Themed Section: Inflammation: maladies, models, mechanisms and molecules

REVIEW

Microglial activation and progressive brain changes in schizophrenia

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Schizophrenia is a debilitating disorder that typically begins in adolescence and is characterized by perceptual abnormalities, delusions, cognitive and behavioural disturbances and functional impairments. While current treatments can be effective, they are often insufficient to alleviate the full range of symptoms. Schizophrenia is associated with structural brain abnormalities including grey and white matter volume loss and impaired connectivity. Recent findings suggest these abnormalities follow a neuroprogressive course in the earliest stages of the illness, which may be associated with episodes of acute relapse. Neuroinflammation has been proposed as a potential mechanism underlying these brain changes, with evidence of increased density and activation of microglia, immune cells resident in the brain, at various stages of the illness. We review evidence for microglial dysfunction in schizophrenia from both neuroimaging and neuropathological data, with a specific focus on studies examining microglial activation in relation to the pathology of grey and white matter. The studies available indicate that the link between microglial dysfunction and brain change in schizophrenia remains an intriguing hypothesis worthy of further examination. Future studies in schizophrenia should: (i) use multimodal imaging to clarify this association by mapping brain changes longitudinally across illness stages in relation to microglial activation; (ii) clarify the nature of microglial dysfunction with markers specific to activation states and phenotypes; (iii) examine the role of microglia and neurons with reference to their overlapping roles in neuroinflammatory pathways; and (iv) examine the impact of novel immunomodulatory treatments on brain structure in schizophrenia.

LINKED ARTICLES

This article is part of a themed section on Inflammation: maladies, models, mechanisms and molecules. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2016.173.issue-4

Abbreviations

ACC, anterior cingulate cortex; BP, binding potential; DLPFC, dorsal lateral prefrontal cortex; FC, frontal cortex; GM, grey matter; HLA-DR, major histocompatibility complex class II DR alpha; HPC, hippocampus; Iba-1, ionized calcium-binding adaptor molecule 1; MDT, mediodorsal thalamus; PPI, pre-pulse inhibition; STG, superior temporal gyrus; TC, temporal cortex; TSPO, translocator protein; WM, white matter

Tables of Links

TARGETS			
Ligand-gated ion channels[a]			
NMDA receptor			
Catalytic receptors[b]			
CD11b (Integrin, alpha M subunit)			
Enzymes[c]			
COX1			

LIGANDS			
Aspirin	IL-1ra	IL-25	Olanzepine
BDNF	IL-4	Interferon	PK11195
Glutamate	IL-6	Ketamine	Quetiapine
GM-CSF	IL-8	LPS	TNF-α
IGF1	IL-13	Nitric oxide (NO)	TSPO
IL-1β			

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology. org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c]Alexander *et al.*, 2013a,b,c).

Introduction

Brain structural abnormalities are widely reported in schizophrenia across all stages of the illness. Although such abnormalities are widespread, the most consistent findings have been ventricular enlargement (Olabi *et al.*, 2011), grey matter (GM) loss in prefrontal, temporal and subcortical structures (Ellison-Wright and Bullmore, 2009; Fornito *et al.*, 2009), as well as white matter (WM) tracts connecting these regions (Bora *et al.*, 2011; Zalesky *et al.*, 2011). Longitudinal studies have shown that grey matter loss is particularly accelerated in the early stages of schizophrenia and psychosis, which has led to suggestions that the initial phase of illness may be characterized by neuroprogression or a disturbance of neurodevelopmental processes (Pantelis *et al.*, 2003a,b; 2005; 2007). However, although such structural brain studies are informative, they are also inherently limited, as the mechanisms that might underlie such changes remain unknown. A number of factors might affect the brain changes seen in schizophrenia, including medication, substance use, lifestyle, genetic and pathophysiological processes. Although the relative contributions of these factors remain controversial (see commentary by Zipursky *et al.*, 2013), evidence for structural brain abnormalities in medication-naïve patients (e.g. Fusar-Poli *et al.*, 2013) and cohorts characterized by low substance use (e.g. Jung *et al.*, 2011) points to a role for these considerations in the primary disease processes. One such candidate pathophysiological mechanism that has received increasing attention is microglial-mediated neuroinflammation. However, despite theoretical proposals linking neuroinflammation or microglial pathology with brain structure and function in schizophrenia, there are few reviews that have comprehensively examined evidence for this relationship. Understanding the neurobiological mechanisms for the structural brain changes in schizophrenia would open a new paradigm for treatment of psychosis and schizophrenia and would pave the way towards more targeted treatments for the disorder.

This review focuses on inflammation in schizophrenia and its relationship to structural brain changes. A comprehensive description of the structural brain changes in schizophrenia was beyond the scope of this review and has been extensively covered elsewhere (Ellison-Wright and Bullmore, 2009; Fornito *et al.*, 2009; Olabi *et al.*, 2011). We provide a case for inflammation in schizophrenia, followed by a comprehensive review of studies examining the role of microglial dysfunction. Both imaging and neuropathological studies will be reviewed due to the complimentary nature of the information they provide. Subsequently, we address the link between microglial dysfunction and brain changes through a review of recent, primarily rodent, studies investigating a potential interaction between microglial activation and neuronal/white matter dysfunction. We discuss potential mechanisms involved in this interaction and propose directions for future research.

A case for inflammation in schizophrenia

There are multiple lines of evidence supporting the notion of inflammation in schizophrenia, including epidemiological, biomolecular and genetic studies, and clinical trials of adjunctive anti-inflammatory treatments. Substantial epidemiological data implicates prenatal inflammatory disturbances in the development of schizophrenia (Yolken *et al.*, 2009; Brown, 2011). These data are derived from population studies linking influenza epidemics to schizophrenia in adult offspring and birth cohort studies that have identified various immune-related genetic variants and infectious agents (e.g. herpes, toxoplasmosis and rubella) that confer an elevated risk for the disorder (Yolken *et al.*, 2009; Brown, 2011). Studies identifying an association between maternal levels of cytokines (e.g. TNF-α and IL-8) and risk for schizophrenia (Buka *et al.*, 2001; Brown *et al.*, 2004) suggest that pro-inflammatory cytokines may also represent potential mediators between prenatal exposure and risk. Biomolecular studies have consistently reported elevated levels of pro-inflammatory factors such as IL-6, IL-1β, TNF-α, calprotectin and C-reactive protein, and altered immune cell function, in plasma and serum of schizophrenia patients (Foster *et al.*, 2006; Miller *et al.*, 2011; Fineberg and Ellman, 2013). In addition, immune system-related genes such as the major histocompatibility complex (MHC) have been associated with schizophrenia and are among the most robust hits in genome-

wide association studies in the disorder (Consortium SPG-WAS, 2011; Consortium SWGotPG, 2014). Taken together, there is converging evidence implicating a potentially exaggerated and/or chronic immune response in the aetiology of schizophrenia. Furthermore, adjunctive treatments with anti-inflammatory agents, such as aspirin, oestrogens, fatty acids and N-acetyl cysteine, have been efficacious in some individuals (Amminger and McGorry, 2012; Sommer et al., 2014).

While inflammatory processes are implicated in the pathophysiology of schizophrenia, the effect of immune-related gene mutations and peripheral cytokines on the CNS is still elusive. While it is possible for peripheral cytokines to cross the blood–brain barrier and invade the CNS (Banks, 2009), the brain itself may be subjected to an inflammatory assault via the activation of microglia, the brain's innate immune cells (Munn, 2000; Monji et al., 2009). Indeed, as microglial cells have been shown to participate in pro-inflammatory cascades and modification of neuronal synapses (Moran and Graeber, 2004; Tremblay et al., 2010), synaptic pruning (Zhan et al., 2014) and white matter connections (Ignarro et al., 1993; Chew et al., 2013), microglial-mediated inflammatory processes have been proposed as a potential mechanism for the structural brain changes identified in schizophrenia (Munn, 2000; Monji et al., 2009). Furthermore, treatments that modulate their activity may improve symptoms of schizophrenia. For example, oral minocycline, an antibiotic that reduces microglial activation (Kobayashi et al., 2013), has efficacy in ameliorating symptoms of schizophrenia (Miyaoka et al., 2008; Levkovitz et al., 2010; Miyaoka et al., 2012). Findings from animal studies showing that minocycline can cross the blood–brain barrier suggests that it acts directly on microglia to ameliorate symptoms (Dean et al., 2012). Antipsychotics have also been shown to inhibit microglial activation by suppressing inflammatory and oxidative reactions (Kato et al., 2011). In particular, in vitro and in vivo evidence has demonstrated that pretreatment with typical and atypical antipsychotics reduces LPS- and interferon-induced secretion of cytokines such as TNF-α, SOD and NO from activated microglia (for review, see Kato et al. (2011)).

Despite these proposals, the nature of the microglial abnormalities in schizophrenia is far from established, and few studies have directly examined the relationship between microglial pathology and brain structure in this disorder. Characterizing microglial pathology and its relationship with brain structure at various stages of schizophrenia is a necessary step in developing a framework that unites microglial dysfunction, a proposed aetiological theory of schizophrenia (Monji et al., 2013) and the well-documented disturbances in the grey matter (Byne et al., 2007; Fornito et al., 2009; Bora et al., 2011; Mileaf and Byne, 2012) and white matter (Uranova et al., 2011; Zalesky et al., 2011; Kubicki and Shenton, 2014; Uranova et al., 2014) underlying this disorder.

Microglial cells – a brief introduction

Microglial cells, discovered by Pio Del Rio-Hortega, represent the first line of immune defence in the CNS against insults and foreign invaders (Kettenmann et al., 2011). Microglia derive from progenitors of myeloid lineage and invade the brain from the embryonic yolk sac via the circulatory system

(Ginhoux et al., 2010; Schulz et al., 2012; Nayak et al., 2014). After infiltrating the CNS parenchyma, microglial cells transition into a ramified state, which possess a small soma with long motile processes.

Under healthy physiological conditions, ramified microglia actively survey the entire brain for pathogens or debris (Nimmerjahn et al., 2005). Upon detecting a threat, microglia rapidly shift phenotype, morphology and function, traditionally defined as 'microglia activation'. Activated microglia acquire an amoeboid morphology, with swollen cell bodies and short processes to enable migration to the pathogen site (Kettenmann et al., 2011) (Figure 1). It has been suggested that microglial activation may correspond to the binary activation profile of peripheral monocytes, characterized by M1/M2 phenotypes (Mantovani et al., 2005). The M1 phenotype arises in response to inflammation and is accompanied by the release of TNF-α, IL-6, IL-1β, ROS and glutamate, whereas the M2-type microglia serve to resolve the inflammatory response and express IL-4, IL-13, IL-25, IL-1ra, insulin-like growth factor 1 (IGF1), BDNF and COX1 (Réus et al., 2015). However, caution is warranted when applying this binary profile to microglia, as studies have shown that the gene expression profile of microglia differs from the M1/M2 profile of peripheral monocytes (Chiu et al., 2013; Yamasaki et al., 2014). In particular, microglia are highly plastic and may operate on a spectrum ranging from pro-inflammatory to neurotrophic phenotypes depending on the local microenvironment (Biber et al., 2014).

The dynamic functions of microglial cells have emerged mostly through rodent studies of immune challenge and CNS damage. These dynamic cells help maintain a range of homeostatic functions in the healthy brain, including
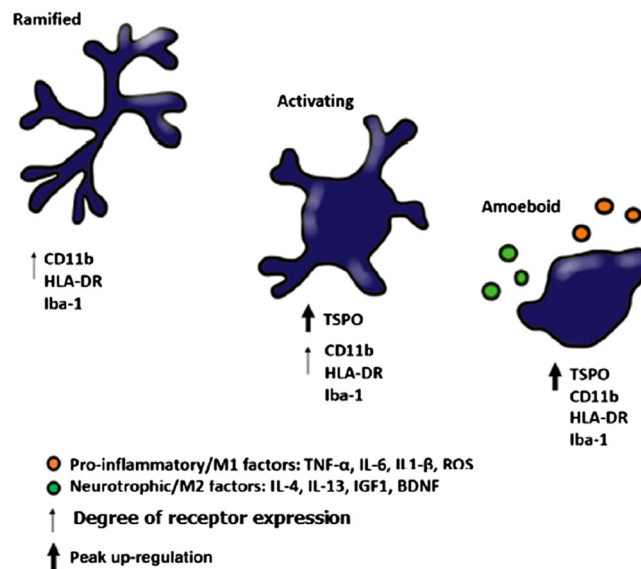

Figure 1

Microglial cell transitioning from ramified to amoeboid (activated state). The TSPO receptor is up-regulated from the intermediate ('activating') stage of microglial activation, while CD11b, HLA-DR and Iba-1 reach peak up-regulation in the amoeboid state. Activated microglia release a variety of pro-inflammatory and neurotrophic factors that are used to identify microglia in the M1 and M2 states respectively.

neuronal cell death, neuronal survival, synaptogenesis and synaptic pruning (Nayak *et al.*, 2014). During activation, microglia up-regulate a variety of molecules involved in antigen presentation, phagocytosis of cellular debris and cytokine production (Meda *et al.*, 1995; Nakamura *et al.*, 1999; Mack *et al.*, 2003; Lauterbach *et al.*, 2006; Neher *et al.*, 2011; Brown and Neher, 2014). Microglial cells are not only activated under most pathological conditions and the drivers of repair but can also exacerbate a disease process depending on their activation profile (Napoli and Neumann, 2010). Furthermore, mutant microglia can cause behavioural symptoms of both obsessive–compulsive disorder and autism spectrum disorder in genetic mouse models, which resolved upon correction of the microglial genetic mutation (Chen *et al.*, 2010; Derecki *et al.*, 2012). Their neurotoxic and neuroprotective capacities suggest microglia are 'double-edged swords', which has prompted interest in their potential role in neuropsychiatric disorders such as schizophrenia (Frick *et al.*, 2013).

Microglial activation in schizophrenia – evidence from neuropathological studies

Post-mortem studies in schizophrenia have primarily focused on assessing microglial cell number or density rather than microglial activation. The assessment of microglial number in *post-mortem* samples is performed using immunohistochemical staining methods, which involve labelling microglial cells and counting these cells blinded to diagnosis utilizing stereological sampling techniques. The density of microglial cells is then obtained as counts per unit area. Overall, these studies have produced mixed results. While some studies have found increased microglial cell number in several brain regions in schizophrenia (Radewicz *et al.*, 2000; Wierzba-Bobrowicz *et al.*, 2005; Fillman *et al.*, 2013; Rao *et al.*, 2013), others found no difference (Table 1; Steiner *et al.*, 2006; Steiner *et al.*, 2008; Busse *et al.*, 2012).

These differences could be attributed to methodological variations including different methods of visually identifying and counting microglial cells and the use of different immunohistochemical markers. The majority of studies examining microglial density use either HLA-DR or ionized calcium-binding adaptor molecule 1 (Iba-1) to label microglial cells. Both these markers, however, have a similar immunohistochemical staining profile, in that they label both activated and quiescent microglia (Steiner *et al.*, 2006; Steiner *et al.*, 2008) in addition to lymphocytes and peripheral monocytes (Kelemen and Autieri, 2005). It is instructive nonetheless to note that two studies examining the microglial density in white matter and conducted in the same brain region, the dorsal lateral prefrontal cortex (DLPFC), yielded conflicting results (Fillman *et al.*, 2013; Hercher *et al.*, 2014). The main methodological difference between these studies was the immunohistochemical marker used to label microglia, with Fillman *et al.* (2013) using HLA-DR and finding increased microglial density, while Hercher *et al.* (2014) used Iba-1 and found no increase. An alternative explanation for this discrepancy is that the studies differed in the visual selection process of microglial cells during the counting stage. In particular, Hercher counted only immunostained cells that were not encircling blood vessels, due to the fact that the cells encircling blood vessels are more likely to be peripheral monocytes rather than brain-resident microglial cells.

Although the marker used by Fillman *et al.* (2013) similarly labels both monocytes and microglia, they did not follow the strategy by Hercher *et al.* (2014) of eliminating potential monocytes from their cell counts, thereby, potentially overestimating microglia numbers. Of course, this would not change the results unless schizophrenia patients have increased peripheral monocytes compared with controls, an intriguing possibility that has yet to be assessed due to the lack of a suitably sensitive immunohistochemical marker.

Other technical difficulties that may account for the discrepancies between neuropathological studies of microglia in schizophrenia are differences in *post-mortem* interval, brain pH (correlated in Hercher *et al.*, 2014, with microglial density), as well as differences in age, clinical variables, illness duration and medication history in the *post-mortem* samples used. Owing to the paucity of detailed *ante-mortem* clinical information (Sundqvist *et al.*, 2008), only two studies examined a potential correlation between clinical variables and microglial density, with one study finding no correlation (Arnold *et al.*, 1998), while another found that increased microglial density was confined to the paranoid schizophrenia subgroup (Busse *et al.*, 2012). Antipsychotic medication is another variable that may affect microglial numbers; however, the results of the studies examining this association are mixed. Two studies found no correlation between lifetime antipsychotic dosage and microglial density (Steiner *et al.*, 2006; Rao *et al.*, 2013), while another study found a negative correlation (Arnold *et al.*, 1998). Finally, while the majority of *post-mortem* studies include secondary analyses controlling for demographic variables, sample sizes may be insufficient for such analyses, and thus, caution should be exercised when interpreting these results (Fornito *et al.*, 2008).

Another problem for neuropathological studies is that the immunohistochemical markers (HLA-DR and Iba-1) label both quiescent and amoeboid microglia; therefore, it is difficult to assess microglial activation. Attempts have been made to assess microglial activation through morphological characterization of these cells; although this is limited by the subjective nature of this classification. In their qualitative study, while no group differences were found in microglial density, Hercher *et al.* (2014) found that 15% of brains with schizophrenia showed an increased number of activated microglia, identified by their amoeboid morphology. Rao *et al.* (2013) performed a similar morphological characterization of microglial cells and found that the cell body of these cells in the frontal cortex (FC) of schizophrenia patients was more defined and their processes were less fine, indicating that microglia were potentially showing some degree of activation in patients, although not fully amoeboid. This morphological difference indicates that microglia from schizophrenia patients may be in a different state of activation when compared with controls, which may constitute a normal response to neuronal pathology or hint at an underlying, potentially genetic or epigenetic microglial dysfunction.

To overcome the subjective nature of these studies, alternative methods to quantify microglial activation include the use of markers such as [³H]-PK11195, [³H]-PBR28 and CD11b, which (unlike HLA-DR and Iba-1) are up-regulated exclusively on the surface of activated microglial cells (Banati *et al.*, 2000; Frick *et al.*, 2013; Kreisl *et al.*, 2013). The earliest *post-mortem* study using the [³H]-PK11195 ligand found decreased binding on

Table 1

Microglial density/number in schizophrenia from *post-mortem* studies

Study	Sample	Marker	Brain region	Density/no.	Cytokine levels	Age mean (SCZ/HC) (years)	Illness duration mean ± SD (range) (years)
Kurumaji et al. (1997)	13 patients 10 controls	PK11195	Putamen; VA1, superior parietal cortex	↓ activation	N/A	77/63	N/A
Arnold et al. (1998)	23 patients 10 controls	CD-68	TC; FC; OC	≈	N/A	80/75	55 ± 9
Bayer et al. (1999)	14 patients 13 controls	HLA-DR	FC; HPC	4/14 SCZ positive for HLA-DR	N/A	64/58	(7–43)
Radewicz et al. (2000)	12 patients 11 controls	HLA-DR	DLPFC; STG	↑	N/A	80/70	N/A
Wierzba-Bobrowicz et al. (2005)	9 patients 6 controls	HLA-DR	FC; TC	↑	N/A	56/56	24 (N/A SD) (10–35)
Steiner et al. (2006)	16 patients 16 controls	HLA-DR	DLPFC; HPC; ACC; MDT	≈	N/A	55/58	23 ± 10 (3–39)
Steiner et al. (2008)	16 patients 10 controls	HLA-DR	DLPFC; HPC ACC; MDT	≈	N/A	53/54	21 ± 12 (1–41)
Busse et al. (2012)	17 patients 11 controls	HLA-DR	HPC	≈ except between paranoid versus residual SCZ (↑ in paranoid)	N/A	52/56	19 ± 10 (2–34)
Kreisl et al. (2013)	45 patients 47 controls	[³H]PBR28	DLPFC	↑ BP in SCZ (after controlling for binding affinity)	N/A	55/42	N/A
Fillman et al. (2013)	37 patients 37 controls	HLA-DR	DLPFC	↑ density in WM ≈ in GM	↑ IL-6 and IL-8 ≈ in Cox2 or IL-1	51/51	28 ± 14
Rao et al. (2013)	10 patients 10 controls	CD11b and HLA-DR	FC	↑ Cd11b mRNA and protein	↑ IL-1b, TNF-α, NF-κB (but not IL-1r) gene and protein expression	50/59	N/A
Hercher et al. (2014)	20 patients 20 controls	Iba-1	DLPFC	≈ in WM	N/A	45/45	24 ± 10.9

≈No between-group difference.
↑Increased in schizophrenia.
↓Decreased in schizophrenia.
VA1, visual area 1; CD-68, cluster of differentiation 68; TC, temporal cortex; OC, occipital cortex; ACC, anterior cingulate cortex; MDT, mediodorsal thalamus; HPC, hippocampus; SCZ, schizophrenia.

microglial cells in patients (Kurumaji *et al.*, 1997), while subsequent studies reported increased binding (Kreisl *et al.*, 2013; Rao *et al.*, 2013). A notable factor in the Kurumanji study is that it included an unusually high proportion of patients (7/13) that had been off antipsychotics for 40 days or more prior to their death. Kreisl *et al.* (2013) found significantly increased binding of [³H]-PBR28 in the DLPFC of schizophrenia patients, after controlling for genetically determined binding affinity. This study illustrates the difficulty in devising immunohistochemical markers that are both specific to microglia and equally applicable across populations. However, in keeping with this study, Rao *et al.* (2013) found increased microglial activation in the frontal cortex using CD11b. They also found increased expression of pro-inflammatory cytokines IL-6, TNF-a and NF-κB in these patients, which may also be indicative of increased microglial activation, given that pro-inflammatory cytokines are released by activated microglia (Kettenmann *et al.*, 2011). Interestingly, Fillman *et al.* (2013) also found increased levels of IL-6, IL-8 and IL-1β in the white matter of patients with schizophrenia, which provides further evidence that

pro-inflammatory cytokine gene expression is increased in *post-mortem* brains of patients with schizophrenia. Therefore, evidence from *post-mortem* studies suggests that there is increased microglial activation in the frontal cortex of schizophrenia patients as assessed by protein quantification (Kreisl *et al.*, 2013; Rao *et al.*, 2013), which is accompanied by increased expression of pro-inflammatory cytokines in the same region (Rao *et al.*, 2013), as well as in white matter (Fillman *et al.*, 2013).

As we have seen however, there are conflicting results regarding the measurement of microglial density and number in schizophrenia, which may be because increased inflammation and microglial number occur only in a subgroup of patients with schizophrenia and that given the small sample sizes of earlier *post-mortem* studies, it was difficult to discern the existence of such a subgroup. There is support for this hypothesis from a recent study by Fillman *et al.* (2013), who found that schizophrenia patients could be divided into a high and low inflammatory group on the basis of their gene expression levels of pro-inflammatory cytokines. A subgroup of patients with a higher inflammatory profile (potentially consisting of patients in a particular stage or state of the illness) may exhibit increased microglial cell number and activation. Further evidence for the existence of a patient subgroup with a high inflammatory profile stems from the study by Busse *et al.* (2012), which showed that there was a significant difference in microglial number between patients with paranoid versus residual schizophrenia. This may indicate that patients experiencing active psychosis (paranoid schizophrenia group) may show a greater microglial proliferation than the patients in a non-acute or quiescent state (residual schizophrenia group). It is also instructive to note that in the study by Busse *et al.* (2012) five out of the 17 patients with paranoid schizophrenia committed suicide, whereas none of the patients with residual schizophrenia took their own life, which again indicates that the paranoid schizophrenia group demonstrated both increased level of illness acuity and increased microglial number (Busse *et al.*, 2012). Furthermore, when suicide was examined as a factor within the paranoid group, it was found to be non-significant, suggesting that suicide was not the driving factor behind the increased microglial number. Rather, a possible driver for the increase in microglial number may have been illness acuity, medication cessation or symptom severity; although this hypothesis was not examined in their study (Busse *et al.*, 2012). Suicide has been associated with increased microglial number in patients diagnosed with depression and schizophrenia, independently of their respective diagnosis (Steiner *et al.*, 2008), suggesting that factors associated with suicide such as illness acuity or stress may have driven the microglial changes. Indeed, it has been proposed that microglial activation may be most apparent during acute illness relapses, which would also be consistent with the timing of structural brain changes (Cropley *et al.*, 2013; Cropley and Pantelis, 2014).

In summary, the investigation of microglia in *post-mortem* brains in schizophrenia is at a relatively early stage. The *post-mortem* determination of microglial density suffers from potential confounds such as sampling bias towards violent death and variation in methodological techniques across laboratories, which may explain the mixed findings. Encouraging steps have been taken recently towards assessing microglial activation rather than density, which include the use of immunohistochemical markers specific to microglial activation (Kreisl *et al.*, 2013; Rao *et al.*, 2013) as well as cytokine quantification in the brain as a corollary of microglial activation (Fillman *et al.*, 2013; Rao *et al.*, 2013). These studies have all shown an increase in microglial activation in *post-mortem* brains of patients with schizophrenia, which complement the positive findings seen in neuroimaging studies of microglial activation in this disorder discussed below (van Berckel *et al.*, 2008; Doorduin *et al.*, 2009).

Microglial activation in schizophrenia – evidence from PET studies

PET using specific radioligands for the 18-kDa translocator protein (TSPO) allows quantification of activated microglia *in vivo* (Banati *et al.*, 2000). TSPO is expressed primarily on the mitochondrial membrane of microglia and to a lesser extent on reactive astrocytes in the CNS (Chen and Guilarte, 2008; Lavisse *et al.*, 2012). The relative contribution of microglia and astrocytes to the TSPO signal remains unclear but may depend on the timing and nature of the neuronal insult (Cosenza-Nashat *et al.*, 2009). Importantly, TSPO expression is negligible in the healthy brain but is increased in activated microglia (Ching *et al.*, 2012) and, therefore, has been used as an indicator of microglial activation and neuroinflammation (Banati *et al.*, 2000). However, TSPO up-regulation does not exclusively indicate classically activated microglial cells, which are amoeboid, phagocytic and release pro-inflammatory cytokines (Banati, 2002). Rather, its expression has also been associated with partially activated microglia, which appear less ramified with thicker and shorter processes (Marshall *et al.*, 2013).

A number of radioligands have been developed to examine TSPO. The most commonly used is isoquinoline carboxamide, $[^{11}C]$-(R)-PK11195, which has shown increased binding in multiple sclerosis and autoimmune encephalomyelitis (Shah *et al.*, 1994; Vowinckel *et al.*, 1997; Banati *et al.*, 2000). However, this tracer has been reported to produce low penetration into the target tissue and low specificity, in part due to its lipophilic nature, which promotes binding within fatty structures of the brain (Petit-Taboué *et al.*, 1991; Shah *et al.*, 1994; Chauveau *et al.*, 2009). To overcome these limitations, over 40 second-generation tracers for TSPO have been developed, with some yielding higher binding affinity and lower liphophilicity compared with $[^{11}C]$-(R)-PK11195, such as $[^{18}F]$-FEPPA and $[^{11}C]$-PBR28 (Imaizumi *et al.*, 2008; Wilson *et al.*, 2008; Fujimura *et al.*, 2009). Despite improved signal, inter-subject variability in the rs6971 polymorphism can alter the binding affinity of second-generation tracers. Therefore, PET studies using these ligands require plasma assays or genetic testing to control for differences in TSPO polymorphisms (Kreisl *et al.*, 2010; Owen *et al.*, 2012).

Five studies have applied PET imaging with TSPO ligands to assess microglial activation in schizophrenia (Table 2). The earliest report was by van Berckel *et al.* (2008), who examined $[^{11}C]$-(R)-PK11195 ligand binding to TSPO in recent-onset patients. They found increased ligand retention in the whole-brain grey matter of recent-onset patients compared with healthy controls. This suggests that an active immune pathology, characterized by increased TSPO expression, exists at the early stage of the illness. A

Table 2

PET studies examining microglial activation in schizophrenia

Study	Sample	Mean age (years)	Mean DOI (years)	Radioligand	BP results	Correlations
van Berckel et al. (2008)	10 patients	24	3.1	[^{11}C]-(R)-PK11195	↑ BP in whole brain in patients	
	10 controls	23				
Banati and Hickie (2009)	16 patients	39.4	3 months–30 years (range)	[^{11}C]-(R)-PK11195	↑ BP 15 of 28 regions. More marked on the right side.	
	8 controls	37.6				
Doorduin et al. (2009)	7 recovering from psychosis	31.3	5.3	[^{11}C]-(R)-PK11195	↑ BP in the HPC of patients.	
	7 controls	26.8			30% ↑ BP in whole-brain GM and WM.	
Takano et al. (2010)	14 patients	43.9	18.8	[^{11}C]-DAA1106	≈ in BP	Relationship between BP and age, DOI, duration of drug treatment and positive symptom scores in patients.
	14 controls	42.5				
Kenk et al. (2015)	16 patients	42.5	14.8	[^{18}F]-FEPPA	≈ in BP	Positive correlation between BP and number of acute crises in the striatum.
	27 controls	43.5				

≈No between-group difference.
↑Increased in schizophrenia.
↓Decreased in schizophrenia.
DOI, duration of illness.

later study by Banati and Hickie (2009) applied regions of interest to examine the spatial distribution of [^{11}C]-(R)-PK11195 binding in patients with schizophrenia. This approach identified increased binding in a subset of patients within 15 of 28 regions investigated, suggesting widespread pathology. In contrast, Doorduin et al. (2009) reported a focal increase in [^{11}C]-(R)-PK11195 binding potential (BP) in the hippocampus (HPC) of patients recovering from an acute psychotic episode. Regional discrepancies between studies may indicate a marked variation in TSPO expression in people with schizophrenia, possibly related to patient characteristics, such as symptom acuity.

More recently, Takano et al. (2010) used a second-generation ligand for TSPO and did not detect a difference in [^{11}C]-DAA1106 BP between chronic patients and healthy controls but found a positive correlation between BP and positive symptom severity. Kenk et al. (2015) recently replicated these results in a larger sample (16 schizophrenia and 27 healthy controls). Notably, the mean illness duration was 18.8 years in Takano et al. (2010) and 14.8 years in Kenk et al. (2015), in contrast to former studies (3.1 years in van Berckel et al., 2008, and 5.3 years in Doorduin et al., 2009). These findings suggest that TSPO expression may differ as a function of illness duration or illness stage. This notion is supported by trajectories of brain loss observed in schizophrenia, which progresses faster around illness inception

and plateaus later after 4–5 years (Takahashi et al., 2009a,2009b; Cropley and Pantelis, 2014).

These studies implicate microglial activation in some individuals with schizophrenia; in particular, those in the early stages of schizophrenia and with increased symptom acuity. However, positive findings were produced by studies using [^{11}C]-(R)-PK11195 and tended to target individuals with shorter illness durations. Therefore, it is difficult to determine whether discrepant findings across studies were due to illness duration or the specific radioligand utilized. This could be addressed in a future study that directly compared microglial activation between recent-onset and chronic patients with schizophrenia, using the same radioligand. Furthermore, differences in signal detection across studies may be due to a variation in the region-of-interest selection during image processing. In particular, four of the five studies either examined whole-brain BP or applied coarse regions of interest to detect patterns of activation, which may lack specificity. Voxel-based methods may be more suited to capturing the spatial distribution of microglial activation. Lastly, TSPO expression may be attributed to microglial or astrocytic cell expression, as well as microglia across various activation states and phenotypes; therefore, in vivo PET studies would benefit from markers specific to microglia phenotype and activation state to identify precise therapeutic targets.

Linking microglia to brain changes: the search for mechanisms

Microglia dysfunction may involve both M1/inflammatory and M2/neuroprotective profiles, which would have wide-ranging implications in the protection of the CNS and its development and maintenance. In particular, a balance between these two profiles has been shown to be crucial for the recovery of the brain from acute injury (Bodhankar et al., 2015; Han et al., 2015). However, little is known regarding impaired M2 polarization and its effect on the CNS, particularly with respect to schizophrenia. Microglia in a pro-inflammatory state are recognized to contribute to neuronal and axonal degeneration in human neurodegenerative diseases (Schmitz and Chew, 2008; Bernstein et al., 2009; Ilieva et al., 2009). The 'neuroinflammatory hypothesis' states that the cytotoxic effects of persistent microglial activation might cause secondary neuronal degeneration, decreased neurogenesis and synaptic dysfunction, and thus, disease progression (Munn, 2000). This hypothesis has been used to explain the progression of not only schizophrenia (Munn, 2000; Monji et al., 2009), but other neuropsychiatric syndromes including bipolar disorder (Stertz et al., 2013), delirium (Cerejeira et al., 2010), Alzheimer's disease (Rojo et al., 2008) and normal ageing (Bilbo et al., 2012). However, there are few empirical studies that address this issue. In vivo, increased $[^{11}C]$-(R)-PK11195 binding in dementia was reported to overlap with regions showing progressive atrophy on MRI scans (Cagnin et al., 2001) and, further, tissue loss indexed by volumetric brain changes in relapsing multiple sclerosis was associated with periods of active inflammation preceded by an initial volume increase (Cheriyan et al., 2012). Together, these findings implicate microglial activation and inflammatory processes in structural brain changes.

In schizophrenia, both neuropathological and MRI studies suggest that grey matter alterations are most pronounced in frontal and temporal regions (Glantz and Lewis, 2000; Fornito et al., 2009; Olabi et al., 2011; Konopaske et al., 2014). This overlap extends to studies of microglial dysfunction, with increases reported in the DLPFC and superior temporal gyrus (STG) (Radewicz et al., 2000; Wierzba-Bobrowicz et al., 2005; Banati and Hickie, 2009; Rao et al., 2013). Similarly, grey matter alterations have been detected in frontal and subcortical structures, such as the HPC (Uranova et al., 2007; Whitford et al., 2007; Andreasen et al., 2011; Uranova et al., 2011; Fung et al., 2014), which also show microglial activation (Doorduin et al., 2009; Fillman et al., 2013). These studies support the notion that structural brain changes co-occur with microglial dysfunction in both white and grey matter. However, findings from studies examining microglial cells (Arnold et al., 1998; Steiner et al., 2008; Takano et al., 2010; Busse et al., 2012; Hercher et al., 2014; Kenk et al., 2015) and structural brain change (Ikeda et al., 2004; Eastwood and Harrison, 2005; Connor et al., 2009; Mitelman et al., 2009) are mixed, involve multiple brain regions and have not been examined in the same sample; therefore, the spatial overlap remains tentative. Crucially, anatomical co-occurrence of microglial alterations and brain pathology does not imply that the two are necessarily functionally related. This assessment is critical and should be examined in future studies in order to elucidate whether microglial dysfunction contributes to the morphological changes seen in schizophrenia.

Very few studies in schizophrenia have addressed a possible association between inflammatory processes and structural brain changes in the same sample. Most of these studies examined a potential interaction between peripheral cytokine levels and the changes in white and/or grey matter in schizophrenia. Specifically, decreased anti-inflammatory cytokine levels have been associated with smaller hippocampal volume (Bossu et al., 2015), while increased pro-inflammatory cytokines were associated with decreased prefrontal cortical thickness (Cannon et al., 2015), reduced grey matter volume (Fillman et al., 2015), as well as decreased white matter integrity (Prasad et al., 2014). The finding that decreased anti-inflammatory cytokines are associated with reduced brain volume may indicate a deficiency in the M2/neurotrophic role of microglia in schizophrenia. Conversely, the finding that increased pro-inflammatory cytokines are associated with reduced cortical thickness and white matter integrity implicates the M1 pro-inflammatory phenotype. These findings are supported by associations between genetic polymorphisms of these cytokines and alterations in the structure (Meisenzahl et al., 2001; Papiol et al., 2005; Kalmady et al., 2014) and function (Papiol et al., 2007; Fatjo-Vilas et al., 2012) of the brain in schizophrenia. While these studies are informative, they did not examine microglial function. To our knowledge, the only study that examined microglial activation (TSPO) and regional grey matter volume (MRI) did not find any association between the two (Kenk et al., 2015). However, the association between microglial activation and brain changes may exist in an 'inflammatory' subset of patients (e.g. Fillman et al., 2013) and vary as a function of illness severity or duration. Therefore, further clinical studies are required to clarify the existence of a link between various functions of microglia and structural brain changes in subgroups of schizophrenia patients.

Despite the paucity of clinical studies directly examining microglial activation in association with structural brain changes, recent animal models have addressed this link. Below, we focus on a range of animal models of schizophrenia that: (i) investigate the association between microglial activation and behavioural impairments of schizophrenia and (ii) explore the impact of microglial dysfunction on the brain. While rodent models cannot capture the full scope of the disorder, they can be used to model certain features or endophenotypes and, unlike clinical studies, allow for the investigation of mechanisms.

A number of animal studies indicate an association between microglial activation and a range of schizophrenia endophenotypes such as sensorimotor gating measured by pre-pulse inhibition (PPI) and working memory deficits. These studies employ a pre- or postnatal infection paradigm that involves the exposure of rodents to pro-inflammatory agents such as human immunodeficiency virus (HIV; Paris et al., 2015), polyinosinic-polycytidylic acid (poly I:C; Ribeiro et al., 2013; Van den Eynde et al., 2014) and GM-CSF (Zhu et al., 2014). Notably, the rodents in all these studies exhibited at least one behavioural correlate of schizophrenia, specifically impaired PPI (Ribeiro et al., 2013; Liaury et al., 2014; Zhu et al., 2014; Paris et al., 2015) and cognitive deficits (Ribeiro et al., 2013; Liaury et al., 2014; Van den Eynde et al., 2014), in conjunction with increased microglial density or activation. Both the behavioural impairments and microglial activation were then reversed upon treatment with atypical antipsychotics (Ribeiro et al., 2013) or treatments targeting microglia and inflammation (e.g. minocycline (Zhu et al., 2014). In one study, the rodent strain itself demonstrated spontaneous symptoms of schizophrenia that were then alleviated by

similar treatments (Liaury *et al.*, 2014). Taken together, these preclinical studies: (i) support the epidemiological evidence for an association between prenatal/perinatal infection and an increased risk of schizophrenia and (ii) imply a causative role for microglia in mediating this process, as treatments targeting microglia (e.g. minocycline) are successful in alleviating both microglial activation and behavioural impairments.

It is noteworthy that some of these animal studies show that microglial activation does not arise instantaneously in response to the infectious agent but rather grows steadily throughout the lifespan, reaching a peak in late adolescence and early adulthood, which coincides with the emergence of behavioural impairments (Ribeiro *et al.*, 2013; Van den Eynde *et al.*, 2014). These studies indicate that a pre- or perinatal infection may serve to prime rather than explosively activate microglia, which then interact with cells in the developing nervous system leading to a subtle rearrangement of synaptic circuitry that may over time result in behavioural impairments in adolescence. These studies point to a subtle role for microglia and provide a compelling argument for schizophrenia emerging within an overarching neurodevelopmental context. Future studies are required to elucidate whether the symptoms of schizophrenia arise from an acute inflammatory reaction, a chronic low-grade microglial response or an interplay between the two states played out against the background of the developing nervous system.

While the above studies address a potential interaction between microglial activation and behavioural impairment, they do not address the mechanism by which microglial activation can mediate brain pathology. This question is addressed by the following set of preclinical studies that illustrate a wide variety of potential mechanisms by which microglial dysfunction may contribute to brain changes and behavioural deficits in schizophrenia. Three main findings emerge from animal studies investigating the effect of microglial activation on grey matter. The most replicated finding is decreased hippocampal neurogenesis in response to microglial activation (Furuya *et al.*, 2013; Mattei *et al.*, 2014). Pro-inflammatory cytokines (TNF-α and IL-1β) were shown to mediate the relationship between microglial activation (M1 phenotype) and hippocampal neurogenesis (Mattei *et al.*, 2014), which implicates a disruption of this inflammatory cascade in schizophrenia. Importantly, both studies linking microglial activation to neurogenesis, resulted in behavioural impairments analogous to schizophrenia, including PPI (Mattei *et al.*, 2014) and working-memory deficits (Furuya *et al.*, 2013).

In addition to neurogenesis, microglial activation has been shown to decrease reelin expression in the HPC, which was accompanied by impairments in working-memory and motor skills (Ratnayake *et al.*, 2012). Interestingly, decreased reelin expression has been reported in *post-mortem* studies of schizophrenia (Eastwood and Harrison, 2003) and may underlie impaired neuronal migration and connectivity during development (Folsom and Fatemi, 2013). Finally, and in support of impaired connectivity in schizophrenia, aberrant synapse formation was found in response to microglial activation (Sargin *et al.*, 2009). With regard to white matter, several studies report that elevated microglial cells are accompanied by myelin and oligodendrocyte loss particularly in the frontal cortex (Zhang *et al.*, 2008; Morita *et al.*, 2014; Zhang *et al.*, 2014), which were reversed by the administration of the antipsychotics quetiapine (Zhang *et al.*, 2008) and olanzapine (Zhang *et al.*, 2014). The association

between microglial activation, myelin and oligodendrocyte loss in these animal models may underlie connectivity impairments observed in schizophrenia (Zalesky *et al.*, 2011). These findings are in contrast to results from *post-mortem* studies predominantly showing morphological deficits rather than reduced oligodendrocyte number (Uranova *et al.*, 2011). However, such studies did not examine oligodendrocyte number in conjunction with microglial activation. Nonetheless, these rodent models demonstrate a wide variety of mechanisms by which microglial activation may induce grey and white matter deficits in schizophrenia.

Given the diverse mechanisms through which microglial activation affects the brain, it is plausible that the changes in the brain in response to microglial dysfunction will be similarly complex. The role of synaptic pruning in neuronal circuitry is of particular interest in a neurodevelopmental context (Carr, 2015; Riccomagno and Kolodkin, 2015). However, few studies have addressed the link between microglial dysfunction, synaptic impairment and whole-brain connectivity. One notable exception is Zhan *et al.* (2014), who examined synaptic plasticity in CX_3CR1 (fractalkine receptor)-knockout mice. These mice exhibited a transient reduction in microglial number, which resulted in impaired synaptic pruning and concomitant functional dysconnectivity as shown through MRI in the adult knockout mice. This indicates that microglia abnormalities are sufficient to cause circuit-level functional dysconnectivity, mediated through abnormal synaptic maturation. Although this study does make significant inroads in associating microglial dysfunction with synaptic plasticity, it is noteworthy that this rodent model produced social interaction deficits, which are seen in a variety of psychiatric disorders including schizophrenia, suggesting that the process may be relevant to a number of psychiatric and neurological conditions and depend on specific circuits that are disrupted (Ratnayake *et al.*, 2012).

Furthermore, it is possible that microglial cells are themselves responding to a pre-existing brain pathology and, therefore, the direction of this relationship remains unclear. For example, myelin damage in a mouse was shown to induce microglial activation, while both myelin damage and microglial activation were alleviated by administration of the antipsychotic quetiapine (Zhang *et al.*, 2008b). This indicates that the pathology of white matter may be the primary factor triggering an inflammatory-degenerative process. This 'chicken or egg' question is further complicated by studies demonstrating neuronal damage in the absence of microglial activation. For example, Hou *et al.* (2013) demonstrated that chronic ketamine exposure in mice was associated with increased oxidative stress, decreased hippocampal neurogenesis and cognitive and sensorimotor symptoms analogous to schizophrenia, notably without microglial increase. As ketamine is an NMDA receptor antagonist and the hypofunctioning of the NMDA receptor is a key aetiological theory of schizophrenia (Moghaddam and Javitt, 2012), this study indicates that microglial activation may represent one of many pathogenetic mechanisms underlying neuronal damage.

Summary and road map

Neuroimaging and neuropathological studies have revealed microglial activation or dysfunction in some schizophrenia

patients. The existence of a neuroinflammatory subset could contribute to the mixed findings across studies, as sample sizes may have been insufficient to expose such a subset. The 'neuroinflammatory' hypothesis proposes that this group of patients would undergo progressive brain changes as a result of microglial dysfunction. However, the relationship between microglial activation and brain abnormalities remains unclear, as there are limited clinical studies addressing this link. Nonetheless, animal models of schizophrenia have addressed potential mechanisms that may underlie this relationship and implicate decreased neurogenesis and reelin expression, as well as reduced oligodendrocyte number and myelination in response to microglial activation.

What emerges from these preliminary investigations is that microglia are highly diverse cells, serving both pro-inflammatory and neuroprotective functions. Therefore, disrupted microglia in schizophrenia would likewise have diverse and wide-ranging consequences for brain function. In light of this complexity, future studies should focus on elucidating the functions of microglia during healthy neurodevelopment, which would provide a foundation for understanding microglial dysfunction in relation to key developmental windows of relevance to schizophrenia and other neurodevelopmental disorders. Furthermore, microglial markers could be developed that identify microglia across different activation states and phenotypes. This could determine the relative contribution of the M1/pro-inflammatory and M2/neurotrophic phenotypes to the pathophysiology of schizophrenia. In particular, the effect of the M1 and M2 microglial activation states on neurons could be examined in relation to microglial functions such as synaptic pruning and strengthening. Such molecular investigations may shed light on the manner in which microglial activation is associated with the macroscopic structural brain changes in schizophrenia. Furthermore, given that MHC class proteins are expressed on neurons, as well as microglia (Boulanger and Shatz, 2004), immune system markers capable of identifying neurons could determine potentially shared mechanisms between CNS and immune system pathways, which may have implications for the proposed inflammatory hypothesis of schizophrenia. In particular, schizophrenia may not be primarily a disorder of inflammation but arise from disturbances of overlapping downstream molecular pathways, common to both the immune system and CNS.

Future PET and *post-mortem* studies could address unresolved questions pertaining to microglia in schizophrenia. Firstly, increased sample sizes in patients with carefully documented clinical characteristics could clarify whether a subset of patients exhibit microglial dysfunction. These studies could address the characteristics of a 'neuroinflammatory' subset; in particular, the relative contribution of genotype, illness severity and duration, medication history and age. Secondly, more work is required to establish a link between microglial dysfunction and brain changes in schizophrenia. This could be achieved through longitudinal and multimodal imaging studies concurrently measuring microglial activation and structural brain changes. In doing so, these studies can determine whether microglial activation precedes or follows structural brain change, which may point to potential novel therapeutic targets. Furthermore, given microglia modify neuronal synapses; diffusion imaging could be used to identify connectivity impairments in conjunction with PET in order to elucidate a potential association between microglial activation

and connectivity. Finally, treatment intervention studies could address whether microglia play a casual role in brain changes by utilizing a variety of novel drugs targeting microglial cells and assessing their effect on microglia-specific markers and brain structure in schizophrenia.

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Conflict of interest

Authors report no competing interests.

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