REVIEW

Associations Between Neuropsychiatric Symptoms and Inflammation in Neurodegenerative Dementia: A Systematic Review

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Background: Neuropsychiatric symptoms are common in dementia and linked to adverse outcomes. Inflammation is increasingly recognized as playing a role as a driver of early disease progression in Alzheimer's disease (AD) and related dementias. Inflammation has also been linked to primary psychiatric disorders, however its association with neuropsychiatric symptoms in neurodegenerative dementias remains uncertain.

Methods: We conducted a systematic literature review investigating associations between inflammation and neuropsychiatric symptoms in neurodegenerative dementias, including AD, Lewy body, Frontotemporal, Parkinson's (PD) and Huntington's disease dementias.

Results: Ninety-nine studies met our inclusion criteria, and the majority (n = 59) investigated AD and/or mild cognitive impairment (MCI). Thirty-five studies included PD, and only 6 investigated non-AD dementias. Inflammation was measured in blood, CSF, by genotype, brain tissue and PET imaging. Overall, studies exhibited considerable heterogeneity and evidence for specific inflammatory markers was inconsistent, with lack of replication and few longitudinal studies with repeat biomarkers. Depression was the most frequently investigated symptom. In AD, some studies reported increases in peripheral IL-6, TNF-a associated with depressive symptoms. Preliminary investigations using PET measures of microglial activation found an association with agitation. In PD, studies reported positive associations between TNF-a, IL-6, CRP, MCP-1, IL-10 and depression.

Conclusion: Central and peripheral inflammation may play a role in neuropsychiatric symptoms in neurodegenerative dementias; however, the evidence is inconsistent. There is a need for multi-site longitudinal studies with detailed assessments of neuropsychiatric symptoms combined with replicable peripheral and central markers of inflammation.

Keywords: dementia, immune, depression, psychosis, biomarkers

Introduction

Dementia is a major cause of morbidity and mortality.[1] Neurodegenerative dementias, including Alzheimer's disease (AD), dementia with Lewy Bodies (DLB), Parkinson's disease dementia (PDD) and frontotemporal dementia, are all associated with abnormal protein folding, protein aggregation and neuronal loss. Their etiology is complex and poorly understood, but increasing evidence suggests that inflammation may represent a common pathway contributing to pathological protein aggregation and neuronal loss across different neurodegenerative dementias.[2,3]

AD is defined by the presence of amyloid plaques and neurofibrillary tangles and is the most common cause of dementia.[4] It is a clinical syndrome of progressive cognitive decline,[5] usually beginning with a prodromal Mild Cognitive Impairment (MCI) stage.[6] Neuroinflammation is well recognized in AD. In response to amyloid-β plaques, microglia

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secrete inflammatory cytokines[7,8] and upregulate interferon response genes.[9] Imaging microglia in vivo with positron emission tomography (PET) of the translocator protein (TSPO) receptor has identified increased ligand binding, interpreted as microglial activation, in AD.[10] TSPO binding correlates with amyloid and tau pathology, as measured by 18-[F]-flumetamol and 18-[F]-AV1451 PET imaging.[11] TSPO binding has also been associated with tau spreading[12] and subsequent cognitive decline.[13]

DLB, the second most common cause of dementia,[14] is characterized by visual hallucinations, parkinsonism, rapid eye movement (REM) sleep behavior disorder and cognitive fluctuations.[15] α-synuclein, a hallmark of DLB pathology,[16] induces an immune response in vitro and in animal models.[17] There is evidence for cortical recruitment of T-lymphocytes,[18] higher levels of peripheral cytokines including interleukin (IL)-6 and tumor necrosis factor (TNF)-α,[19] and PET imaging of microglial activation in early DLB.[20]

FTD presents with behavioral-executive and language (primary progressive aphasia, including semantic variant and non-fluent) variants. Peripheral and central inflammation are well recognized across the FTD spectrum, with alterations in serum cytokines, CSF cytokines, and T-cell phenotypes in patients compared to controls.[21]

Neuropsychiatric symptoms (NPS) are prevalent in dementia and associated with carer stress and poor outcomes. Common NPS include depression, apathy, anxiety, delusions, hallucinations, and agitation among others.[22] They often precede dementia diagnosis as they can occur in the prodromal stages of AD[23] and DLB.[24–26] NPS are associated with patient outcomes. This varies by neurodegenerative disease and symptom domain. For example, in longitudinal studies of Alzheimer's dementia psychosis, agitation, and depression were associated with cognitive progression and increased dependence.[27] Psychosis, affective symptoms, and agitation/aggression were associated with earlier death.[28] A recent meta-analysis in PD has found that psychosis and depression are associated with cognition and disease progression.[29] In DLB, higher scores on a composite NPS scale were associated with caregiver burden and depression.[4] In AD, total neuropsychiatric symptoms are more closely associated with caregiver distress than cognition,[30] with studies also reporting a bidirectional relationship between NPS and distress.[31] Apathy in gene carriers at the presymptomatic stage of FTD predicts cognitive decline.[32] Across dementia subtypes, a factor including a range of BPSD was associated with hospital admission.[33] NPS are predictive of nursing home placement in AD,[34] specifically with depression, delusions, and agitation increasing the risk of institutionalization across cognitive disorders.[35] In PD, hallucinations are a predictor of future nursing home placement.[36]

NPS have been associated with specific imaging,[37] neurotransmitter,[38–40] and pathological changes,[41,42] but there is a need for a greater understanding of the mechanisms of these symptoms to develop effective therapies,[43] especially in dementias apart from AD where the evidence base in more limited.[44,45] Current treatments primarily target neurotransmitters and are of limited effectiveness[46] or associated with significant risks.[47,48]

NPS are common in inflammatory diseases.[49] There is evidence that anti-inflammatory or immunomodulatory treatments may play a role in relieving depression comorbid autoimmune conditions.[50] There is increasing evidence that inflammation plays a causal role in the development[51] and symptoms[52] of psychiatric disorders, and trials of anti-inflammatory of immune modulatory treatments are ongoing in depression.[53] Several mechanistic pathways have been proposed for the relationship between inflammation and NPS. In depression, chronic stress has been linked to the release of pro-inflammatory cytokines, which has been linked to increased glutamate in magnetic resonance imaging (MRS) studies. This leads to decreased activity in corticostriatal reward networks and symptoms such as anhedonia.[54] Cytokines also regulate indoleamine 2.3-dioxygenase (IDO), which metabolizes tryptophan to kynurenine, leading to quinolinic acid production, an N-methyl-D-aspartate (NMDA) receptor agonist, with this pathway linked to depression in animal models and clinical studies.[55] In NMDA receptor (NMDAR)-antibody encephalitis, antibody mediated internalisation of the NMDAR leads to reduced signals in inhibitory neurons, which has been proposed as a mechanism for the psychotic symptoms.[56]

There are several potential mechanisms linking Alzheimer's disease and the immune response. Firstly, as a core part of the disease pathology – microglial genes represent a large proportion of the risk for AD,[57] specific microglial response to amyloid-beta and tau pathology associated with cytokine release, and microglial activation in vivo as measured by PET imaging of the translocator protein (TSPO) linked to amyloid-β[58] and tau.[59] This central inflammation could lead to peripheral inflammation via the release of cytokines that cross the blood–brain barrier, however there is a paucity of studies with paired measures of central and peripheral inflammation.[58,60]

Secondly, there is evidence that chronic diseases, such as diabetes[61] and cardiovascular disease,[62] are associated with risk of AD, or more rapid progression. One proposed mechanism is that the chronic low-grade inflammation associated with chronic disease or acute inflammatory events such as sepsis influence central immune responses and increase the risk of neurodegeneration.[63]

Mid and late life depression are risk factors for dementia.[64] The mechanisms of this association are not fully understood. It could represent prodromal symptoms of neurodegenerative disease, or alternatively the chronic inflammation associated with depression could increase dementia risk. In support of this, individuals with MCI and a history of depression treated with serotonin selective reuptake inhibitors (SSRIs) showed reduced rate of progression to AD,[65] and meta-analysis has shown that treatment with SSRIs is associated with a reduction in proinflammatory cytokines.[66]

Whether the inflammatory response is generated as part of the underlying neurodegenerative process, or secondary to other chronic disease or associated with depression, if this response is causally associated with the development of NPS, this could represent a potential therapeutic target for symptomatic relief.

Therefore, a greater understanding of the biological mechanisms underpinning NPS and the associations with inflammation is needed to develop more effective therapies. Identifying immune biomarkers associated with NPS could guide treatment trials, including repurposing of existing immunomodulatory medications and allowing stratification of clinical trials, to identify which patients are most likely to benefit from these drugs.[67] Previous reviews have specifically looked at cytokines with behavioral and psychological symptoms in dementia (BPSD) in dementia,[68] apathy in AD,[69] and depression in Parkinson's disease.[70] We undertook a systematic review exploring peripheral and central measures of inflammation across different neurodegenerative disorders.

As there is evidence that common pathways such as protein aggregation and neuronal death are associated with common immune pathways, such as toll-like receptor signalling[3] and microglial activation[2] across neurodegenerative diseases. There is also evidence for distinct immune responses that depend on specific protein pathologies – such as microglial states depending on amyloid-β or tau pathology,[71] and the association of CD4 cells with α-synuclein.[72] For this reason, we were broad in our inclusion of neurodegenerative dementias, including AD, LBD, FTD, PSP, and their prodromes but excluding non-neurodegenerative causes, which lack these shared features.[73]

In order to capture the full extent of the literature, we were broad in our definition of an inflammatory marker: we aimed to identify studies that measured a biomarker[74] that was related to an immune or inflammatory process. This will include cytokines, chemokines, immune cell subsets, and PET imaging of microglia. As there is evidence for both peripheral and central inflammation in dementia,[63] our intention is to include markers measured in both compartments. We have also been broad in our definition of NPS as symptoms associated with changes in perception, thought, mood and/or behaviour,[75] including psychosis, agitation, apathy, depression, and sleep disturbance.[76]

Methods

We searched MEDLINE, Embase, and PsycINFO databases through OVID on 25/07/23 with the terms:

((microglia) OR (TSPO) OR (interleukin) OR ("translocator protein") OR ("tumour necrosis factor") OR (TNF) OR ("c-reactive protein") OR (CRP) OR (cytokine)) AND ((Dementia) OR ("Alzheimer's disease") OR (Lewy) OR ("Parkinson's disease") OR ("mild cognitive impairment") OR (MCI) OR ("progressive supranuclear palsy")) AND ((depression) OR (psychosis) OR (apathy) OR (anxiety) OR (hallucination) OR (delusions) OR (neuropsychiatric) OR (agitation))

We included no publication date restrictions but limited the search to articles in the English language. Therefore, the timeframe of the search was as follows: 1966–2023 for MEDLINE, 1947–2023 for EMBASE and 1967–2023 for PsychINFO. We included additional articles identified from the citations or those known to the authors. Our inclusion criteria were as follows: Firstly, studies of a neurodegenerative dementia (including but not limited to Alzheimer's disease, Lewy body dementias, frontotemporal dementia or progressive supranuclear palsy) or their prodromal stages (such as mild cognitive impairment due to Alzheimer's disease or mild cognitive impairment due to Lewy Bodies) or Parkinson's disease. Secondly, an outcome measure of peripheral or central inflammation (such as inflammatory markers in plasma, serum, or cerebrospinal fluid (CSF), immune cell subsets, or PET imaging of immune markers). Thirdly, an outcome measure of neuropsychiatric symptoms, and finally a reported test for association or relationship between the inflammatory markers and neuropsychiatric symptoms.

Our exclusion criteria were case reports (or small cohorts with less than five participants), fundamental science research, animal studies, or non-neurodegenerative dementia. Our primary outcome was the association between an inflammatory or immune marker and neuropsychiatric symptoms in neurodegenerative dementia groups. Duplicates were removed in Endnote, and the search results were then imported into Rayyan. Articles were then screened by title and abstract, then for potentially suitable papers full text of articles was obtained. These were further screened against the inclusion and exclusion criteria. Reasons for exclusion were recorded and reported in Figure 1. From included articles we extracted from the full text into Excel the study design, setting, diagnosis (and diagnostic criteria), number
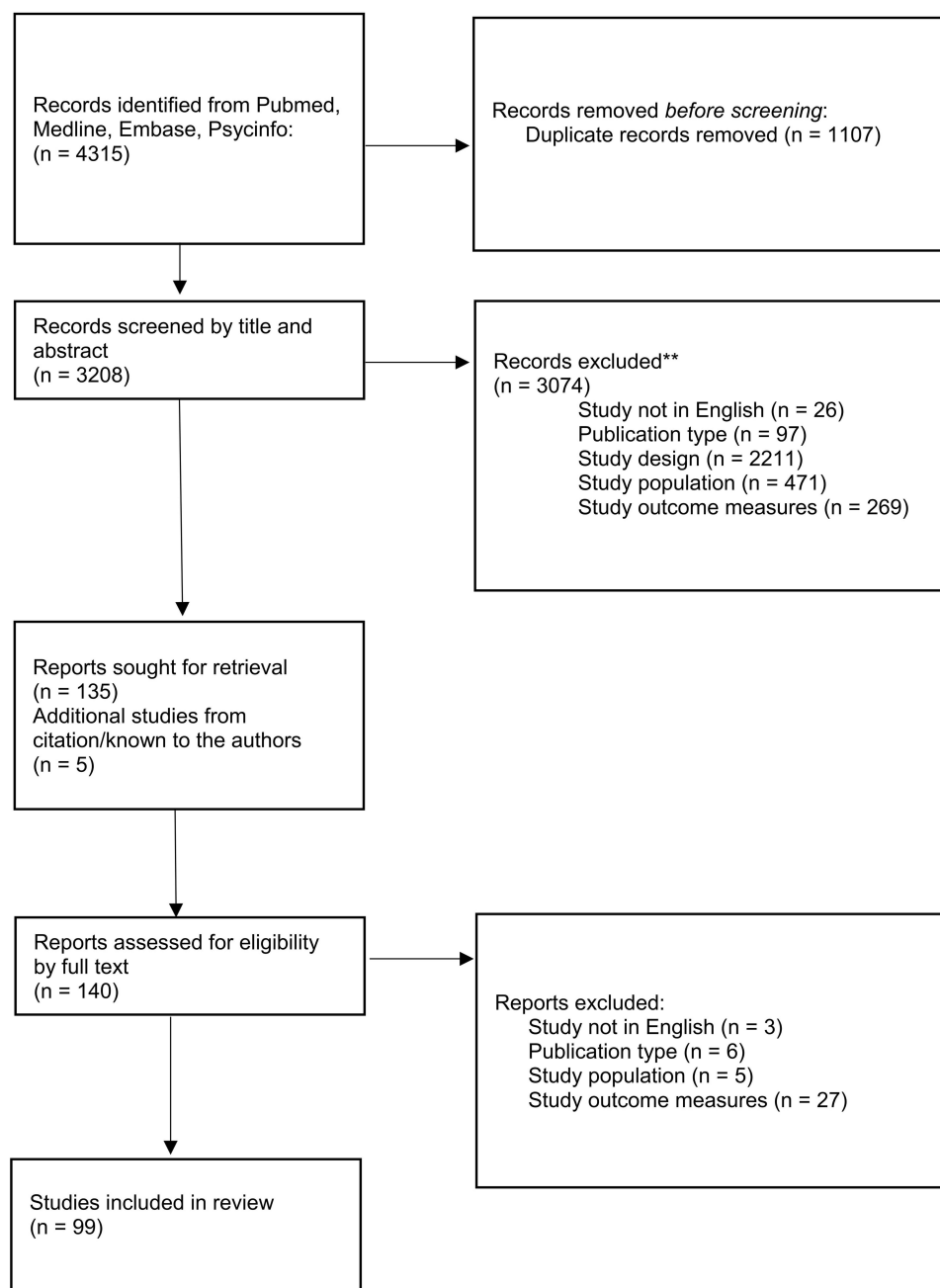
Figure 1 Flow diagram describing the systematic review process.
Notes: **Publication type included abstracts or conference proceedings with insufficient details, book chapters, editorials/letters without new data, or protocol papers. Study design describes reviews with no original data, case reports, animal studies, or fundamental science papers. Study population describes studies with no neurodegenerative disease group. Study outcome describes studies with no psychiatric outcome, no inflammatory measure, or no testing for association between psychiatric and inflammatory measures. This flow diagram is based on PRISMA reporting guidelines.[162]

of participants, demographics, inflammatory marker measured, assay source and details, psychiatric symptom measurement and by which scale, and the overall findings of the study. We did not exclude studies based on formal quality criteria (beyond the lower limit of number of participants). Our aim was to be inclusive, and extract data that allowed the quality of studies to be compared qualitatively, including the diagnostic criteria used (case definition), the source of recruitment, inclusion of controls, the specific assays used for biomarker measurement and scales used to measure NPS.

Results

Our search identified 3208 articles after duplicates were removed. A total of 3074 articles were excluded by title and abstract, with 135 articles sought for full-text retrieval. These were supplemented with 5 articles known to the authors or identified from the citations. Ninety-nine articles were included in the final review (Figure 1). Many excluded studies recorded an inflammatory measure and psychiatric outcome but did not report testing for an association.

Firstly, we will describe four key themes that emerged across studies, regardless of diagnosis, inflammatory marker, or neuropsychiatric symptom. These were the number and selection of participants, the study design, the choice of outcome measure, and the quality of the assay.

Secondly, we will report the results from each neurodegenerative diagnosis in order from most to least studied, broken down firstly by neuropsychiatric outcome, and within each outcome, assay type.

Participants

Most articles included participants with either AD (including mild cognitive impairment, n = 58) or Parkinson's disease (n = 35). Very few articles included participants with DLB (n = 3), FTD (n = 2) or Huntington's disease (n = 2). One study[78] did not specify dementia subtype, and one study included a mixed group.[79] Comparator groups included cognitively unimpaired controls, major depressive disorder (MDD), delirium, subjective cognitive impairment (SCI), vascular dementia (VD), or other neurodegenerative diseases. Whilst studies frequently included unspecified MCI or MCI due to AD (MCI-AD), there was only one study that included MCI-LB (alongside MCI-AD).[80] A wide range of diagnostic criteria were used. Ten studies did not describe standardized diagnostic criteria. A graphical summary of the distribution of studies by diagnostic group is given in Figure 2. The overall study sizes ranged from 10 participants to 3073, with several large multicenter research cohorts with paired blood and CSF.[81–83] However, many studies were small including less than 20 participants per group.[84,85] Full descriptions of the diagnostic criteria provided in each study are summarized in Supplementary Table 1.

Study Design

Most studies were cross-sectional (n = 72), with many fewer (n = 13) including longitudinal follow-up. These studies primarily focused on baseline biomarkers on disease progression rather than measuring biomarkers at multiple timepoints.[86,87] Studies were focused on outpatients, with five studies including participants as inpatients (including nursing homes).

Outcome

The most common symptom domains studied were depression and anxiety (PD, n = 19, AD/MCI-AD, n = 26, DLB/MCI-LB, n = 1). Less frequently studied were psychosis, apathy, agitation, and sleep disturbance. Many studies used a composite measure of NPS (AD/MCI-AD, n = 20, DLB/MCI-LB n = 3) with fewer studies separating the symptom domains.[88] A graphical summary of the number of studies by neuropsychiatric symptom outcome is given in Figure 3. Controlling for disease severity was variable. Those with NPS often had lower cognitive scores,[89,90] or studies identified groups with increased inflammation, more psychiatric symptoms, and more cognitive or motor symptoms.[91,92]

Assays

Most studies used blood biomarkers of inflammation (n = 58), with fewer having paired CSF (n = 9), or CSF alone (n = 8). Studies on blood were primarily performed on serum and plasma, with some using peripheral blood mononuclear cells (PBMCs). Less commonly used were genetic, epigenetic or RNA sequencing. There were only two imaging studies, both

Number of studies by diagnosis
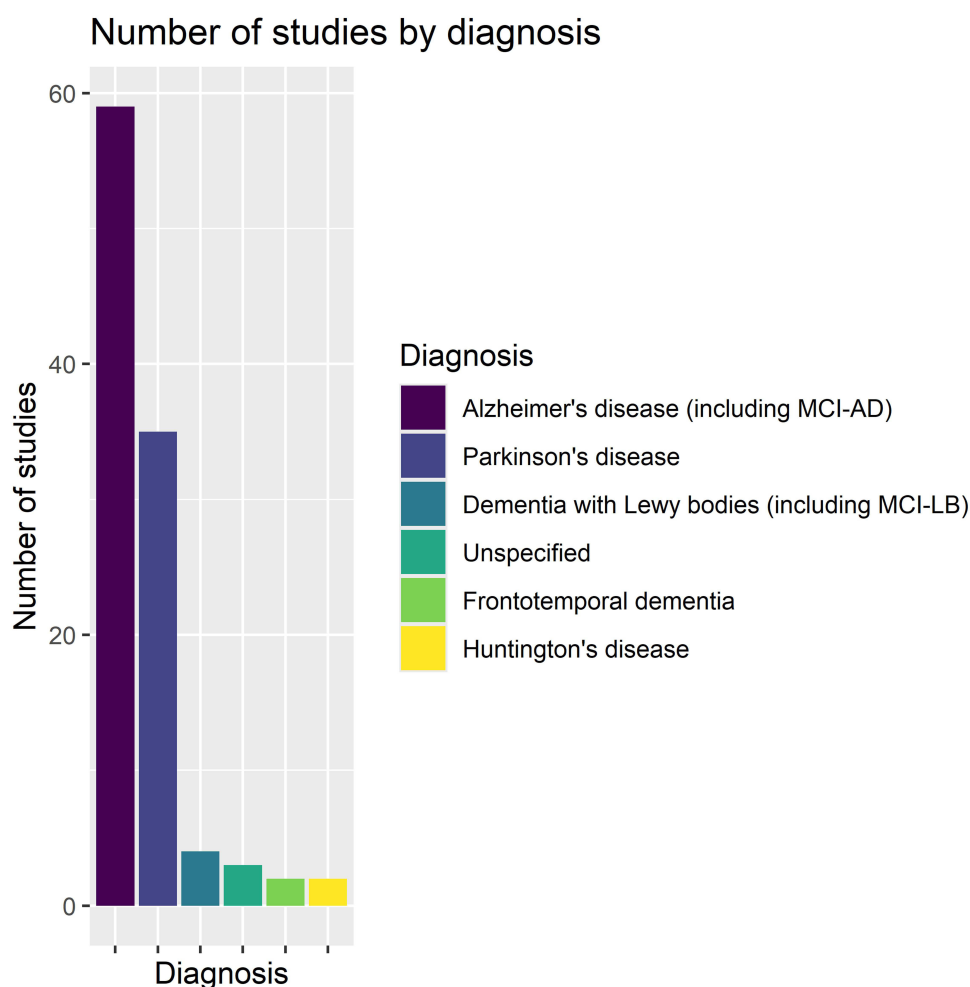
**Figure 2** Graphical summary of number of studies by diagnostic group.
Notes: Bar chart showing the number of studies by diagnosis. Different bars represent diagnostic groups and are identified with the color key on the right. The height of the bar represents the number of studies identified by the systematic review studying each diagnostic group.

in AD.[93,94] Both used PET imaging of the TSPO receptor (one with 11[C]-DPA-713 and one with 11-[C]-PBR28). A summary of number of studies by assay source and sample size is given in Figure 4. Some studies provided detailed descriptions of the assay used, and the parameters around sample collection,[95] whilst others provided minimal details.[96] Individual studies mostly measured single or small numbers of select inflammatory markers using separate ELISAs, with multiplex methods becoming more common over time (Figure 5).[97] Major immune biomarkers like C-reactive protein (CRP), IL1-β, IL-6 and TNF-α were frequently assayed. Across studies there was a spread of biomarkers assessed, with a range of in-house and commercial assays, and limited consistency between studies. These include, but are not limited to, interleukins (such as IL-2, IL-4, IL-6, IL-8, IL-10, and IL-12), interferons (such as IFN-γ), immune cell subsets as measured by flow cytometry (including CD3, CD4, CD8 subsets, and dendritic cell subsets) either stimulated or unstimulated, and mRNA expression from whole blood. There were several studies that looked at immune gene single nucleotide polymorphisms (SNPs) in association with psychiatric symptoms[98–107] in small cohorts. Full descriptions of the assays are provided in Supplementary Table 1.

Alzheimer's Disease and MCI-AD

Studies in AD predominantly examined the relationship between inflammation and depression (n = 26), followed by those using composite scores (n = 20). Few studies looked at other individual symptom domains (agitation, apathy,
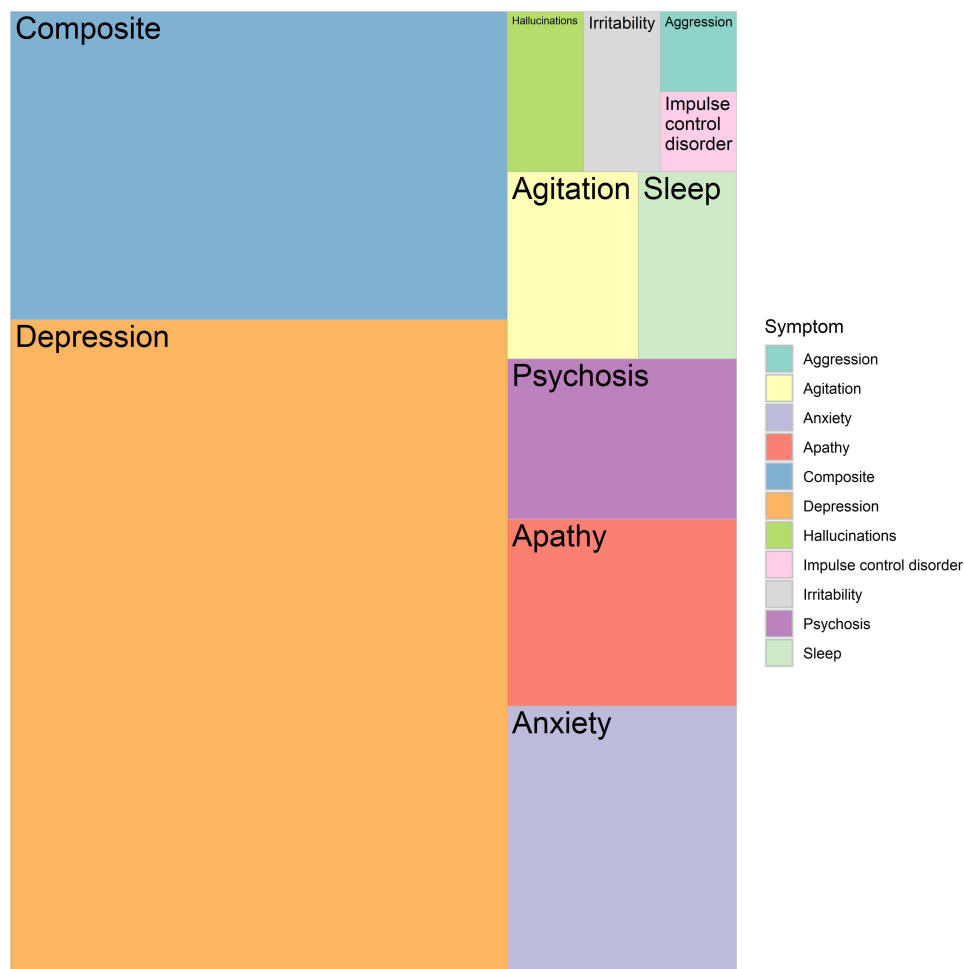
Figure 3 Graphical summary showing the proportions of studies by neuropsychiatric symptom outcome measure.
Notes: Tree plot showing the proportions of studies exploring each neuropsychiatric symptom. The size of the area within the grid represents the number of studies, and each colored area represents a different neuropsychiatric symptom, as described by the key on the right. Composite symptoms represent those using an outcome with multiple symptom domains summed together, like the total NPI score.

psychosis, and sleep disturbance). All studies looked at sporadic AD or did not specify whether genetic cases were included. Full descriptions of the studies are included in Supplementary Table 2.

AD-Depression

Neuropathology

Two studies used brain tissue. The first[108] focused on neutrophil gelatinase-associated lipocalin (NGAL), an innate immune protein associated with Alzheimer's pathology and depression. They identified increased NGAL levels in the hippocampus of AD patients with depression. This relationship varied by region, with areas of the cingulate having higher NGAL levels in those without depression. This study combined neuropathology with serum and CSF. There were no differences in serum levels of NGAL, but a significant decrease in CSF NGAL. A second study[109] used a range of microglial, cell adhesion, and cytokine markers and identified IL-4 as significantly increased in AD-depression compared to AD cases without depression.

Paired CSF and Blood

A large study[81] examined a panel of immune biomarkers in CSF, plasma and serum focusing on the link between inflammation and the metabolism of tryptophan via the kynurenine (Kyn) pathway, which has been linked to depression.[110] This study identified a higher Kyn/5-HT ratio associated with peripheral immune markers, and this ratio

Studies by size and assay source
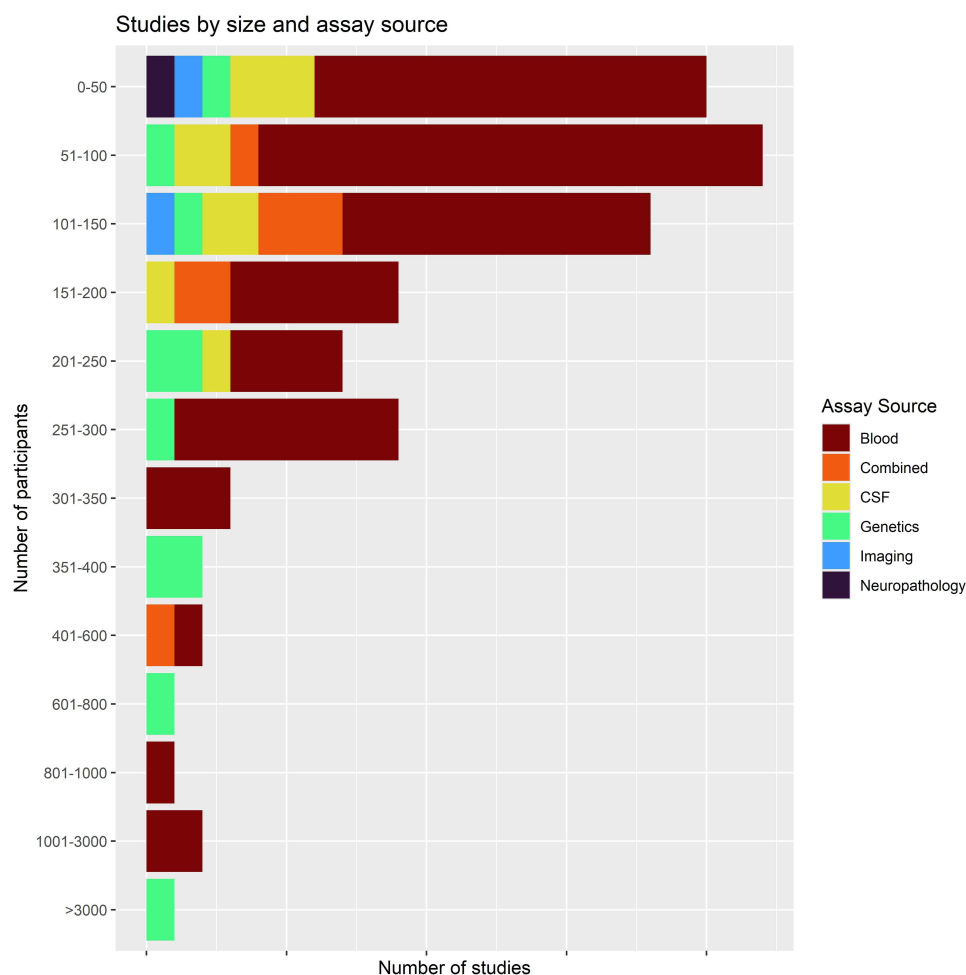
Figure 4 Bar chart of number of participants in each study.
Notes: Bar chart showing the number of participants in each study, colored by the assay source. The x-axis displays the number of studies, and each bar on the y-axis represents the number of participants in each study. The assay source is shown by the color key on the right.

was associated with increased depression and anxiety scores. This study identified a possible shared mechanism between primary depression and depression in AD.

CSF
Total depression scores were not associated with CSF IL-6 or brain-derived neurotrophic factor (BDNF), but there were associations with individual symptom domains (psychomotor slowing and nighttime disturbance).[111] Although a single exploratory study, it is of interest as inflammation-driven reductions in BDNF have been implicated in depression[112] and psychomotor slowing.[113] One study found a micro-RNA (miR-451a) that regulates toll-like receptor (TLR) 4 was lower in AD with depression and correlated with depressive symptom scores.[114]

Serum and Plasma
There are three studies that measured IL-6 in AD with depression and found an association.[89,115,116] This is not without caveats; AD with depression groups often had lower cognitive scores,[89,116] or findings had wide confidence intervals and limited details of assays.[115] One large study in AD did not find any associations with IL-6 and depression scores,[117] and another in MCI[118] does not does not report similar findings; however, this was in outpatients with diabetes with MCI diagnosed based on cognitive scores.[119] One study measured IL-6 with a composite outcome measure including depression and is detailed in the section below.[86] Details of studies measuring either IL-6 or TNF-α in association with depression or anxiety in AD are given in Table 1.

Number of studies by assay type
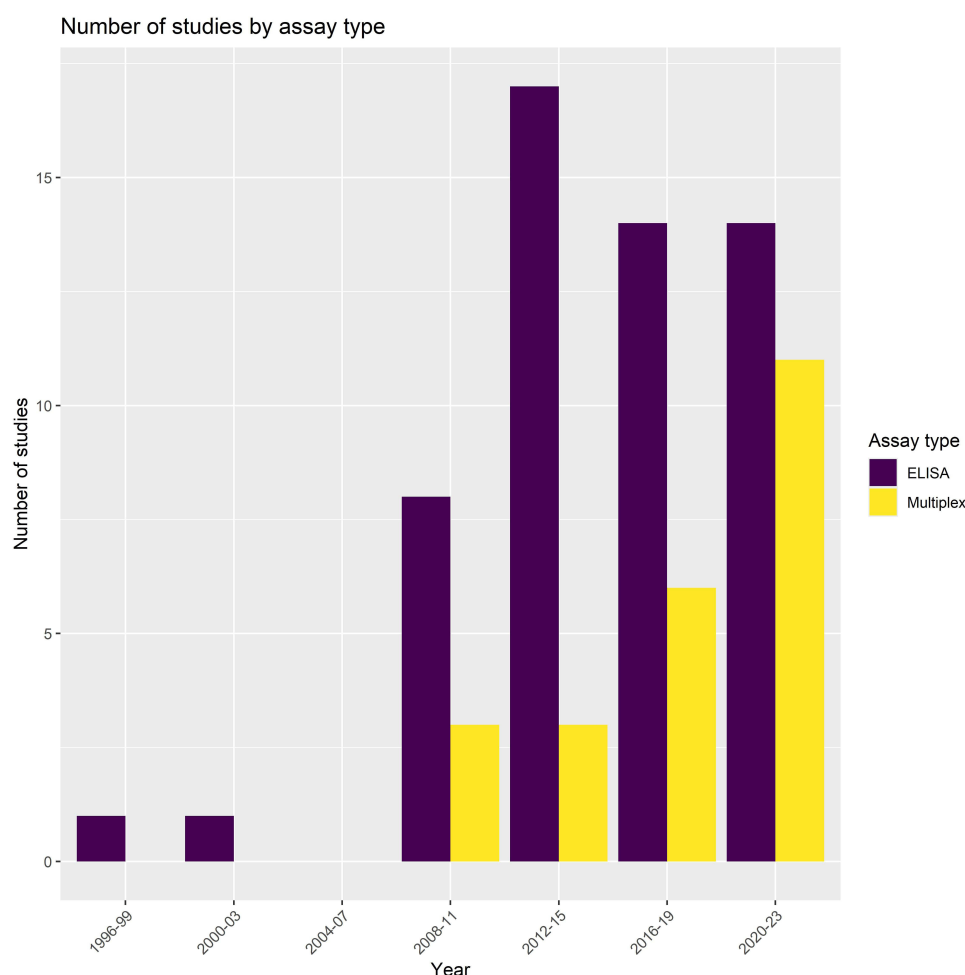
Figure 5 Bar chart showing the change in assay type for studies measuring fluid inflammatory markers.
Notes: Each bar represents an epoch of years, and the y-axis shows the number of studies in each year measuring fluid inflammatory markers, split into those using single ELISAs (purple) and those using multiplex assays (yellow).

Two studies from a large multi-centre research cohort (the Texas Alzheimer's Research and Care Consortium) have studied the impact of inflammatory biomarkers on depressive symptoms. CRP was a significant predictor of the apathy domain of depression scores, and in combination with MIF and ICAM accounted for 26% of the variance in apathy scores in one study.[121] In another study from this cohort, this effect appeared to be driven by female AD cases.[122] Another study[123] found no association between CRP, IL-1β, or transforming growth factor (TGF)-β and total geriatric depression scale (GDS) scores, despite significant group differences of IL-1β and TGF-β compared to controls, and correlations with cognitive scores.

Two studies[89,116] also found higher levels of TNF-α in AD cases with depression, with the second finding a correlation between TNF-α and depressive symptoms, and a further study finding TNF-α contributed to an apathy in men.[117] One study did not find an association,[120] but this was a small study (n = 20) and did not include details of disease stage or cognitive scores. One study measured TNF-α with a composite outcome measure including depression and is detailed in the section below[86] (Table 1 and Figure 6).

Studies found higher levels of vascular endothelial growth factor (VEGF)[124,125] in AD cases with depression compared to AD cases without depression, or controls, including two large studies[81,95] as part of a multiplex panel, and significantly lower levels of the associated protein endocan.[126]

One study[127] found associations between IL-7 and depressive symptoms, but these correlations were inverted depending on the assay source (positive correlation in serum and negative correlation in plasma), and differential effects

Table 1 Studies Measuring Peripheral IL-6 or TNF-α in Association with Depression or Anxiety in Alzheimer's Disease. Number of Asterisks Denote Significance Level (* P<0.05, ** P<0.01, *** P<0.001)

Assay Source	Authors	Participants	Study Design	Scale	Inflammatory Marker	Results
Serum	Banerjee et al, 2017[89]	AD (34 with depression, 26 without depression) HC = 60	Cross sectional case control	DSM-IV	IL-6 and TNF-α	IL-6 increased with AD with depression compared to AD without depression*** TNF-α increased in AD with depression compared to AD without depression** IL-6 (r = −0.472** and TNFα r = −0.651*** negative correlations with MMSE in AD with depression but no correlations in AD without depression.
Serum	Gorska-Ciebiada et al, 2015[118]	MCI = 62 (25 with depression), HC = 132 (57 with depression)	Cross sectional case control	GDS	CRP, IL-6, TNF-α	GDS-30 correlated with CRP (0.56***) and TNF-α (0.77**) in MCI with depression group. Multivariate logistic regression revealed IL-6* among other factors (CVD, poor glycaemic control) increased likelihood of having MCI in depressed patients.
Serum	Khemka et al, 2014[116]	AD = 55 (31 with depression and 24 without depression), HC = 37	Cross sectional case control	DSV-IV criteria	IL-1-β, IL-6, TNFα	IL-6 and TNFα were higher in AD with depression compared HC and AD without depression***. Increased IL-1β in both groups of AD patients compared to controls***
Serum	Johnson et al, 2016[115]	AD = 107	Cross sectional study	GDS	Inflammatory marker panel (details not described)	7 proteins showed significantly higher risk of depression: MIP1*, IL-6 *, VCAM1*, Adiponectin*, Factor VII **, IL-5 *, ICAM1*
Serum and Plasma	Alvarez et al, 1996[120]	AD = 20	Cross sectional cohort	HRSD	Histamine, IL1-β, TNF-a	Negative correlation between histamine and HRSD (−0.63**)
Serum	Holmes et al, 2011[86]	AD = 275	Longitudinal cohort study	NPI	CRP, TNF-α, IL-6	Patients with low TNF-α had lower NPI scores over 6 months**. Increased TNF-α was associated with more frequent symptoms of agitation*, depression**, anxiety**. Lower IL-6 was associated with lower NPI scores over period of 6 months*. Increased IL-6 associated with increased frequency of hallucinations* and apathy*.
Serum	Hall et al, 2012[117]	AD = 91, HC = 161	Cross sectional case control	GDS	IL-6, IL-10, IL-1, CRP, TNF-α and MIF	TNF accounted for 12% variance in apathy score in men. MIF weak predictor R2 $\leq$ 0.03* of total GDS score and 3/4 symptom clusters in all participants. MIF predictor of depression in men with AD accounting for 12% of the variance in apathy sore, and 15–51% of the variance in 3 symptom clusters. In females, MIF, ICAM and CRP accounted for 26% variance in apathy.

in males compared to females. This highlights the need to consider assay source. A study that measured messenger ribonucleic acid (mRNA) by reverse transcription polymerase chain reaction (RT-PCR) in PBMCs[128] found that whilst a number of cytokines had increased transcripts (interferon (IFN)-γ, TNF-α, IL-1R2) were increased in late life depression, those with AD and depression had downregulation of IL1-β. Measuring triggering receptor expressed on myeloid cells (TREM)1 mRNA in blood identified a significant negative correlation with depressive scores.[129] TREM1 is related to TREM2, identified as a key inflammatory risk gene in AD.

AD- Composite
Imaging
Two studies[93,94] looked at the association between neuropsychiatric inventory (NPI) scores and regional bindings of PET ligands to the TSPO receptor. The first[93] found agitation associated with increased TSPO binding in temporal regions, not explained by cognition or AD pathology (although could potentially be explained by differences in TSPO binding
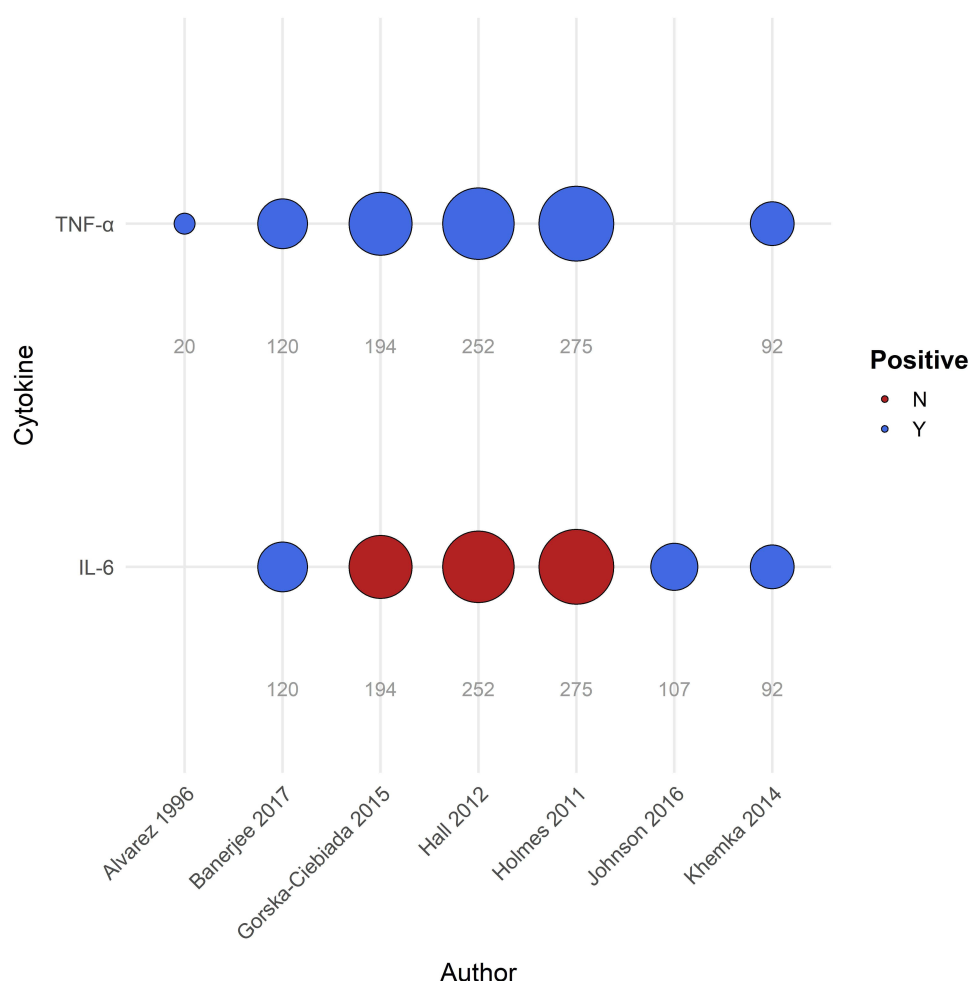
Figure 6 Graphical summary of studies testing the association of TNF-α or IL-6 in association with depression or anxiety in AD.
Notes: Studies measuring either TNF-α or IL-6 in association with depression or anxiety in AD. Size of the point and the number represent the study size, and color whether the study demonstrated broadly positive (blue) or negative (red) results. Studies in the figure are Alvarez et al 1996,[120] Banerjee et al, 2017,[89] Gorska-Ciebiada et al, 2015,[118] Hall et al, 2012, Holmes et al, 2011,[86] Johnson et al, 2012[115] and Khemka et al, 2014[116] (see "AD-Depression" section in the main text and Supplementary Table 2 for full details of individual studies).

between controls and those with MCI/AD). This study was from a large well-characterized cohort with multimodal PET imaging. Interestingly, the second[94] also identified agitation associated with TSPO binding, again excluding confounders.

Paired CSF and Blood
A longitudinal study measured CSF and serum inflammatory markers in cognitively unimpaired older adults, those with MCI, and those with AD, in association with NPS measured by the NPI-Questionnaire (NPI-Q).[92] This study identified markers in both the CSF (IL-8, IL-15, soluble intracellular adhesion molecule (sICAM)-1 positively, and inducible protein (IP)10 and CRP negatively) and serum (macrophage inflammatory protein (MIP)-1α, IL-6, Eotaxin-3 positively and CRP negatively) associated with the presence of NPS, suggesting different pathways may be involved peripherally and centrally. These relationships varied when controlling for cognitive impairment and AD biomarker profiles, with CRP levels appearing the most robust. sICAM-1 was associated with longitudinal decline, highlighting how central nervous system (CNS) inflammation contributes to both NPS and cognitive decline.

CSF
There was an inverse relationship between IL-10 and NPS in one study.[78] This study specifically targeted recruitment towards those with NPS, capturing a greater range of severity. Studies also identified inflammatory markers

associated with cognition (IL-1β, IL-6, and IL-12p70)[130] or disease state (gasdermin, a pyroptosis marker)[131] but not NPS.

Serum and Plasma

A number of small studies found no relationship between single peripheral cytokines measured by ELISA (TNF-α or IL-1β) and NPS.[132,133] Others using multiplex assays[134] found no significant relationships; however, one study[135] found that relationships depending on APOE status, with lower IL-15 being a significant predictor of NPS in APOE4 carriers, and lower IL-18 and TNF-α were significant predictors in non carriers, although this study did not control for disease stage or severity. A large[86] (n = 275) longitudinal study with repeat biomarker measurement found that lower TNF-α predicted lower NPI scores over six months, and higher TNF-α was associated with increased agitation, depression and anxiety, with raised IL-6 associated with hallucinations and apathy. There were no associations between CRP and NPI scores.

Homocysteine, involved in a number of biological processes correlated with inflammatory markers, was associated with increased risk of NPS in a single study.[136]

PBMCs

Two studies used stimulated PBMCs[84,137] which overcomes some challenges of measuring cytokines in serum,[138] and found that IL-6 expression was associated with total NPI scores, and psychosis subscale scores. An unstimulated PBMC study found an association between NPI depression subscale and myeloid dendritic cells.[139]

AD-Agitation

Four studies looked specifically at agitation in AD disease, and each of these studies included an inpatient setting. One study included CSF,[140] finding a relationship between the TSPO ligand diazepam-binding inhibitor (DBI) and agitation. DBI was correlated between CSF and serum, and this study is particularly notable as agitation and irritability were both the primary NPS associated with PET imaging of the TSPO receptor. Other studies using serum or plasma identified Il1-β, IL-6, natural killer cell activity (NKCA), and TNF-α associated with agitation.[141–143]

AD-Apathy

One of the largest studies identified[82] (n = 1319) measuring a panel of inflammatory markers identified IL-6 and IL-10 as significant predictors of apathy scores, whilst two small studies identified associations with soluble TNF receptors,[85] ICAM-1, and IL-1.[144]

AD-Psychosis

One study identified reduced IL1β from stimulated PBMCs as associated with psychosis in AD,[145] and another found significantly higher IL-8[146] and decreases in other cytokines in AD patients without psychosis, which may relate to antipsychotic treatment. A large study that included AD among dementia subtypes found no relationship between CRP and psychosis.[79] Although this study grouped together a wide range of dementia diagnosis, it was one of the few performed on an inpatient ward.

AD-Sleep

Two studies by the same author[96,147] looked at the relationship between inflammation and sleep in AD using actigraphy, and found no associations in MCI, and IL-6 associated with increased total sleep time and reduced sleep latency in dementia. There were limited details described in these studies, but they are unique in using a biosensor to measure outcomes.

AD-Summary

In summary, there are some potential associations between peripheral and central markers of inflammation and NPS in AD, but primarily without replication or with divergent results between studies. There is interest in how these

relationships may be affected by the assay source[127] or mediated by APOE status.[135] Studies included potential mechanisms for associations, such as tryptophan metabolism[81] and reductions in BDNF.[111] The most studied combination is peripheral IL-6 and depression, with replication across three studies (although with a high degree of uncertainty). A large study found an association with IL-6 and apathy.[82] The other largest studies identified positive associations with NPS and markers including homocysteine,[136] TNF-a,[86] and CRP,[148] or combinations of markers in multiplex panels.[81,95] Whilst there are only two PET imaging studies, both found associations between microglial activation and agitation[93,94] suggesting there may be both central and peripheral immune associations with NPS.

Parkinson's Disease

Thirty-five studies explored the relationship between inflammation and NPS in PD. Similarly to AD, the majority of studies looked at the relationship with depression and anxiety. A few studies explored hallucinations. The majority were in idiopathic PD, however two studies included participants with the LRRK2 mutation.[91,149] The most common diagnostic criteria used was the UK Brain Bank criteria. Full descriptions of the studies are included in Supplementary Table 3.

PD-Depression

CSF

There were eight studies testing the relationship between inflammatory markers in the CSF and depression in PD.[150–157] A variety of markers were examined; however, the most common were IL-6, TNF-α, and IL-1β. The only markers with replicated findings were CRP and IL-10, showing positive associations in two studies.[150,153,154,156]

Serum and Plasma

Eight studies examined serum inflammatory markers and symptoms of depression or anxiety[87,91,149,157–160] with one[161] looking at depression as part of a composite measure. Four studies examined inflammatory markers in plasma.[77,162,163] The most consistent positive associations were for IL-6 and TNF-α, although results were generally mixed. Details of studies measuring either IL-6 or TNF-α in association with depression or anxiety in PD are given in Table 2 and displayed in Figure 7.

The most studied individual biomarker was IL-6, with nine studies examining the association with peripheral IL-6 and depression or anxiety in PD. Four studies found an association with depression or anxiety. Two studies[158,162] found

Table 2 Studies Measuring Peripheral IL-6 or TNF-α in Association with Depression or Anxiety in Parkinson's Disease. Number of Asterisks Denote Significance Level (* P<0.05, ** P<0.01, *** P<0.001)

Assay source	Authors	Participants	Sudy design	Scale	Inflammatory marker	Results
Serum	Fu et al 2023[158]	PD = 273, HC = 91	Cross sectional case control	HAMD-24, HAM-A, NMSS	TNF-α, IL-6, IL-8	IL-6 positively correlated with HAMD*** and NMSS*** in PD patients. IL-8 and TNF-α showed no significant correlations
Serum	Rastegar et al 2019[149]	PD = 160 (80 with LRRK mutation)	Longitudinal cohort study	GDS	MIP1β, IL-6, IFNY, IL-1RA, IL-5, GM-CSF, TNFα, CCL5, IL-2, IL-1β, CCL11, bFGF, VEGF, PDGF, CXCL10, IL-13, IL-4, MCP-1, IL-8, MIP1α, IL-10, GCSF, IL-15, IL-7, IL-12(p70), IL-17A, and IL-9	The following baseline inflammatory markers correlated with fold change in GDS over 2 years in all patients: IL5 = 0.609**, IL8 = 0.415**, GCSF = 0.438**, MIP1β = 0.294*, IL10 = 0.435**, MIP1β = 0.294*, IL6 = 0.320*, IL1RA = 0.546**, TNFα = 0.436**, CCL5 = 0.337*, bFGF = 0.301*, VEGF = 0.640**, MIP1α = 0.435**, IL7 = 0.350*, IL15 = 0.643**. There were no other significant correlations with other markers.

*(Continued)*

Table 2 (Continued).

Assay source	Authors	Participants	Sudy design	Scale	Inflammatory marker	Results
Serum	Veselý et al 2018[87]	PD = 47	Longitudinal cohort study	MADRS	CRP, C3, C4, IL-6	Increased baseline levels of IL-6 associated with higher MADRS scores at follow up (2 years), rho = 0.366*
Plasma	Selikhova et al 2002[162]	PD = 45 (27 with depression, 18 without depression), HC = 15	Longitudinal cohort study	BDI, STAI	IL-6	Higher IL-6 in PD with depression compared to PD**. Increases in IL-6 correlated with BDI scores r=0.64*** and anxiety scores r=0.65*** in PD group.
Blood (Unspecified)	Wan et al 2023[164]	PD = 51 (with depression) HC = 51	Cross sectional case control	HAM-A, HAMD	IL-6, S100β, mi-RNA-218-5p and mi-RNA-320a-5p	Negative correlation between miR-218-5p and HAM-A r = −0.4163**, HAMD r = −0.4927**. No other significant findings between inflamamtory markers and depression scores.
Blood (Unspecified)	Wang et al 2016[165]	PD = 62 Control = 62	Cross sectional case control	HAMD, HAMA	IL-1β, IL-6, IFNY, hsCRP, sIL-2R, TNF-α	In PD group, correlations between TNF-α r=0.345***, hsCRP r=0.393***, sIL-2R r=0.452*** and HAMD scores. Correlations with the same inflammatory markers and HAMA scores r=0.386*** r=0.423***, r = 0.364***
Serum (with paired CSF)	Karpenko et al 2018[153]	PD = 117, HC = 60	Cross sectional case control	BDI, HADS, NMSS	IL-1β, IL-1RA, IL-6, IL-10, TNF-α	Correlation between HADS anxiety score r = 0.42*, HADS depression score r = 0.36* and serum IL-10 in PD. No significant associations found for CSF cytokines/other serum cytokines
Serum	Kim et al 2022[166]	PD = 58 (45 at 3 year follow up), HC = 20)	Longitudinal cohort study	NMSS	IL-1β, IL-2, IL-6, IL-10, TNF-α, hsCRP	High PC3 (mainly loaded by IL-6 and IL-2) scores associated with worse NMSS over time*. High PC3 was associated with aggravation of mood and apathy*
Serum	Lindqvist et al 2012[161]	PD = 86, HC = 40	Cross sectional case control	FACIT, HAD, SCOPA-S	IL-6, TNF-α, sIL-2R, CRP	No significant correlations between non-motor symptoms and IL-6 or CRP. Regression analysis showed sIL-2R predicted FACIT scores β=−0.31*, HAD depression scores β=0.36***, and HAD anxiety scores β=0.32***. TNF-α predicted HAD depression score β= 0.31* in analysis with an outlier.
Plasma	Menza et al 2010[163]	PD = 52 (comorbid depression)	Cross sectional cohort	HAMD-17, PDQ-8, SF36, CGI, PSQI	IL-1β, IL-6, IL-10, TNF-α	TNF-α correlated with higher PSQI r=0.347*, and HAMD-17 r= 0.44*** scores. After adjusting for multiple comparisons, correlation between TNF-α and HAMD-17 remained significant.

a positive correlation with IL-6 and depression scores, and two longitudinal cohorts[87,149] found that IL-6 positively correlated with an increase in depression scores over 2 years, suggesting that increased inflammation predicts subsequent NPS. Other studies[165] found no association, or did not directly test the association directly but via miRNA intermediaries.[164] The largest studies found positive associations,[149,158] except for one which was stratified based on a range of variables beyond NPS.[91] The discrepancies between the studies may also be explained by the use of plasma or serum, assay choice, depression scale, and inclusion of covariates. In studies that reported cognitive scores, IL-6 was also associated with worse cognition and more rapid disease progression.[158,162]

Three studies[149,161,163] found an association between depression and peripheral TNF-α, with one showing that along with 13 other cytokines, TNF-α correlated with increases in GDS scores over two years. Four studies found no association between depression and TNF-α. Here there were similar sized studies, with differing assay methods and
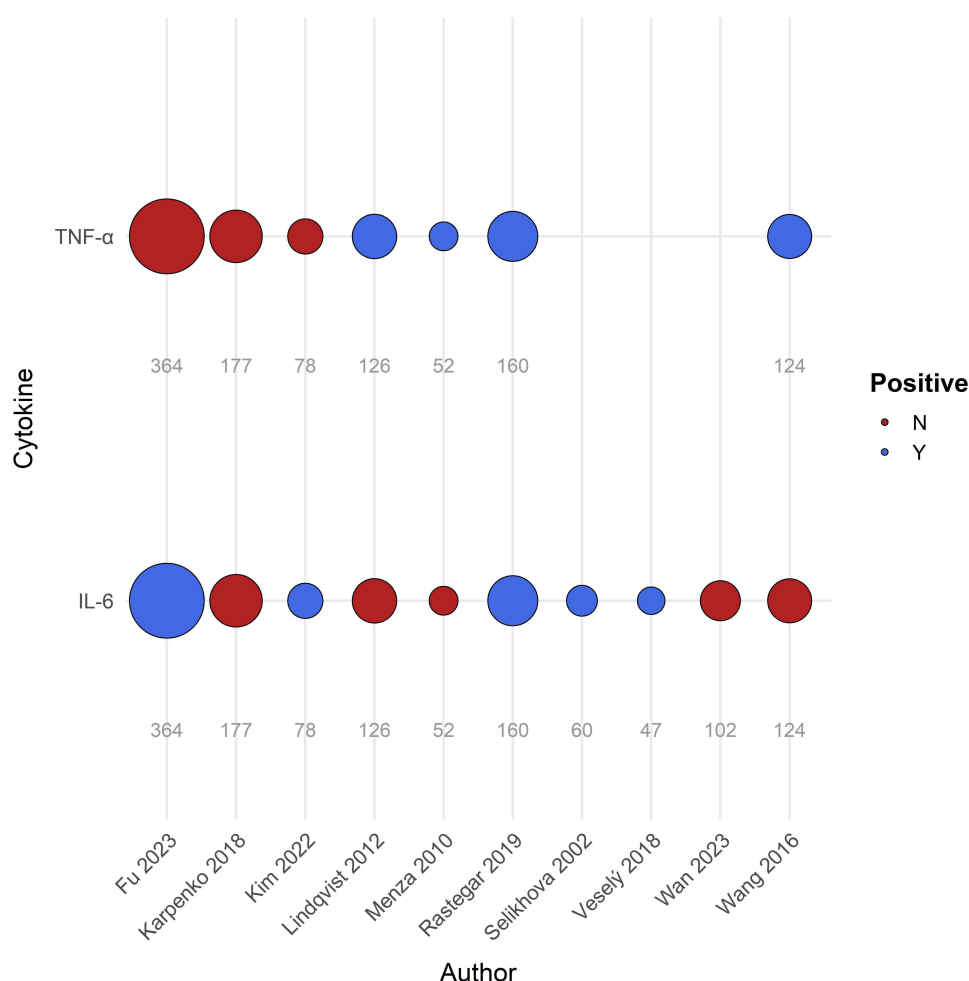
Figure 7 Graphical summary of studies testing the association of TNF-α or IL-6 in association with depression or anxiety in PD.
Notes: Studies measuring either TNF-α or IL-6 in association with depression or anxiety in PD. Size of the point and number represent the study size, and color whether the study demonstrated broadly positive (blue) or negative (red) results. Studies in the figure are Fu et al, 2023,[158] Karpenko et al, 2018,[153] Kim et al, 2022,[166] Lindqvist et al, 2012,[161] Menza et al, 2010,[163] Rastegar et al, 2019,[149] Selikhova et al, 2002,[162] Veselý et al, 2018,[87] Wan et al, 2023,[164] and Wang et al, 2016[165] (see main text and Supplementary Table 3 for full details of individual studies).

depression scales finding divergent results,[149,153] and differences between studies including both idiopathic PD and LRRK2 cases.[91,149]

A large study[91] stratified participants into three groups based on clinical variables and found that IL-8 (involved in neutrophil recruitment) was higher in a "malignant" subtype of PD patients with the LRRK2 mutation. This subgroup had higher levels of inflammatory markers, including monocyte chemoattractant protein (MCP)-1, and more severe symptoms, including higher levels of depression. One other study found no association with MCP-1[149] and another found an association with MCP-1 but in the CSF, but do not report serum results,[161] with a separate study finding an association with plasma MCP-1 and depressive symptoms.[167]

Two studies examined IL-10[91,149] finding positive correlations with baseline and longitudinal GDS scores.

Three studies measuring CRP in serum[87,160,161] found no association with depression, representing the larger cohorts, whilst two studies[77,165] found higher rates of depressive symptoms were associated with elevated CRP. sIL-2r was found to be associated with depression in two studies.[161,165] Other studies measuring single inflammatory markers (VIP, S100β, miR-218-5p) found potential associations that would need replication.

PBMCs

Three papers examined PBMCs in relationship to depression in PD.[168–170] These studies used different panels looking at different immune cell populations and activation markers. Two[168,170] found an association between natural killer (NK) cell populations (one an association between %CD56+ve cells, and one higher levels of p11, a protein involved in endo/ exocytosis and linked to mood disorders). The third found an association with depression and myeloid dendritic cells, an association found in AD by the same group.[169]

Genetics

The largest study identified by our search[83] incorporated genetics with disease phenotype in three independent long-itudinal cohorts. This identified a cluster where anxiety and depression were associated with a severe non-motor phenotype, rapid disease progression, and AD pathology. This group was associated with increased risk genes expressed in microglia, implicating an inflammatory driver of a severe, neuropsychiatric disease phenotype.

An epigenetics study[171] found 35 CpG regions enriched in immune pathways (IFN-γ signaling and T-cell receptor signaling) associated with depression in PD, and the PD with depression group had higher neutrophils, lower CD4 cells, and a higher neutrophil-to-lymphocyte ratio.

PD-Psychosis

Three studies looked at the relationship between inflammatory markers and psychosis in PD. One study[172] found increased CRP in PD participants with either illusions or hallucinations, but these participants were also older and had lower cognitive scores, one found no associations with a range of cytokines,[173] and one found an association with an IL-6 polymorphism and visual hallucinations. This study looked specifically at the development of visual hallucinations during dopaminergic drug treatment, and measuring a single genetic polymorphism in a small sample size risks a false positive result.

PD-Composite

A longitudinal study using the non-motor symptom scale (NMSS) found no correlations between individual cytokines and symptoms scores either at baseline or follow-up, but using principal components analysis identified a latent variable, representing IL-6 and IL-2, that was associated with worsening NMSS scores, mood, and apathy symptoms over time.[166] One study of CSF[155] found that lower TNF-α was associated with lower neuropsychiatric symptom scores. Another[174] found no association between CRP and non-motor symptom scores.

PD- Fatigue and Sleep

Two studies looked at fatigue in PD, finding associations with sIL-2R[161] and IL-6.[90] Studies in sleep[157] found lower CSF TNF-α and higher prostaglandin E2 (PGE2) in those with sleep disturbance, and no association between CRP[174] and sleep quality.

PD - Summary

In summary, most studies measured the association between inflammatory markers and depression in PD. There was a replicated finding of peripheral IL-6 and depression, including increased depression scores at follow-up. IL-6 was also associated with composite NPS and fatigue. A large genetic study identified a cluster that linked inflammation to an overall more severe and rapidly progressive phenotype associated with NPS,[83] as did a clinical cohort including LRRK2 participants.[91] This suggests peripheral inflammation may be associated with NPS in PD, or may represent a more aggressive phenotype. Further studies are needed to draw conclusions about the impact of inflammation on other neuropsychiatric symptoms, like hallucinations and sleep disturbance, in PD.

Dementia with Lewy Bodies

Two studies specifically focused on DLB, with one study including those with MCI-LB. One used flow cytometry paired with a serum cytokine panel found no relationship between either immune cell subsets or cytokines with depression and

NPI scores.[175] Another study looked specifically at the relationship of domains of the NPI and cytokines (TNF-α and IL-6) in DLB.[88] They identified increased TNF-α (but not IL-6) was associated with overall NPI score. Hallucinations, depression, sleep disturbance and eating disturbance domains were associated with higher TNF-α, although some of these associations could be due to age as a confounder. One study included DLB in a mixed dementia group that, as discussed, found no relationship between CRP and psychosis.[79] In the only study of MCI-LB, there were no associations between a multiplex panel of cytokines and NPS.[80] Full descriptions of the studies are included in the Supplementary Table 4.

Frontotemporal Dementia

One study looked specifically at the role of inflammation in apathy, a key neuropsychiatric symptom in FTD[176] and found an association with B-Cell activating factor (BAFF) with apathy in behavioral variant FTD (bvFTD).

Huntington's Disease

Two longitudinal studies[177,178] investigated the role of peripheral inflammation in apathy, irritability, and depressive symptoms in HD using the problem behavior assessment scale. One found no associations with a cytokine panel, and the other found an association with CRP and apathy, but queried whether this was due to the initiation of antipsychotic medication rather than a disease process.

Full descriptions of the studies including frontotemporal dementia and Huntington's disease are included in the Supplementary Table 5.

Conclusions and Future Directions

This systematic review identified a number of studies reporting associations between inflammatory biomarkers and NPS in neurodegenerative dementia. However, the results are inconsistent with limited replication. Disease severity is a common confounder, making it difficult to identify whether there is a direct role for inflammation in NPS, or inflammation and NPS are epiphenomena of a more severe disease phenotype. Firstly, we will briefly discuss the heterogeneity, study design and methodological challenges that may contribute to the inconsistent findings and propose areas for further study. Secondly, despite these challenges, there are some tentative mechanisms that may overlap between psychiatric disorders and dementia we shall discuss, and finally we will suggest some recommendations for future research.

Heterogeneity

Our inclusion criteria were broad in order to capture the range of inflammatory markers measured both peripherally and centrally across neurodegenerative diseases, but despite this there was still considerable heterogeneity in study participants, design, outcome measures, and assays. These differences may contribute to the discrepancies in results. For example, a range of different diagnostic criteria were used for AD, with some using standardized criteria including biomarkers,[93] and others a single score on a cognitive test.[118] Some studies recruit a specific stage of disease, such as mild-moderate,[132] although the majority of studies do not specify this. One potential source of heterogeneity is the use of clinical criteria in the selection of participants for cohorts. There is an increasing shift in neurodegenerative diseases to move to biological definitions rather than clinical criteria, where diagnosis depends on the detection of disease-specific biomarkers.[179,180] Although diagnostic criteria are validated against neuropathological diagnosis[181] and some of the studies included biomarkers of amyloid-beta and tau in AD[93] or specific genetic diagnosis of PD,[91] a major potential source of bias is the reliance of clinical criteria, unsupported by biomarkers, as case definitions. This may lead to participants with a variety of underlying neuropathology under the same category and fail to capture cases with mixed pathology. As biomarkers for major neurodegenerative diseases become more widely accessible,[182,183] future studies could incorporate cohorts with biomarker evidence of pathology, or examine the relationships between pathology, immune response and NPS independently of clinical diagnosis. Measures of outcomes also vary, for instance, depression can be measured with a clinical diagnosis,[89] a self-reported measure such as the GDS[81] or as a composite in an informant-related scale such as the NPI.[135] Finally, for the same inflammatory marker, there are multiple assays used

for quantification. TNF-α is measured using ELISAs from different manufacturers,[132,147] as part of multiplex panels,[175] with a range of preanalytical variables inconsistently reported.

Study Participants

Small studies, without defined diagnostic criteria, can lead to inconsistent results. Larger studies,[81,86,92] including participants from multiple sites, and replicating in independent cohorts[83] can allow standardization of recruitment, diagnostic criteria, and increase power to detect or refute effects. This is especially important for non-AD dementias, such as DLB and FTD. Despite prominently being associated with NPS and with few treatment options, there is limited research in these groups.

A combination of validated diagnostic criteria supported by biomarkers can improve reliability of results, and this is increasingly possible with novel blood biomarkers.[184]

It is also important to study the spectrum of disease, including the early and prodromal stages, such as MCI-AD and the more recently recognized MCI-LB,[24] where inflammation is increasingly recognized as important.[20,185] This is with an awareness that NPS are most common in inpatient settings,[186] and whilst research can be more complex in these settings, there may also be a greater need for novel interventions.

Study Design

The role of inflammation develops as disease progresses.[187] For example, triggering receptor on myeloid cells 2 (TREM2), a lipid sensing receptor on microglia and macrophages, rises and falls with disease progression.[188] Therefore, the relationship between inflammation and NPS may change over time, which would require longitudinal studies to detect. There is an advantage to longitudinal studies with biomarker sampling at multiple time points, alongside cognitive and NPS scales, to assess disease progression.[86] This would allow the dynamic changes in immune response across a disease course to be captured, and disentangle relationships between inflammation and symptoms that may be confounded by disease stage or severity. In the studies identified, there are very few longitudinal studies, and those with repeat biomarkers are even rarer. For example, there is evidence for microglial markers[188] changing with disease progression in AD and microglial activation as an early event in DLB.[20] Other factors such as neurodegeneration may contribute increasingly to neuropsychiatric symptoms over time. This raises the question as to whether the associations between microglial or other inflammatory markers and NPS vary across the disease continuum. There was evidence from some studies in MCI[92,118] of associations between CSF and peripheral inflammatory markers and NPS, although some studies found no relationship in MCI.[96] Others, such as the relationship between dendritic cell subsets and depression, found this relationship only emerged with the progression of dementia from MCI.[139] One study found that the mediating impact of cytokine pathways on the relationship between blood metabolites and depression varied depending on amyloid-β status.[81] Other studies did not report the differences depending on MCI or AD diagnosis.[95] We would recommend longitudinal studies from the prodromal stages including microglial markers, and measures of neurodegeneration to answer these questions.

Many studies did not incorporate other markers of pathology, neurodegeneration, disease stage, severity, or hetero-geneity (such as APOE4 status in AD) that may explain the apparent relationships between NPS and inflammation. Studies that explored the relationship between clinical symptoms[91] and disease progression[92] found inflammatory biomarkers associated with a more severe disease phenotype. For example, the neuropathology of AD has been associated with psychosis, with evidence for higher Braak stage, increased neuritic plaques, and the presence of Lewy body pathology.[189] Two studies incorporated neuropathology in AD in this review[108,109] and whilst they used Braak staging to confirm the diagnosis, they did not measure the links between pathology, inflammation and NPS. Therefore, the differences in inflammatory response could reflect different severity of pathology, or the presence of co-pathology, rather than be the direct cause of NPS. Incorporating biomarkers of pathology, alongside markers of inflammation, could help delineate these respective causes.

Another challenge in the studies identified is the limited replication. Multisite studies have the advantage of being able to recruit larger number of participants, which is associated with more robust results,[82] and other studies made use of

independent replication cohorts to support findings.[83] These study designs are essential to progress beyond the limited replication in many smaller studies.

Due to the importance of both peripheral and central inflammation,[8] studies were powerful when they measured biomarkers in both blood and CSF, and future studies could capture this by combining blood biomarkers with neuroimaging. Only two imaging studies were identified in this review, both in AD. This is despite numerous studies on primary psychiatric disorders such as major depression and schizophrenia, and studies focusing on dementia and cognition.[190] PET ligands in development[191] may better capture the spectrum of microglial states,[192] and future studies could better capture how microglial phenotype relates to NPS across neurodegenerative diseases. We must acknowledge the challenges associated with CSF collection and PET imaging in terms of patient acceptability and cost, particularly for longitudinal studies, and the ultimate goal would be to validate widely accessible peripheral markers that capture neuroinflammation. One such approach is the use of brain-derived exosomes, which are emerging as potential biomarkers in neurodegenerative disease.[193] This could include microglial-derived exosomes detected in blood, although there are challenges in extracting these due to the shared surface markers between microglia and peripheral immune cells.[194]

Genetic studies reported single SNPs[98,99] in small cohorts. Future studies could build on this, such as GWAS of psychiatric symptoms in dementia[195] or Mendelian randomisation.[196]

Outcomes

It can be challenging to accurately measure NPS in dementia, with overlap between depression scales and those for behavioral and psychological symptoms. There are also multiple biopsychosocial mechanisms that contribute to symptoms,[43] making it challenging to identify single contributors in cohort studies. Looking at individual symptom domains alongside total scores or using data-driven clustering may help identify patterns of NPS associated with inflammation.[197]

Assays

Various details around sample handing[198] can impact cytokine results, as can the choice between serum and plasma,[199] and choice of anticoagulant.[200] Factors such as time of day,[201] diet, alcohol and smoking[202] can impact cytokine levels. Whilst not all of these factors can be controlled for, studies can report the minimum standards of information and where possible organize consistent pre-analytical variables. This makes it challenging to draw firm conclusions, and inconsistent results could be explained by choice of inflammatory marker, preanalytical variability, assay source or variability, before even considering disease stage or heterogeneity.

Studies are increasingly moving from measuring single markers by ELISA to multiplex assays. This has the advantage of capturing the range and interrelationships of inflammatory marker patterns, including using principal component analysis to identify latent variables of inflammation associated with psychiatric symptoms[83,166] or cluster clinical phenotypes with inflammatory marker profiles.[91] Multiplex or proteomic studies have the advantage of capturing a greater range and complexity of immune dynamics, however clusters or latent variables may be challenging to replicate in independent cohorts. Using proteomics for discovery, followed by creating more selective biomarker panels and replication in independent cohorts could be a way forwards.[203]

Shared Mechanisms

Despite these limitations, there are a few areas of overlap between studies identified by our search, and the literature on psychiatric disorders.

Peripheral Inflammatory Markers

Several studies found associations between IL-6 and depression or apathy in AD[82,89,115,116] or PD.[87,149,151,153,158,161,162] IL-6 levels are associated with depression in population studies,[52] and there is genetic evidence that this effect is potentially causal.[204] IL-6 inhibition in inflammatory diseases reduces depressive symptoms, and there are ongoing trials in major depressive disorder (MDD).[205] Similarly, the AD and PD studies found associations with TNF-α and depression[89,116,149,161,163] or agitation,[86] although results were not consistent.[132] TNF-α levels are raised in MDD, and

trials for TNF-α inhibitors in a post-hoc analysis showed an improvement in depressive symptoms in those with MDD and higher levels of baseline inflammation.[67] Similarly, inconsistent results were found for the association of CRP in neurodegeneration with some studies in AD[121] and PD[77,165] finding positive results. Low-grade inflammation, at least in a proportion of patients, is associated with the diagnosis of depression.[206] A possible mechanism that links peripheral cytokine changes to depressive symptoms is the impact on functional connectivity[207]

Tryptophan Metabolism

One study[81] found links between peripheral inflammation, tryptophan metabolism, and depression in AD. In MDD, studies have shown peripheral inflammation associated with TNF-α, leading to a shift in tryptophan metabolism via the kynurenine pathway,[208] and this is linked to hippocampal and amygdala volumes.[209]

Neutrophils

In AD, neutrophils were associated with depression in a neuropathology study[108] and in PD, with increased IL-8[91] and higher neutrophil-to-lymphocyte ratio.[171] Neutrophil infiltration has been linked to depressive behavior in animal models.[210] Genes regulating neutrophil function are differentially expressed in MDD.[211] Neutrophils are increased in the blood of MDD patients and associated with symptom scores.[212] In animal models, stress-induced neutrophils accumulate in the brain and are associated with blood–brain barrier breakdown and alterations in the nucleus accumbens leading to anhedonia.[213]

TSPO Pet

Two PET studies found TSPO binding in AD to be associated with NPS, such as irritability and agitation. TSPO binding in the anterior cingulate is increased in depression.[214] Some studies showing this normalizes following treatment, and baseline TSPO expression predicts depressive symptom response to anti-inflammatory drugs.[215] Animal models of AD pathology have shown that sleep deprivation is associated with microglial reactivity, so it is important to consider that NPS that disrupt sleep may themselves be the cause of increased neuroinflammation, rather than the result.[216]

Conclusion and Recommendations for Future Research

This systematic review identified a number of papers that tested for associations between inflammatory biomarkers and NPS in neurodegeneration. There are a number of studies that report associations, suggesting potential for a targetable mechanism of this crucial contributor to distress, poor outcomes and disease progression. In order to make progress, we would suggest several recommendations. In the design of studies, we would recommend using standardized clinical criteria, supported by diagnostic biomarkers for the selection of participants. We have made a case for longitudinal studies with multiple biomarker assessments and detailed neuropsychiatric symptom measures, where possible incorporating multicenter cohorts with an aim to replicate in independent samples. Detailed information about disease stage and comorbidity would reduce the impact of confounding on results. Pilot studies could be used to identify the optimum assays that are disease relevant and replicable, or robust biomarkers that are not assay dependent. This could lead to standardization of immune biomarkers across studies. We would recommend studies that aim to have, at least in subgroups, measures of both peripheral and central inflammation. This would support the identification of accurate peripheral markers of neuroinflammation, but also to separately assess the relative contributions of peripheral and central immune responses. There is also a lack of studies of non-AD dementias, which may have shared or distinct immune mechanisms. These studies could assess the relative contribution of inflammation, pathology, and neurodegeneration to NPS, identify mechanisms behind associations, and link peripheral to central inflammation. Longitudinal, multi-site studies are most likely to identify (or refute) associations robustly and explore how relationships vary with disease stage and progression, ultimately leading to translatable biomarkers or novel therapeutic targets.

Abbreviations

5-HT, 5-hydroxytryptamine; AD, Alzheimer's disease; AFP, Alpha-fetoprotein; AMDP, Amsterdam Dementia Screening Test; APOE, Apolipoprotein e; ASA, Activities-specific Balance Confidence Scale; BA24, Brodmann area 24; BAFF, B cell-activating factor; BDI, Beck Depression Inventory; BDNF, Brain-derived neurotrophic factor; bFGF, Basic

fibroblast growth factor; BPRS, Brief Psychiatric Rating Scale; BPSD, Behavioral and psychological symptoms in dementia; bvFTD, Behavioral variant frontotemporal dementia; C3, Complement component 3; C4, Complement component 4; CCL11, C-C motif chemokine ligand 11; CCL18, Chemokine ligand 18; CCL2, C-C motif chemokine ligand 2; CCL24, C-C motif chemokine ligand 24; CCL5, C-C motif chemokine ligand 5; CCR2, C-C motif chemokine ligand 2; CCR7, C-C chemokine receptor type 7; CCR7+, C-C chemokine receptor type 7-positive; CD14, Cluster of Differentiation 14; CD19, Cluster of Differentiation 19; CD2, Cluster of Differentiation 2; CD3, Cluster of Differentiation 3; CD4, Clusters of differentiation 4; CD45, Cluster of Differentiation 45; CD45RA, Cluster of Differentiation 45RA; CD45RA+, Cluster of Differentiation 45RA-positive; CD56, Cluster of Differentiation 56; CD64, Cluster of differentiation 64; CD68, Cluster of differentiation 68; CD8, Cluster of Differentiation 8; CDR, Clinical Dementia Rating; CDR-SoB, Clinical Dementia Rating Scale-Sum of Boxes; CMAI, Cohen-Mansfield Agitation Inventory; CRP, C-reactive protein; CSDD, Cornell scale for depression in dementia; CSF, Cerebrospinal fluid; CXCL10, C-X-C motif chemokine ligand 10; DBI, Diazepam binding inhibitor; DLB, Dementia with Lewy Body; DSM-III, Diagnostic and Statistical Manual of Mental Disorders; DSM-IV, The diagnostic and Statistical Manual of Mental Disorders; EDTA, Ethylenediaminetetraacetic acid; EEG, Electroencephalogram; ELISA, Enzyme linked immunosorbent assay; ENA-78, Epithelial-derived neutrophil-activating peptide 78; ESS, Epworth Sleepiness Scale; ET-1, Endothelin-1; FABP, Fatty acid-binding protein; FACIT-f, Functional Assessment of Chronic Illness Therapy-Fatigue; FTD, Frontotemporal dementia; FU, Follow-up; GCSF, Granulocyte colony stimulating factor; Geriatric depression scale, GDS; GH, Growth hormone; GSDMD, Gasdermin-D; GWAS, Genome wide association study; HADS, Hospital Anxiety and Depression Scale; HAMD/HAM-D, Hamilton depression rating scale; HAMD17, Hamilton Depression Rating Scale (17-item version); HAMD24/HAMD-24, Hamilton Depression Rating Scale-24; HC, Healthy control; HD, Huntington's disease; Histamine: HPLC, Histamine measured using High-Performance Liquid Chromatography; HLA-DR, Human Leukocyte Antigen-DR isotype; HLA-DR+, Human Leukocyte Antigen-DR-positive; HRSD, Hamilton rating scale for depression; hsCRP, High sensitivity CRP; Iba1, Ionised calcium-binding adaptor molecule 1; ICAM, Intercellular adhesion molecular; ICD-10, International Classification of Diseases; IFN-γ, Interferon gamma; IGF-1, Insulin-like Growth Factor 1; IL-10, Interleukin-10; IL12p40, Interleukin 12 p40; IL-12p70, Interleukin-12p70; IL-13, Interleukin-13; IL-15, Interleukin-15; IL-17, Interleukin 17; IL-17A, Interleukin-17A; IL-18, Interleukin 18; IL-18BP, Interleukin-18 binding protein; IL-1B-511, Interleukin 1 Beta (gene); IL1-R2, Interleukin 1 receptor type 2; IL-1R2, Interleukin 1 receptor, type II; IL-1ra, Interleukin 1 receptor antagonist; IL-1-α, Interleukin 1 Alpha; IL1-β, Interleukin-1β; IL-2, Interleukin-2; IL-23, Interleukin 23; IL-3, Interleukin 3; IL-37, Interleukin-37; IL-4, Interleukin-4; IL-5, Interleukin 5; IL-6, Interleukin-6; IL-7, Interleukin-7; IL-8, Interleukin-8; IL-9, Interleukin-9; IP-10, Interferon gamma-induced protein 10; Kyn, Kynurenine; LOAD, Late-Onset Alzheimer's Disease; LP, Lumbar Puncture; LRRK2, Leucine rich repeat kinase 2; MADRS, Montgomery-Åsberg Depression Rating Scale; MAES, Multiple Abilities Self-Report Questionnaire; MCI, Mild cognitive impairment; MCI-LB, Mild cognitive impairment with Lewy Body; MCP-1, Monocyte chemoat-tractant protein-1; MCP-4, Monocyte Chemoattractant Protein 4; M-CSF-1, Macrophage colony stimulating factor 1; MDC, Macrophage-Derived Chemokine; MDD, Major depressive disorder; MDS-PD, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MIF, Macrophage migration inhibitory factor; MIP1, Macrophage inflamma-tory protein 1; MIP-1 α, Macrophage Inflammatory Protein 1 Alpha; MIP1a, Macrophage Inflammatory Protein-1; MIP1-β, Macrophage Inflammatory Protein 1-beta; MMP-3, Matrix metalloproteinase-3; MMP-9, Matrix metalloproteinase-9; MMPS, Matrix metallo-proteinase 3; MMSE, Mini-Mental Sate Examination; MOAS, Modified overt aggression score; MoCA, Montreal Cognitive Assessment; mRNA, Messenger ribonucleic acid; MSA, Multiple System Atrophy; NGAL, Neutrophil gelatinase-associated lipocalin; NIA-AA, National Institute on Aging and Alzheimer's Association; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS, National Institute of Neurological Disorders and Stroke; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association; NK, Natural killer; NKCA, Natural killer cell activity; NLR, Neutrophil-to-lymphocyte ratio; NMSS, Non-motor symptoms scale; NPI, Neuropsychiatric inven-tory; NPI-D, Neuropsychiatric Inventory-Distress; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, Neuropsychiatric symptoms; OAS, Overt aggression score; PACAP, Pituitary adenylate cyclase-activating polypeptide;

PBA, Problem Behaviors Assessment; PBMCs, Peripheral blood mononuclear cells; PCR, Polymerase chain reaction; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PDSS-2, Parkinson's Disease Sleep Scale; PET, Positron emission tomography; PFS-16, Parkinson Fatigue Scale-16; PGE2, Prostaglandin E2; PPQ-B, Parkinson's Psychosis Questionnaire-Brief.; PPRS, Parkinson's Psychosis Rating Scale; PSP, Progressive Supranuclear Palsy; PSQI, Pittsburgh Sleep Quality Index; RANTES, Regulated on activation Normal T Expressed and Secreted; RBM, Rules-based medicine; RNA, Ribonucleic acid; RT-PCR, Reverse transcriptase – polymerase chain reaction; S100β, S100 calcium-binding protein B; SAA, Serum Amyloid A; SCF, Stem cell factor; SCI, Subjective cognitive impairment; SCID-D, Structured Clinical Interview for DSM-IV Dissociative Disorders; SCOPA-S, Scales for Outcomes in Parkinson's Disease-Sleep; sE-selectin, Soluble endothelial molecule; sFLT-1, Soluble Fms-like Tyrosine Kinase 1; sICAM-1, Soluble intercellular adhesion molecule-1; sIL-2R, Soluble interleukin-2 receptor; SNP, Single nucleotide polypeptide; SORL1, Sortilin-Related Receptor 1; STAI, State-Trait Anxiety Inventory; sTNFR1, Soluble Tumor Necrosis Factor Receptor 1; sTNFR2, Soluble Tumor Necrosis Factor Receptor 2; sVCAM-1, Circulating vascular cell adhesion molecule; TARC, Thymus and Activation-Regulated Chemokine; TF, Tissue factor; TGF-β, Transforming Growth Factor Beta; TGF-β1, Transforming Growth Factor Beta 1; TIE-2, Tyrosine Kinase with Immunoglobulin-like and EGF-like domains 2; TIMP 1, Tissue inhibitor of metalloproteinases 1; TNF RII, Tumor Necrosis Factor Receptor 2; TNF-R1, Tumor Necrosis Factor Receptor 1; TNF-R2, Tumor Necrosis Factor Receptor 2; TNF-α, Tumour Necrosis Factor alpha; TPO, Thrombopoietin; TRAIL, TNF-related apoptosis-inducing ligand; TREM2, Triggering receptor on myeloid cells 2; TSPO, Translocator protein; TTR, Transthyretin; UPDRS, Unified Parkinson's Disease Rating Scale; VaD, Vascular Dementia; VCAM1, Vascular cell adhesion molecule 1; VD, Vascular dementia; VEGF, Vascular endothelial growth factor; VEGF-C, Vascular Endothelial Growth Factor C; VEGF-D, Vascular Endothelial Growth Factor D; VIP, Vasoactive intestinal peptide.

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