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Review article

Is there an association between peripheral immune markers and structural/functional neuroimaging findings?

Thomas Frodl [a,b,c,*], Francesco Amico [a]

[a] Department of Psychiatry, Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland
[b] Adelaide and Meath incorporating the National's Children Hospital, Dublin, Ireland
[c] St. James's Hospital, Dublin, Ireland

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ABSTRACT

Objectives: There is mounting evidence that inflammatory processes play a key role in emotional as well as cognitive dysfunctions. In this context, research employing magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MR spectroscopy) suggests a possible link between structural/functional anomalies in the brain and an increase of circulating inflammation markers. The present paper reviews this research, with particular focus on major depressive disorder (MDD), cognitive impairment in older adults, Alzheimer's disease (AD) and schizophrenia.

Results: In MDD, cognitive impairment and AD, inflammatory processes have been found to be associated with both structural and functional anomalies, perhaps under the influence of environmental stress. Not enough research can suggest similar considerations in schizophrenia, although studies in mice and non-human primates support the belief that inflammatory responses generated during pregnancy can affect brain development and contribute to the etiology of schizophrenia.

Conclusions: The present review suggests a link between inflammatory processes and MRI detected anomalies in the brain of individuals with MDD, older adults with cognitive impairment as well as of individuals with AD and schizophrenia.

Contents

Abbreviations: ACC, anterior cingulate cortex; AD, Alzheimer's disease; AI, anterior insula; BG, basal ganglia; dACC, dorsal anterior cingulate cortex; CC, cingulate cortex; CA, cornu ammonis; CA3, cornu ammonis region 3; CA4, cornu ammonis region 4; CRP, C-reactive protein; DTI, diffusion tensor imaging; CNS, central nervous system; CSF, cerebrospinal fluid; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; GAD, glutamic acid decarboxylase; GILZ, glucocorticoid-induced leucine zipper; GM, gray matter; GMV, gray matter volume; HPA, hypothalamic–pituitary–adrenal axis; IL-1β, interleukin-1β; IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-12, interleukin-12; IgG, immunoglobulin-G; iNOS, cytokine-inducible nitric oxide synthase; LPS, lipopolysaccharide; LTP, long-term potentiation; MCI, mild cognitive impairment; MCP-1, monocyte chemo-attractant protein-1; M-CSF, macrophage colony-stimulating factor; MDD, major depressive disorder; MIP-1, macrophage inflammatory peptide-1alpha; MPIO, micro-sized particles of iron oxide; MR spectroscopy, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; NO, nitric oxide; OFC, orbitofrontal cortex; OMPFC, orbito medial prefrontal cortex; PFC, prefrontal cortex; pro-IL-1β, pro-interleukin-1beta; sACC, subgenual anterior cingulate cortex; SGK, serum and glucocorticoid-induced kinase; sIL-4R, soluble interleukin-4 receptor; VBM, voxel-based morphometry; VCAM-1, endothelial vascular cell adhesion molecule-1; WM, white matter; WMV, white matter volume; WMH, white matter hyperintensity; (11)C-(R)-PK11195, (R)-N-(11)C-methyl-N-(1-methylpropyl)-1-(2-chlorophenyl) isoquinoline-3-carboxamide ((11)C-(R)-PK11195).

* Corresponding author at: Department of Psychiatry, Institute of Neuroscience, University Dublin, Trinity College, Ireland. Tel.: +353 1896 4181; fax: +353 1 896 3183.
E-mail address: frodlt@tcd.ie (T. Frodl).

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1. Introduction

Experimental work has shown that exposure to an inflammatory challenge can have effects on both cognitive functions and/or emotion regulation. Studies suggest also effects of C-reactive protein (CRP), microglia, cytokines, the glucocorticoid system and the tryptophan/kynurenine pathway in the central nervous system (CNS), as well as an involvement in Alzheimer's disease (AD), major depressive disorder (MDD) and schizophrenia.

1.1. MDD

There is common agreement that neuroinflammation is linked to depressive mood in healthy individuals and that it plays a critical role in the onset as well as perpetuation of depressive symptoms (Eisenberger et al., 2009; Miller et al., 2009; Reichenberg et al., 2001; Wright et al., 2005). This might be consistent with animal research showing that inflammatory activity can increase anhedonic-like behavior (De La Garza, 2005) as well as research in humans demonstrating a role for altered reward-related neural responding in depressive states (Nestler and Carlezon, 2006).

The glucocorticoid system plays a central role in the pathophysiology of MDD and there is evidence that specific neuronal circuits, particularly in the developing brain, are damaged by environmental stress inducing changes in the hypothalamic–pituitary–adrenal axis (HPA) and inflammatory pathways (Krishnan and Nestler, 2008). Experimental studies have shown that stress or cortisol administration may lead to depressive-like states and atrophy of neurons in the hippocampus (Duman, 2002). Therapy with antidepressants reverses these changes (Santarelli et al., 2003). Moreover, chronic hypercortisolism has been shown to enhance tryptophan breakdown in the brain and induce neurodegenerative changes (Capuron and Miller, 2011). Importantly, chronic social stress has been shown to induce glucocorticoid-mediated pyramidal dendrite retraction in the hippocampus and changes in dendrite arborization in the prefrontal cortex (PFC) (Kole et al., 2004; Magarinos et al., 1996; Wellman, 2001; Woolley et al., 1990), which might be associated with the behavioral manifestations of stress-related disorders like MDD (Macqueen and Frodl, 2011). Other research has shown that both physiological and psychological stress can induce the production of pro-inflammatory mediators that can stimulate tryptophan catabolism in the brain (Myint et al., 2012a), with consequences on neurotransmitter metabolism, neuroendocrine function, synaptic transmission, and neurocircuits that regulate mood, motor activity, motivation, anxiety and alarm (Capuron and Miller, 2011).

Cytokines are known to have central effects, either crossing the blood–brain barrier or through the transmission of signals across the vagus nerve (Dantzer et al., 2008). Importantly, cytokines can affect dopamine and serotonin levels in the brain more generally (Miller et al., 2009) and in the striatum specifically. In this regard, it has been suggested that cytokines could influence reward processing and promote the increase of depressive symptoms through altered activity of dopaminergic and serotonergic systems (Ikemoto and Panksepp, 1999; Ressler and Nemeroff, 2000). Interestingly, pro-inflammatory cytokines can contribute to glutamate toxicity also stimulating microglial cells to release IL-1 and TNF-α (reviewed in McNally et al., 2008). Both IL-1 and TNF-α are expressed in the normal brain and play an active role in cellular events that induce structural changes at the synaptic level. However, increased levels of TNF-α have been found to inhibit LTP and impair memory formation (reviewed in Khairova et al., 2009).

In MDD (and also cognitive impairment), activity of the tryptophan/kynurenine pathway has been shown to modulate inflammatory processes, with kynurenine being directly associated with depressive symptoms and/or cognitive loss (Oxenkrug, 2007). Products of the "kynurenine" pathway include N-methyl-D-aspartate (NMDA) agonists (e.g., quinolinic and picolinic acids) (Jhamandas et al., 2000) and antagonists as well as free radical generators—e.g., 3-hydroxykynurenine and 3-hydroxyanthranilic acids—(Forrest et al., 2004; Thomas and Stocker, 1999). The neurotoxic effects of these compounds are thought to be implicated in the development of cognitive impairment in neurodegenerative disorders. Striatal injection of quinolinic acid in rats significantly stimulates the activity of cytokine-inducible nitric oxide (NO) synthase (iNOS) (Perez-Severiano et al., 1998; Ryu et al., 2006) the enzyme that is responsible of NO synthesis from arginine. While, at low concentrations, NO is essential for maintaining normal physiological functions in blood vessels (Oxenkrug, 2005), it can induce cellular death at higher concentrations following iNOS activation (mainly) in response to inflammation (Brown, 2007; Brown and Neher, 2010). As a free radical, NO damages metabolic enzymes and takes part in highly oxidative reactions (Akhtar et al., 2012). Importantly, iNOS-derived NO is thought to be capable of triggering pro-oxidant and proinflammatory changes in the endothelium of brain microvessels, which MRI scans can detect as white matter hyperintensities (WMHs) (Sloane et al., 1999). It has been suggested that the iNOS-derived NO might be responsible for the initial stage micro vessel inflammation in the brain, usually associated with working memory deficits and WMH (Oxenkrug, 2007).

1.2. AD and cognitive impairment

Several studies suggest a link between cognitive dysfunctions and inflammation. For example, increased levels of CRP are thought to be implicated in memory loss in older adults (Gunstad et al., 2006; Noble et al., 2010) by disrupting long-term potentiation (LTP) in the hippocampus (Lin et al., 2009; Murray and Lynch, 1998; Semmler et al., 2005; Terrando et al., 2010). This is consistent with the results of previous research on the downstream consequences of inflammatory processes in the brain (Allan and Pinteaux, 2003; Giovannini et al., 2003; Teunissen et al., 2003; Yaffe et al., 2003).

Recent studies suggest an active role for microglia in the mediation of amyloid toxicity and following tissue damage through the release of cytokines and cytotoxic molecules (Barger and Harmon, 1997; Tan et al., 1999). For example, elevated levels of interleukin-1β (IL-1β) are observed in patients with mild cognitive impairment (MCI), specifically in those with impairment in multiple cognitive domains (Forlenza et al., 2009). Also, interleukin-6 (IL-6) is strongly associated with AD senile plaques (Strauss et al., 1992) and there is evidence suggesting that amyloid plaque formation in AD might be mediated by interleukin-1 (IL-1)/IL-6 acute phase reaction (Vandenabeele and Fiers, 1991). More specifically, in AD, expression of IL-6 is increased in the parietal cortex and decreased in the temporal cortex, occipital cortex and cerebellum compared to age matched controls. Further, in individuals with AD, expression of the IL-6 receptor has been found increased in frontal and occipital cortices and decreased in the temporal cortex and cerebellum (Hampel et al., 2005). A post mortem in vitro study that compared AD and non-demented age matched controls has also found increases in the production of pro-interleukin-1beta (pro-IL-1β), IL-6, tumor necrosis factor-α (TNF-α), monocyte chemo-attractant protein-1 (MCP-1), macrophage inflammatory peptide-1alpha (MIP-1), interleukin-8 (IL-8), and macrophage colony-stimulating factor (M-CSF) after exposure to pre-aggregated β-amyloid peptide in microglia cultures