initial illness. Although the sample was small, the study offers evidence that long COVID may involve ongoing changes in the way the brain and vascular system interact, and it shows the need for larger studies that can follow people over time to clarify how these patterns evolve [6].

Structural Brain Changes and Cognitive Impairment in Long COVID

Although this next study did not directly measure inflammatory markers or glial activation, the structural brain changes identified by Pacheco-Jamie et al. are very consistent with the downstream effect of chronic neuroinflammation [15]. Increased cortical thinness, reduced white matter integrity, and difficulties with working memory and processing speed are common patterns seen in conditions involving prolonged immune activation [9]. Because earlier research has shown persistent immune activity in long COVID, the structural and cognitive findings in this study offer an important complementary perspective. Instead of capturing inflammation directly, this study shows how possible neuroimmune processes might shape brain structure and cognitive functioning almost two years after infection. This helps link the immune related patterns show in PET and cytokine studies with the structural differences now being observed in long COVID.

Pacheco-Jamie et al. examined if adults with post-COVID condition (PCC) have long-term changes in brain structure and how these changes relate to cognitive performance [15]. This study stands out from other research because it used a comprehensive MRI protocol, which evaluated cortical thickness, gray matter volume, white matter structure, and included a full neuropsychological assessment. Using both imaging and cognitive testing allows researchers to see if the difficulties patients describe show up as identifiable brain changes [15].

The study included 128 adults with long COVID and 37 healthy adults between the ages of 18 and 65. All participants completed a neuropsychological battery that assessed domains that are commonly affected in long COVID, such as working memory, learning, verbal fluency, processing speed, and executive functioning [15]. Participants were labeled as cognitively altered if they had at least two test scores that fell 1.5 or more standard deviations below the mean. Using this cut-off strengthens the study because it separates individuals with measurable cognitive impairment from those reporting symptoms but performing within normal limits [15]. Across several cognitive domains, PCC participants performed significantly worse than healthy controls. Deficits were most pronounced in working memory, immediate recall, delayed recall, and processing speed, which are all areas that are often vulnerable in inflammatory or neuroimmune conditions [15]. These patterns are consistent with other literature that describes slowed mental processing, increased cognitive fatigue, and memory issues in long COVID [4,9].

To examine structural brain differences, the researchers used a multimodal MRI protocol, which included both structural imaging and diffusion tensor imaging. The structural MRI showed that participants with PCC had increased cortical thickness in regions of the right frontal lobe, particularly the superior and middle frontal gyrus [15]. While cortical thinning is typically associated with neurodegeneration, cortical thickening can be linked with prolonged immune activation [16]. Individuals who had more thickening in these frontal regions also tended to perform worse on working memory tasks. This pattern suggests that the brain changes might be part of the problem rather than the brain trying to compensate [15].

The diffusion MRI findings provided additional insight into white matter pathways. The PCC participants showed reduced white matter integrity in several major pathways, including the corpus callosum, superior longitudinal fasciculus, and right uncincate fasciculus [15]. These tracks support attention, memory, and processing speed, which fits well with the domains where PCC participants showed weaknesses [15]. Although these white matter differences did not strongly predict objective test performance, they were linked with participants memory complaints. This pattern indicates that mild cognitive changes might be present even when formal tests do not show clear impairment.

Methodological Limitations

Although this study offers valuable insight into possible structural and cognitive changes associated with long COVID, several limitations are present. One limitation involved the neuropsychological battery itself. While the study used a broad set of cognitive tests, standardized assessments could miss subtle or fluctuating cognitive issues that individuals notice in their daily lives. This might explain why the white matter abnormalities were more closely related to participants subjective memory complaints than to their objective scores. If the battery was not sensitive enough to detect the types of cognitive fatigue or slowed thinking that many people with long COVID report, some participants may have been labeled as unimpaired even though they were still experiencing noticeable difficulties in daily life.

Another limitation is that the study was cross sectional, meaning all data were collected at one point in time. Because of this design, it is difficult to know when these brain changes began or how they might change as symptoms continue. It is unclear whether the cortical thickening and white matter differences represent lasting changes or if they could improve or worsen over time. The sample was also drawn from a single research center, which may limit how well the findings apply to the broader long COVID population, especially given how much people vary in their symptom patterns and illness duration. In addition, the study did not include any biological measures of inflammation or vascular stress, which would have made it easier to connect the structural findings to specific neuroimmune processes. Including these types of markers would help clarify what is driving brain differences that were identified.

Integration of Findings

The four studies reviewed in this paper provided converging evidence that long COVID involved persistent immune-related changes that affect the brain and cognition. Although each study uses a different method and focuses on a slightly different aspect of long COVID, they point in a similar direction. The PET imaging work shows increased glial activation in key brain regions involved in mood, motivation, and cognition, which is consistent with ongoing neuroinflammation months after infections [5,6]. The cytokine study demonstrates that individuals with long COVID continue to show elevated inflammatory markers in the bloodstream that are related to slower processing speed, reduced attention, and cognitive fatigue [4]. The structural MRI and diffusion findings show changes in cortical thickness and white matter integrity that align with these cognitive difficulties and are common in conditions involving prolonged immune activation [15].

Although the methods differ, these findings fit together in a coherent way. PET evidence of microglial activation provides a direct window into inflammation within the central nervous system, while elevated peripheral cytokines show that the immune system remains activated outside the brain [5,6]. VanElzakker et al. links PET signal with vascular-related proteins and suggests that neuroinflammation and vascular stress may be occurring together rather than separately, which may help explain why symptoms extend across cognitive, emotional, and physical domains [6]. The structural and diffusion MRI results then show how these immune related processes may be expressed at the level of brain anatomy, particularly in frontal and white matter pathways that support working memory, processing speed, and executive functioning [15]. Across studies, the same general cognitive profile emerges, which includes slowed processing, mental fatigue, and memory difficulties. The fact that different researchers, using different measures and samples, are finding the same profile strengthens the argument that these cognitive issues are consistently linked with ongoing immune-related changes in long COVID.

Beyond their scientific overlap, these studies have a pattern that is clinically meaningful. Each one identifies biological changes that match the cognitive symptoms many people with long COVID describe, which helps validate that these difficulties are not simply subjective or related to stress. The findings suggest that persistent symptoms may stem from ongoing disruptions in neuroimmune and neurovascular processes that influence how the brain regulates energy, attention, and information processing [5,15]. Viewing long COVID through this lens can help shape how clinicians assess these patients and show the value of using biological markers to track people who continue to experience symptoms long after their initial infection.

Conclusion

Overall, the research reviewed in this paper shows that long COVID is best understood as a condition in which prolonged immune activity continues to shape cognitive and emotional functioning well after the acute infection has resolved. Across studies using PET imaging, inflammatory biomarkers, and structural MRI, the findings point toward a shared pattern of disrupted neuroimmune and neurovascular processes that influence how the brain supports attention, memory, and mental energy. Although the methodologies differ, each study contributes a piece of evidence showing that these symptoms have a measurable biological basis. At the same time, the current literature remains limited by small sample sizes, inconsistent definitions, and a lack of longitudinal data, making it difficult to determine when these changes begin or how long they persist. Moving forward, research that follows individuals over time and combines imaging, immune markers and detailed cognitive assessments will be necessary for clarifying the mechanisms that sustain these symptoms. A clearer understanding of these pathways will help guide more consistent approaches to diagnosis and may eventually support more targeted treatments for individuals who continue to experience long COVID-related cognitive and emotional difficulties.

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