INTRODUCTION

Schizophrenia is a psychiatric disorder which affects ~0.5 to 1% of the population in their lifetime.1,2 Psychosis normally arises in the late teenage years or early adulthood, between 18 and 25 years of age.3 Although the cause underlying this mental illness remains to be elucidated, several biological factors have been proposed, including abnormalities in oligodendrocytes,4,5 N-methyl-D-aspartate (NMDA) signaling,6 and dopaminergic transmission.7 Following injury or the exposure to pro-inflammatory conditions, microglia, the resident immune cells of the brain, are found in a ramified (‘resting’) state, surveying the environment. Following injury or the exposure to pro-inflammatory signals such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α, ramified microglia can become activated and release pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IFN-γ or chemokine (c-x-c motif) ligand (CCL) 11.13 Microglia also increase the expression of cyclooxygenase (COX)-2, an enzyme involved in the arachidonic cascade, which can lead to the production of the pro-inflammatory lipid mediator prostaglandin E2.14 Pro-inflammatory cytokines released from microglia, such as IL-1β, can activate astrocytes. In turn, activated astrocytes also have the ability to release pro-inflammatory cytokines and chemokines, such as IL-1β, CCL5 and TNF-α,15 and typically display increased glial fibrillary acidic protein (GFAP) expression.16

Evidence has accumulated supporting a link between inflammation and schizophrenia. Serum or plasma concentrations of pro-inflammatory markers have been investigated in several studies. Two meta-analyses illustrate that IL-6 is consistently elevated in serum and plasma of patients with schizophrenia,17,18 whereas IL-1β and TNF-α were found to be increased in one meta-analysis,19 but not in the other.17 Genetic studies have also linked polymorphisms in major histocompatibility complex (MHC) regions with risk of schizophrenia.18,19

Neuroinflammation has also been associated with schizophrenia. Advancements in in vivo PET imaging has enabled imaging of neuroinflammation in schizophrenic patients.21 However, studies imaging the translocator protein 18 kDa (TSPO), a marker of activated microglia, have yielded mixed results. Early studies utilizing the TSPO ligand [11C]PK11195 suggested that schizophrenic patients have higher levels of activated microglia compared with healthy controls.22,23 More recent studies, using second-generation TSPO ligands, however, had mixed results, with some reporting increased microglia activation in schizophrenia.24
whereas others failed to replicate earlier studies and found no difference between patients and healthy controls.\textsuperscript{25,26} The reasons for the disparities between studies are not clear, but likely related to different TSPO ligands used or different samples studied across research groups.

As schizophrenia has been associated with inflammation, attempts have been made to treat symptoms with non-steroidal anti-inflammatory drugs (NSAID) as an add-on therapy to conventional treatments. Although some studies found added benefits of NSAID on symptoms,\textsuperscript{27-29} one study did not show any beneficial effects.\textsuperscript{30} A meta-analysis of five published and three non-published studies found no effect of NSAID on the Positive and Negative Syndrome Scale total scores, but did detect a small yet statistically significant beneficial effect of NSAID add-on therapy for the treatment of positive symptoms.\textsuperscript{31} Omega-3 polyunsaturated fatty acids (n-3 PUFA), which are also thought to have anti-neuroinflammatory properties,\textsuperscript{32,33} have also yielded mixed results in the treatment of schizophrenia. Administration of 3 g per day of n-3 PUFA in combination with 300 mg per day of alpha-lipoic acid for up to 2 years did not decrease the relapse rate of schizophrenic patients.\textsuperscript{34} An earlier report, however, found that administration of n-3 PUFA was beneficial in reducing the conversion of subthreshold psychosis to a first episode psychotic event in adolescents.\textsuperscript{35}

It is unclear whether neuroinflammation associated with schizophrenia is causing or is a result of the disorder. It has been suggested that microglia activation and cytokine release could lead to neuronal and glial injury,\textsuperscript{36} resulting in dopaminergic and glutamnergic system dysregulation.\textsuperscript{37,38} Neurogenesis and synapse connectivity may also be affected by neuroinflammation.\textsuperscript{39,40} Moreover, activation of astrocytes may also cause abnormal production of kynurenic acid and upregulate the expression of glutamate transporters.\textsuperscript{9,11,41}

Despite the mixed results in both in vivo imaging and clinical trials, it appears plausible that inflammation may have a role in schizophrenia. Numerous postmortem studies have measured pro-inflammatory markers in patients suffering from schizophrenia. To date, no systematic review of the field has been published on the topic. This article set out to systematically characterize the literature on neuroinflammation as measured in postmortem brains from schizophrenia patients.

**MATERIALS AND METHODS**

We performed a systematic search for literature indexed in MEDLINE, Embase and PsyCINFO up to 20th March 2016. Full search criteria can be found in the Supplementary Materials. Only peer-reviewed primary research articles were considered as eligible studies. References of yielded articles were searched for possible eligible articles that were missed by the search.

Once duplicate articles were removed, studies were screened based on title and abstract for several components including studies which were on schizophrenia and (1) carried out with postmortem brain samples, (2) measured neuroinflammatory markers and (3) were compared with matched psychiatrically and neurologically healthy controls. Studies evaluating markers of astroglia, microglia, gliosis, cytokines, arachidonic acid cascade and substance P were included (for full search terms, see Supplementary Materials). Other markers were considered if the authors referred to their implication in neuroinflammation. Although not always stated by the authors as a microglial marker, MHC (also know as human leucocyte antigen, HLA) complex I and II were both considered as possible microglial markers as both have been shown to be elevated in microglia.\textsuperscript{42} Untargeted approaches, such as microarray and shotgun proteomics, were also excluded unless targeted approaches were used to confirm the results. Viruses and infection were not considered for this review and were excluded. Reviews were searched for relevant articles, but themselves were excluded from the results. Finally, non-English papers and conference abstracts were also excluded.

Articles were evaluated and data were extracted onto an electronic data extraction form by MOT. Exclusions were confirmed by a second independent reviewer (KEH). From eligible studies, number of subjects, sex, race, duration of illness, onset of illness, postmortem interval, freezer time, death from suicide, substance abuse, medication, RNA quality and brain pH were extracted as background information. Unless specifically stated, suicide was not assumed as cause of death. Study design information, such as neuroinflammatory markers measured, measuring techniques and in which brain regions the measurements were made were all extracted, along with comparative results between schizophrenia and healthy controls. Thus, all results discussed below are relative to controls unless otherwise stated.

**RESULTS**

Following removal of duplicates, the search yielded 5385 unique results. A total of 5168 articles were excluded based on either title or abstract. The remaining 217 articles were fully screened for potential inclusion. Out of those remaining 217 articles, only 115 articles met the inclusion criteria. Four more articles were found in the reference section of papers yielded from the search (Figure 1).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Systematic search results.}
\end{figure}
ASTROGLIA

Our search yielded a total of 42 studies which assessed astrocytes in postmortem brain in schizophrenia (Table 1).

Of those 42 studies, 33 studies evaluated potential differences in astrocytes in schizophrenia by measuring GFAP expression or immunoreactive distribution. Out of the 33 studies evaluating GFAP expression, 21 did not detect any schizophrenia-associated changes, 6 studies reported a decrease in GFAP expression, whereas 6 studies reported increased expression.

The first study to evaluate GFAP was published in 1986 by Robert et al. In their study of the temporal cortex of 5 schizophrenic patients, immunohistochemical analysis found no differences in GFAP staining in schizophrenia brains compared with healthy controls, and was confirmed in a subsequent study with a larger cohort. Similarly, many quantitative immunohistochemical studies found no differences in GFAP cell density in several other brain regions including the hippocampus, amygdala, subiculum, mediadorsal thalamus, caudate, periventricular nucleus, nucleus basalis, premotor cortex, dorsolateral prefrontal cortex, midfrontal cortex, orbitofrontal cortex, entorhinal cortex, visual cortex, calcarine cortex, and anterior cingulate cortex. When compared with Alzheimer’s and Huntington’s disease patients, schizophrenic patients had lower GFAP-labeled cells. However, schizophrenic patients presenting with dementia had significantly higher GFAP cell density than schizophrenic patients without dementia in multiple brain regions including hippocampus, entorhinal cortex and orbitofrontal cortex. GFAP was also reported to be correlated with duration of neuroleptic treatment. Although Catts et al. found no changes in GFAP mRNA expression in the dorsolateral prefrontal cortex between schizophrenic patients and healthy controls, a difference was observed in schizophrenia patients when they were stratified based on the presence of other neuroinflammatory markers including serpin peptidase inhibitor (SERPIN) A3, IL-1β, IL-6 and IL-8. Individuals with elevated neuroinflammation had a larger proportion of hypertrophic astrocytes compared with low neuroinflammation subjects. On the other hand, GFAP mRNA, as measured by riboprobe was decreased in the white matter of the anterior cingulate cortex.

This effect, however, was not seen in the gray matter.

Other astrocytic markers have also been measured in postmortem brain specimen of patients with schizophrenia. Hwang et al. showed increases in apolipoprotein 1 and adenosine A2A receptor mRNA expression, markers of perivascular astrocytes and implicated in inflammatory responses, in the hippocampus in schizophrenia. Similarly, along with increases in GFAP, schizophrenia was associated with increases in aldehyde dehydrogenase (ALDH) 1 mRNA in several brain regions including the putamen, anterior ventral nucleus, internal capsule and mediadorsal thalamic nucleus. In cutaneous, two other studies found an association between schizophrenia and ALDH1L1 mRNA measured in the deep layer of the cingulate cortex and protein concentration in the dorsolateral prefrontal cortex. Similar results were observed for GFAP and other astrocytic markers including vimentin, excitatory amino-acid transporter (EAAT) and phosphate-activated glutaminase. Katsel et al. however, did find several other astrocytic markers, including S100b and EAAT2 mRNA to be downregulated in the cingulate cortex in schizophrenia. Differences in expression of various astrocytic markers may point to different types of astrocytes being affected in schizophrenia. S100b has been measured in a few other studies with mixed results. While one study found decreases in S100b protein measured by western blot analysis in the corpus callosum, another found no effect in several brain regions including Brodmann area (BA) 9, 10, 40 and 46. When separating paranoid schizophrenia from residual schizophrenia, one study found an increase in S100b-positive cells in paranoid schizophrenia compared with both residual schizophrenia and healthy controls in the dorsolateral prefrontal cortex. No effect was seen, however, in the white matter, as well as other brain regions such as hippocampus, mediadorsal thalamus, anterior cingulate cortex, superior temporal cortex and orbitofrontal cortex.

Astrocytes have also been identified in postmortem brains by microscopic analysis with other staining techniques. Casanova in GFAP cell density in layer V of the dorsolateral prefrontal cortex, whereas GFAP labeling area was reduced by 32%. These changes were layer specific, as no differences were detected in layer III and IV. This is slightly different from what Toro et al. observed, where an increase in GFAP, as measured by autoradiography, were observed in layers II, III and IV of the prefrontal cortex in schizophrenia. Importantly, this increase in GFAP was correlated with antipsychotic use. A decrease in GFAP in the orbitofrontal cortex was also observed. The authors proposed that the increase in prefrontal cortex was due to medication use whereas the decrease in the orbitofrontal cortex was due to the disease. Markova et al. reported increased GFAP positive cell area and reduced anisotropy, indicating glosis, in the olfactory tubercle in schizophrenia. This is in agreement with another study where GFAP-labeled cells had changed in morphology in the prefrontal cortex of schizophrenics, being more stained and stunted, whereas also having a 2.4-fold increase in protein concentration and 30% increase in mRNA expression. Other studies have also shown that GFAP mRNA expression changes in schizophrenia.
| Author          | Brain bank | n          | Sex (m/f) | Age | Death from suicide | Brain region                                      | Technique | Inflammatory markers | Results |
|-----------------|------------|------------|-----------|-----|--------------------|---------------------------------------------------|-----------|----------------------|---------|
| Altschuler et al. | SFNC       | 48         | SFNC      | 9-14| scz 5/4, ctr 8/6    | Basolateral nucleus of the amygdala               | IHC       | GFAP                | ↔       |
| Arnold et al.   | Prospective study | 45       | 7-12      | 6/8 | NA                 | EC, Sb#, CA3*, CA1*, DG*, MFC*, OFC*, VC*          | IHC       | GFAP#, VIM*          | ↔ *†#   |
| Arnold et al.   | Prospective study | 23        | 14        | 12 | NA                 | EC (BA 28) CA1 HPC, SB MFC (BA 26 and 46), OFC   | IHC       | GFAP                | ↔       |
| Barley et al.   | SFNC       | Varies across brain regions | Varies across | Varies across | NA       | DLPFC (BA9)                     | PCR       | GFAP, ALDH1          | ↑       |
| Beasley et al.  | NYSBIC     | 15         | 13        | NA  | None               | Anterior limb of the internal capsule             | ELISA     | GFAP                | ↔       |
| Casanova et al. | NC         | 6          | 7         | 12 | NA                 | DLPFC (BA96)                                    | Holzer's Technique | Astrocytes   | ↔       |
| Catts et al.    | NSWTRC     | 23         | 14        | 12 | NA                 | DLPFC (BA96)                                    | PCR, IHC, WB | GFAP                | ↔       |
| Damadzic et al. | (1) CBDBNIHM (2) | SFNC    | Study (1) scz 7 | 8 study (2) scz 14 | 13/7 | NA       | BA8, 10, 40, 46, WB, PCR         | S100b, GFAP | ↔       |
| Dean et al.     | NA         | 20         | 20        | 13 | NA                 | PMMC, SB, EC, IH, SVZ3V                           | IHC       | GFAP                | ↔       |
| Falk et al.     | DBC        | 33         | 26        | 14 | NA                 | MTN, CT                                          | IHC       | GFAP                | ↔       |
| Falk et al.     | Prospective study | 12        | 11        | 7/4 | NA                 | lateral CB, WB                                   | WB        | GFAP                | ↔       |
| Fatemi et al.   | SFNC       | 15         | 15        | 12 | NA                 | Scz 9/5, Scz 26/9                                | WB        | GFAP                | ↔       |
| Fersten et al.  | SMRIAC     | 35         | 35        | 35 | NA                 | Scz 9/5, Scz 26/9                                | WB        | GFAP                | ↔       |
| Hercher et al.  | SMRIAC     | 20         | 20        | 17 | NA                 | Scz 9/5, Scz 26/9                                | WB        | GFAP                | ↔       |
| Hwang et al.    | SFNC, SMRIAC | 33        | 34        | 14/6 | NA                 | DLPFC (BA9)                                     | IHC       | GFAP                | ↔       |
| Karson et al.   | DCMEO      | 25         | 28        | 22/3| NA                 | DLPFC (BA9)                                     | IHC       | GFAP                | ↔       |
| Karson et al.   | NA         | 14         | 12        | 13 | NA                 | FC, TC, OC, CB, TH, pons                        | WB        | GFAP                | ↔       |
| Katsel et al.   | NA         | 18         | 21        | 10/8| NA                 | Cingulate cortex (BA24/32)                       | PCR       | GFAP                | ↔       |
| Kolomeets et al.| ADMPH      | 19         | 16        | 11/8| NA                 | Cingulate cortex (BA24/32)                       | PCR       | GFAP                | ↔       |
| Markova et al.  | NA         | 12         | 10        | 12 | NA                 | DLPFC (BA9)                                     | IHC       | GFAP                | ↑       |
| Pakkenberg      | NA         | 12         | 12        | 8/4 | NA                 | DLPFC (BA9)                                     | IHC       | GFAP                | ↑* ↔ #   |
| Pantazopoulos et al. | HBTRC | 11        | 15        | 7/4 | NA                 | DLPFC (BA9)                                     | IHC       | GFAP                | ↔       |
| Perrone-Bizzozero et al. | HBTRC | 17        | 18        | 17/0| NA                 | DLPFC (BA9)                                     | IHC       | GFAP                | ↔       |
| Radewicz et al. | Prospective study | 12       | 11        | 18/0| NA                 | DLPFC (BA9)                                     | IHC       | GFAP                | ↑ (layer V only) |
| Rajkowska et al.| CCCO       | 9          | 15        | 54 | NA                 | DLPFC (BA9)                                     | IHC       | GFAP                | ↔       |

Postmortem evidence of cerebral inflammation in schizophrenia MO Trépanier et al.
| Author                  | Brain bank          | n      | Sex (m/f)     | Age | Death from | Brain region | Technique | Inflammatory markers | Results |
|------------------------|---------------------|--------|---------------|-----|------------|--------------|-----------|----------------------|---------|
| Rao et al.             | HBTRC               | 10     | scz 6/4 ctr 7/3 | 59  | NA         | FC (BA10)    | IHC, PCR, WB | GFAP                | ↑       |
| Roberts et al.         | VIBR                | 7      | scz 1/4 ctr 4/3 | 39  | NA         | TL, PC, PU, CT, AG, HPC, TH | IHC      | GFAP                | ↔       |
| Roberts et al.         | Runwell series 1    | 12     | scz 9/4 ctr 9/3 | 69  | NA         | TL           | IHC       | GFAP                | ↔       |
| Schmitt et al.         | DBC, MSMC, BVAMC    | 10     | scz 5/5 ctr 5/5 | 55  | NA         | CA1,2,3,4, SB | Cresyl violet | Astrocytes          | ↔       |
| Steffek et al.         | None                | 27     | scz 17/27      | 72  | NA         | DLPFC#, VC#, ACC#, HPC#, temporal gyrus# | WB               | GFAP                | ↔       |
| Steiner et al.         | MBC                 | 9      | scz 9 r scz 1   | 68  | NA         | ACC#, DLPFC#, OEC#, sTc#, HPC#, MTN# | IHC       | S100b               | ↑ ↔ #    |
| Roberts et al.         | WMSH, HUIN          | 16     | scz 4/5 ctr 7/9 | 54  | NA         | CO            | WB, MS     | GFAP                | ↔       |
| Stevens et al.         | VIBR                | 7      | NA             | 68  | NA         | CT, PVN       | IHC       | GFAP                | ↔       |
| Tkachev et al.         | SFNC                | 15     | scz 4/5 ctr 7/9 | 48  | NA         | PFC (BA9)     | PCR       | GFAP                | ↑ | #       |
| Toro et al.            | SFNC                | 15     | scz 4/5 ctr 7/9 | 48  | NA         | PFC* (BA9,32,46) OFC# (BA11/47) | IAR       | GFAP                | ↑ | #       |
| Uranova et al.         | MHRC                | 26     | scz 11/15 ctr 21/5 | 53  | NA         | PFC (BA10) and VC (BA17) | Electron microscopy | Astrocytic end feet | ↑ (except for VC of non p scz) |
| Williams et al.        | CC                  | 19     | scz 5/5 ctr 11/8 | 58  | 66 scz 1  | Subgenual cingulate cortex*, CO | IHC       | GFAP                | ↓ (only in layer I*) |
| Williams et al.        | CC                  | 16     | scz 6 r scz 7/4 | 57  | 55 scz 2  | Nucleus basalis | IHC       | GFAP                | ↔       |
| Williams et al.        | CC                  | 13     | scz 7/4 ctr 9/4 | 56  | 52 scz 2  | Substantia nigra | IHC       | GFAP                | ↓       |
| Williams et al.        | CC                  | 10     | scz 5/5 ctr 11/8 | 58  | 66 scz 1  | Subgenual cingulate cortex | IHC       | Phosphorylated GFAP | ↔ (except DLPFC blood vessel labeling) |
| Webster et al.         | SFNC                | 15     | scz 9/6 ctr 9/6 | 44  | 48 scz 4  | DLPFC, HPC | IHC       | GFAP                | ↓ (white matter only) |
| Webster et al.         | SFNC                | 15     | scz 9/6 ctr 9/6 | 45  | 48 scz 4  | ACC (BA24) | Riboprobe and in situ hybridization | GFAP |

Abbreviations: ACC, anterior cingulate cortex; ADMPH, Anatomical Department of Moscow Psychiatric Hospital; ADORA2A, adenosine A2A receptor; AG, amygdala; ALDH, aldehyde dehydrogenase; APOL, apolipoprotein; AQP, aquaporin; AVN, anteroventral nucleus; BA, Brodmann area; BVAMC, Bronx Veterans Administration Medical Center; CA, cornu ammonis; CB, cerebellum; CBDBNIMH, Clinical Brain Disorder Branch at the National Institute of Mental Health; CC, Corsellis Collection; CL, calcarine cortex; CO, corpus callosum; CT, caudate; ctr, control; CCO, Cuayhoga Country Coroner’s Office; d, dementia; DBC, Dusseldorf Brain Collection; DCMEO, District of Columbia Medical Examiner’s Office; DG, dentate gyrus; DIO, diidinase; DLPFC, dorsolateral prefrontal cortex; EAAT, excitatory amino-acid transporter; EC, entorhinal cortex; ELISA, enzyme-linked immunosorbent assay; FC, frontal cortex; GFAP, glial fibrillary acidic protein; GL, phosphate-activated glutaminase; GS, glutamine synthase; HBTRC, Harvard Brain Tissue Resource Centre; HPC, hippocampus; HUIN, Heidelberg University Institute of Neuropathology; IAR, immunoautoradiography; IC, internal capsule; IH, inferior horn; IHC, immunohistochemistry; MBC, Magdeburg Brain Collection; MHRC, Mental Health Research Centre; MFC, midfrontal cortex; MS, mass spectrometry; MSMC, Mount Sinai Medical Centre; MTN, mediodorsal thalamic nucleus; NA, not available; NC, Neuman Collection; NSWTRC, New South Wales Tissue Resource Centre; NYSPIBC, New York State Psychiatric Institute Brain Collection; OC, occipital cortex; OFC, orbitofrontal cortex; PC, parietal cortex; PCR, polymerase chain reaction; PFC, prefrontal cortex; PMc, premotor cortex; PP, perforant path; PU, putamen; PVN, paraventricular nucleus; SB, subiculum scz, schizophrenia; scz (p), paranoid schizophrenia; scz (r), residual schizophrenia; SFNC, Stanley Foundation Neuropathology Consortium; SMRIAC, Stanley Medical Research Institute Array Collection; ST, striatum; SVZ, subventricular zone; TC, temporal cortex; TH, thalamus; THBS, thrombospondin; TL, Temporal lobe; VBBN, Victorian Brain Bank Network; VC, visual cortex; VIBR; Vogt Institute of Brain Research; VM, vimentin; WB, western blot; WMSH, Wiesloch Mental State Hospital. *# indicate which variables results are representing.
et al. found no differences in astrocytes identified using Holzer’s technique between the hippocampus of six schizophrenia patients and seven healthy controls. Similar to other studies comparing schizophrenic brains to those with Alzheimer’s disease, Alzheimer’s disease brains had more astrocytes compared to both the schizophrenia and control groups. Similarly, stereological counting of Nissl stained astrocytes showed no differences in cell counts in the hippocampus, basolateral nucleus of the amygdala and pallidum. However, a significant decrease in astrocytes was measured in both the nucleus accumbens and mediodorsal thalamic nucleus.

Changes in astrocytes in schizophrenia have also been investigated by electron microscopy. In a cohort of 19 schizophrenia patients, astrocyte morphology was unchanged in the hippocampus compared with healthy controls. However, when patients were separated based on age, increased astrocytes were observed in patients younger than 50 years old, but this effect was lost in older patients. On the other hand, astrocytic end feet were increased in both paranoid and non-paranoid schizophrenic patients in the prefrontal cortex, however, this effect was not present in the visual cortex in non-paranoid schizophrenics.

**MICROGLIA**

From our search, a total of 22 articles reported on microglial markers in postmortem schizophrenic brains (Table 2). Out of these 22 studies, 11 studies reported an increase in microglial markers in postmortem brains, whereas 8 studies found no effect and 3 studies found a decrease in microglial markers.

Bayer et al. found that 3 of 14 schizophrenic patients had positive HLA-antigen D-related (DR) staining. MHC class II molecules involved in antigen presentation, whereas control subjects showed no staining in the hippocampus and frontal cortex. This is in agreement with two subsequent studies, where HLA-DR was increased in the prefrontal cortex, superior temporal gyrus, inferior temporal gyrus and frontal lobe in schizophrenia. No changes, however, were seen in the cingulate cortex. This increase in HLA-DR labeling in the hippocampus appears to be more pronounced in paranoid schizophrenics, as this group has increased HLA-DR compared with both control and residual schizophrenics, although only significantly different from residual schizophrenics.

Immunohistochemistry revealed differences in morphology of HLA-DR-labeled cells in schizophrenia, presenting a stunted and stronger labeling phenotype in the frontal cortex. It also has been reported that although patients show stronger HLA-DR labeling in the anterior cingulate cortex, microglia appear to be degenerating. Calprotectin, a member of the S100 family, co-expressed with microglial marker CD68 and was increased twofold in the dorsolateral prefrontal cortex in schizophrenic patients compared with healthy controls.

Not all studies found significant differences in microglia density. Steiner et al. found no differences in HLA-DR protein in various brain regions between schizophrenia and healthy controls, but did note that the two individuals who committed suicide in their cohort did show more HLA-DR labeling. A follow-up study by the same group found a similar lack of effect of diagnosis, but that suicide was accompanied with higher HLA-DR-positive cells. In a microarray analysis, an increase in HLA-A, MHC I molecules, mRNA expression in the frontal cortex and superior frontal gyrus was observed between schizophrenia and healthy controls in the frontal cortex. This effect, however, was not statistically significant when mRNA expression was confirmed by qPCR. Schmitt et al. observed, in a microarray analysis of the temporal cortex of 10 schizophrenic patients and controls, lower mRNA expression of HLA-DR3 and HLA-DPA1, subunits of HLA-DR, in schizophrenia. Similar to Saetre and colleagues, however, this effect was once again lost when analyzed by qPCR. Similarly, MHC II-positive cells were also unchanged in the subventricular zone in schizophrenia compared to healthy controls. Nakatani et al. also found no differences in HLA-DRA mRNA expression in the dorsolateral prefrontal cortex in schizophrenia, despite seeing a difference between control and bipolar disorder. Other microglial markers are also unchanged in schizophrenia. For example, ionized calcium-binding adapter molecule (Iba1) as measured by immunohistochemistry showed no differences in microglial density in the cingulate cortex or dorsolateral prefrontal cortex. Two prospective studies following patients who developed schizophrenia found no change in CD68 protein in the caudate nucleus, mediodorsal nucleus of the thalamus, hippocampus and entorhinal and calcineurine cortices in schizophrenic patients.

Similar decreases in HLA-DRA and HLA-DRB4 mRNA expression were observed in the temporal lobe. Despite not seeing changes in HLA-DR-positive cells, a separate study found microglial production of quinolinic acid was reduced in the hippocampus, and more specifically in the cornu ammonis (CA1), of schizophrenic patients. MHC I protein concentration was lower in the dorsolateral prefrontal cortex in a non-smoking schizophrenic population, whereas no differences were seen in the orbitofrontal cortex. This effect was not seen in a smoking population. Systemic inflammation, however, appears to have a role in potential differences between patients with schizophrenia and healthy controls. In one study, schizophrenic patients with no systemic inflammation showed no differences as compared with healthy controls, but schizophrenia displaying systemic inflammation had lower HLA-A mRNA expression compared with psychiatrically healthy controls with systemic inflammation. However, when that same cohort was divided into smokers and non-smokers, regardless of systemic inflammation, HLA-B mRNA expression was increased in schizophrenic patients. The authors did report that HLA-A appeared to co-localize with glutaminergic neurons.

**UNDIFFERENTIATED GLIAL CELLS**

Multiple studies have evaluated glial cells in schizophrenia without the use of cell type-specific markers. Some studies separated the types of glial cells (that is, astrocytes, oligodendrocytes, microglia), as discussed previously. However, many studies using Nissl staining, evaluated the effect of schizophrenia on glial cells without differentiating between cell types. In total, 34 studies evaluated glial cells in schizophrenia, where 25 studies reported no difference, 7 studies found a decrease and 2 found an increase in glial cell densities (Table 3).

Stevens published the first study which met our inclusion criteria on the effect of schizophrenia on glial cells. In a cohort of 18 schizophrenic patients, fibrous gliosis measured by Holzer’s staining was more pronounced in several brain regions including the hippocampus, hypothalamus, amygdala, thalamus, and periventricular areas compared to control. Comparable effects were observed in another study, which found increased fibrous gliosis as measured by Holzer’s technique in the cerebral cortex of patients with schizophrenia. The increase in gliosis measured by Holzer’s technique appears to differ, however, with a study published shortly after the report by Stevens and colleagues, which found, using a Nissl staining technique, a decrease in glial cell density in the CA3 and CA4 of the hippocampus. No effect of schizophrenia, however, was observed in the CA1 and subiculum. Similar decreases in glia were observed by Giemsa staining in the anterior cingulate cortex and by cresyl violet staining in the temporal cortex and planum temporale. A layer specific decrease in glial cell density measured by cresyl violet staining was observed in three studies, where effects were only in layer V of the dorsolateral prefrontal cortex, layer VI of the anterior cingulate cortex...
Table 2. Microglia in postmortem schizophrenia brain

| Author               | Brain bank          | n      | Sex (m/f) | Age | Death from suicide | Brain region | Technique | Inflammatory markers | Results |
|----------------------|---------------------|--------|-----------|-----|--------------------|--------------|-----------|----------------------|---------|
| Arnold et al.         | Prospective study   | scz 23| scz 8/15 | scz 80| NA                | EC (BA 28) CA1, SB, MFC (BA9 and 46), OFC (BA11), CL (BA17) | IHC       | CD68 ↔               |
| Bayer et al.          | INUBMC, INMD        | scz 14| scz 3/11 | scz 64| NA                | FC, HPC      | IHC       | HLA-DR ↑             |
| Busse et al.          | MBC                 | scz (p) 10* | scz (p) 5/5 | scz (p) 50 | NA                | HPC         | IHC       | HLA-DR ↑* #          |
| Comte et al.          | SFNC                | scz 15| scz 9/6  | scz 44| scz 4              | SVZ          | IHC       | MHC II ↔             |
| Connor et al.         | HBTRC               | scz 22| scz 9/13 | scz 68| NA                | ACC (BA24), DLPFC | PCR       | HLA-DRA, HLA-DRB4 ↓  |
| Durrenberger et al.   | INUBMC              | scz 10| scz 5/5  | scz 66| NA                | Temporal lobe (BA22) | PCR       | HLA-DR ↔             |
| Falke et al.          | BBPDGU              | scz 12| scz 3/9  | scz 81| NA                | MTN, CT      | IHC       | CD68 ↔               |
| Fillman et al.        | NSWTRC              | scz 37| scz 24/13| scz 53| NA                | DLPFC (BA46) | WB, IHC   | HLA-DR/DP/DQ ↑       |
| Foster et al.         | SFNC                | scz 15| scz 9/6  | scz 44| scz 4              | DLPFC (BA9)  | ELISA, IHC | Calprotectin* CD68#  |
| Gos et al.            | MBC                 | scz 13| scz 7/6  | scz 51| scz 2              | CA1*,2,3, DG | IHC       | HLA-DR, quinolinic* ↔|
| Hercher et al.        | SMRIAC              | scz 20| scz 13/7 | scz 45| scz 4              | DLPFC (BA9)  | IHC       | lba1 ↔               |
| Kano et al.           | SMRIAC              | scz 35| scz 26/9 | scz 43| scz 7              | DLPFC*, OFC# | WB       | MHC I * ↔ #          |
| Nakatani et al.       | VIFM                | scz 7 | scz 3/4  | scz 61| scz 1              | DLPFC (BA46), PC (BA40) | PCR       | HLA-DRA ↔            |
| Radewicz et al.       | Prospective study   | scz 12| scz 80  | scz 80| NA                | DLPFC (BA9)*, ACC (BA24)*, superior TC (BA22)* | IHC       | HLA-DR * ↔ #         |
| Rao et al.            | HBTRC               | scz 10| scz 6/4  | scz 59| scz 49             | FC (BA10)    | IHC, PCR, WB | HLA-DR, CD11b ↑    |
| Saetre et al.         | SFNC, HBTRC, MBB    | scz 55| scz 58  | scz 58| NA                | FC (BA9 and 9), superior frontal gyrus | PCR       | HLA-A ↔              |
| Schmitt et al.        | BBPDGU              | 10 per group | scz 5/5 | scz 66| NA                | TC (BA22)    | PCR       | HLA-DRB3, HLA-DPA1 ↔ |
| Sinkus et al.         | SRCBB               | scz 42| scz 28/14| scz 51| NA                | HPIC         | PCR       | HLA-A*, HLA-B* * ↔ #|
| Steiner et al.        | MBC                 | scz 4* | scz 33/14| scz 55| NA                | HPC, ACC, DLPFC, MTN | IHC       | HLA-DR ↔ #          |
| Wierzba-Bobrowicz et al. | MBC                  | scz 16* | scz 7/9  | scz 54| scz 56             | Frontal lobe, cingulate gyrus (BA24) | PCR       | HLA-DP/DQ/DR ↑      |
| Wierzba-Bobrowicz et al. | NA                  | scz 12| scz 9/6  | scz 56| NA                | Gyrus temporal inferior (BA20), gyrus cinguli (BA24) | IHC       | HLA-DP/DQ/DR ↑      |

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BBPDGU, Brain Bank for Psychiatric Diseases at the Gottingen University; CA, cornu ammonis; CD, cluster of differentiation; CL, calcarine cortex; CT, caudate; ctr, control; DG, dentate gyrus; DLPFC, dorsolateral prefrontal cortex; EC, entorhinal cortex; ELISA, enzyme-linked immunosorbent assay; FC, frontal cortex; HBTRC, Harvard Brain Tissue Resource Centre; HLA, Human Leukocyte Antigen; HPIC, hippocampus; IHC, immunohistochemistry; Iba, ionized calcium-binding adaptor molecule; INMD, Institute for Nervous and Mental Diseases; INUBMC, Institute of Neuropathology, University of Bonn Medical Centre; MBB, Maudsley Brain Bank; MBC, Magdeburg Brain Collection; MHC, major histocompatibility complex; MFC, midfrontal cortex; MTN, mediiodorsal thalamic nucleus; NA, not available; NSWTRC, New South Wales Tissue Resource Centre; OFC, orbitofrontal cortex; PC, parietal cortex; PCR, polymerase chain reaction; SB, subiculum; scz, schizophrenia; scz (p), paranoid schizophrenia; scz (r), residual schizophrenia; SFNC, Stanley Foundation Neuropathology Consortium; SMRIAC, Stanley Medical Research Institute Array Collection; SRCBB, Schizophrenia Research Center Brain Bank; SVZ, subventricular zone; TC, temporal cortex; VIFM, Victorian Institute of Forensic Medicine; WB, western blot.

* # indicate which variables results are representing.
Table 3. Undifferentiated glial cells and postmortem schizophrenia brain

| Author                          | Brain bank          | n     | Sex (n/f) | Age     | Death from suicide | Brain region              | Technique | Inflammatory markers | Results |
|--------------------------------|---------------------|-------|-----------|---------|--------------------|---------------------------|-----------|----------------------|---------|
| Beasley et al. 129             | SFNC                | scz 15 ctr 15 | scz 9/6 ctr 9/6 | scz 44 ctr 48 | scz 4 | Planum temporal      | Cresyl violet | Gila                  | ↔       |
| Beasley et al. 107             | SFNC                | scz 15 ctr 15 | scz 9/6 ctr 9/6 | scz 44 ctr 48 | scz 4 | Planum temporal      | Cresyl violet | Gila                  | ↓       |
| Beckmann and Lauer 133         | WBC                 | scz 9 ctr 9 | scz 9/0 ctr 9/0 | scz 55 scz 52 | scz 1 | ST, PU, NAS, CT     | Galocyanin     | Gila                  | ↔       |
| Benes et al. 110               | HBTRC               | scz 10 ctr 10 | NA         | scz 60 ctr 66 | scz 1 | PFC (BA10)*, motor cortex (BA4)*, cingulate cortex (BA24)# | Cresyl violet | Gila                  | ↔ #     |
| Benes et al. 125               | HBTRC               | scz 9 scz+md 9 | NA         | scz 53 scz+md | NA | PFC (BA10), ACC (BA24) | Cresyl violet | Gila                  | ↔       |
| Benes et al. 123               | HBTRC               | scz 11 ctr 12 | scz 7/4 ctr 7/5 | scz 52 scz 58 | scz 5 | ACC (BA24)           | Cresyl violet | Gila                  | ↔       |
| Beznahlbyk et al. 112          | SFNC                | scz 13 ctr 15 | scz 8/5 ctr 9/6 | scz 47 ctr 48 | scz 7 | ACC                  | Nissl         | Gila                  | ↑       |
| Bogerts et al. 130             | VIBR                | scz 6 ctr 9 | scz 2/6 ctr 5/4 | scz 51 scz 43 | NA | SN                   | Cresyl violet | Gila                  | ↔       |
| Brauch et al. 106              | SNFC                | scz 13 ctr 14 | NA         | scz 46 ctr 47 | NA | TC                   | Cresyl violet | Gila                  | ↓       |
| Bruton et al. 103              | NA                  | scz 48 ctr 56 | NA         | NA         | NA | TC                   | Holzer’s Technique | Gila                  | ↑       |
| Chana et al. 124               | SFNC                | scz 15 ctr 15 | scz 9/6 ctr 9/6 | scz 45 ctr 48 | scz 7 | ACC (BA24)           | Cresyl violet | Gila                  | ↔       |
| Chana et al. 121               | SFNC                | scz 14 ctr 15 | NA         | NA         | NA | ACC                  | Nissl         | Gila                  | ↓       |
| Cotter et al. 109              | SFNC                | scz 15 ctr 15 | scz 9/6 ctr 9/6 | scz 45 ctr 48 | scz 7 | ACC                  | Cresyl violet | Gila                  | ↔       |
| Cotter et al. 108              | SFNC                | scz 15 ctr 15 | scz 9/6 ctr 9/6 | scz 45 ctr 48 | scz 7 | ACC                  | Cresyl violet | Gila                  | ↓ (only layer V) |
| Cotter et al. 111              | SFNC                | scz 15 ctr 15 | scz 9/6 ctr 9/6 | scz 45 ctr 48 | scz 7 | ACC                  | Cresyl violet | Gila                  | ↔       |
| Cotter et al. 112              | SFNC                | scz 15 ctr 15 | scz 9/6 ctr 9/6 | scz 45 ctr 48 | scz 7 | DLFPC (BA9, 46)     | Cresyl violet | Gila                  | ↓ (layer 3 and 5) |
| Crow et al. 134                | NA                  | scz 22 ctr 26 | NA         | NA         | NA | OFC                  | Holzer’s Technique | Gila, dizeapam binding | ↔       |
| Cullen et al. 120              | NA                  | scz 10 ctr 10 | scz 6/4 ctr 6/4 | scz 60 ctr 60 | NA | Temporal horn        | IHC          | Gila                  | ↓       |
| Di Rosa et al. 119             | NA                  | scz 11 cl 13 | scz 6/5 cl 7/6 | scz 69 scz 68 | scz 1 | Fusiform gyrus       | Cresyl violet | Gila                  | ↔       |
| Falkai and Bogerts 104         | VIBR                | scz 13 11 | scz 2/11 7/4 | scz 43 scz 43 | scz 1 | CA1#, 3*, 4*, PSB, 5* SB# | Nissl         | Gila                  | ↔ #     |
| Falkai et al. 132              | VIBR                | scz 13 11 | scz 11/2 7/4 | scz 43 scz 43 | NA | EC                   | Nissl         | Gila                  | ↔       |
| Hoistad et al. 128             | NA                  | scz 13 13 | scz 13/0 13/0 | scz 52 scz 52 | scz 3 | ACC (BA24)           | Nissl         | Gila                  | ↔       |
| Jonsson et al. 111             | NA                  | scz 4 1 8 | scz 4/0 1/8 | scz 82 scz 77 | NA | HPC                  | Galocyanin     | Gila                  | ↔       |
| Kurumaji et al. 111            | NA                  | scz 13 10 | scz 8/5 7/3 | scz 60 scz 67 | NA | PFC#, TCR, OC*, PC*, PU*, CO, SN#, PL#, TH# | Receptor binding assay | [3H] PK11195 binding (glossis) | ↔ #     |
| Nasrallah et al. 135           | NIMH                | escz 11 lscz 7 | Na         | escz 66 lscz 73 | Na | CO                   | Holzer’s Technique | Gila, dizeapam binding | ↔       |
| Ongur et al. 117               | SFNC                | scz 11 11 | scz 7/3 cl 7/4 | scz 40 scz 39 | scz 4 | sg24                 | Nissl         | Gila                  | ↔       |
| Pennington et al. 126          | SFNC                | scz 15 15 | scz 9/6 cl 9/6 | scz 46 scz 48 | scz 4 | Insular cortex       | Cresyl violet | Gila                  | ↓       |
| Rajkowska et al. 115           | HTBRC, NIMH, UZ     | scz 9 10 | scz 7/2 6/4 | scz 41 scz 44 | scz 5 | PFC (BA9), OC (BA17) | Nissl         | Gila                  | ↔       |
| Selemo et al. 113              | HTBRC, NIMH, UZ     | scz 16 19 | scz 12/4 10/9 | scz 40 scz 47 | scz 10 | PFC (BA9), OC (BA17) | Nissl         | Gila                  | ↔       |
| Selemo et al. 114              | HTBRC, UZ           | scz 9 10 | scz 6/3 7/3 | scz 44 scz 48 | scz 5 | PFC (BA9,46)        | 3F (BA44) and DLPFC (BA9) | Nissl         | Gila                  | ↔       |
| Selemo et al. 135              | SFNC                | scz 15 15 | scz 9/6 9/6 | scz 45 scz 48 | scz 4 | Lateral geniculate nucleus | Nissl         | Gila                  | ↔       |
| Stark et al. 105               | SEH                 | scz 12 14 | scz 7/5 7/7 | scz 40 scz 39 | scz 3 | ACC (BA24)*, BA32# | Glemsa stain   | Gila                  | ↔ #     |
| Stevens 102                    | SEH                 | scz 28 18 | scz 13/15 cl 11/7 | scz 41 scz 37 | NA | Multiple brain regions | Holzer’s Technique | Gila                  | →       |

Abbreviations: ACC, anterior cingulate cortex; AG, amygdala; BA, Brodmann area; CA, cornu ammonis; CO, corpus callosum; CT; caudate; ctr, control; DBC; Dusseldorf Brain Collection, DLPFC; dorsolateral prefrontal cortex; EC, entorhinal cortex; esz, early onset schizophrenia; FC, frontal cortex; HBTRC; Harvard Brain Tissue Resource Centre; HPC, hippocampus; IHC; ice; late onset schizophrenia; md, mood disturbance; MTN, mediadorsal thalamic nucleus; NA, not available; NAS, nucleus accumbens; OC, occipital cortex; OFC, orbitofrontal cortex; PC, parietal cortex; PFC, prefrontal cortex; PL, pallidum; PSB, presubiculum; PU, putamen; SB, subiculum; scz, schizophrenia; SFNC; Stanley Foundation Neuropathology Consortium; sg, subgenual prefrontal cortex; SN; substantia nigra; ST, striatum; SEH, SEH; ST. Elizabeth’s Hospital; TC, temporal cortex; TH, thalamus; UZ, University of Zagreb; VIBR, Vogt Institute of Brain Research; WBC, Würzburg Brain Collection.

* ↔ indicate which variables results are representing.
Gliosis measured by $[^3]H$PK11195 binding, a ligand which binds to the TSPO receptor found on activated microglia and astrocytes, was reduced in schizophrenia in the occipital cortex, parietal cortex, and putamen but not in the prefrontal cortex, temporal cortex, thalamus, pallidum, substantia nigra and caudate.

Twenty-five studies, however, found no effect of schizophrenia on glial cell density in postmortem brains. In a study of 13 schizophrenic postmortem brains from the Stanley Foundation Neuropathology Consortium, Nissl staining revealed no differences in glial cell density or size in the amygdala. Similarly, no changes in glial density were obtained in the prefrontal, occipital, subgenual prefrontal, and entorhinal cortices in schizophrenia compared with healthy controls. By comparison, Huntington’s Disease had an ~50% increase in glial cell density compared with healthy controls. Moreover, Huntington’s disease had increased density of larger glial cells. When glial cell density was measured by cresyl violet staining, no changes were detected between schizophrenia patients and healthy controls in several brain regions including the fusiform cortex, prefrontal gyrus, mediodorsal thalamic nucleus, layer III and V of the Heschl’s gyrus, anterior cingulate cortex, prefrontal cortex, insular cortex, orbitofrontal cortex, hippocampus, planum temporalis, substantia nigra and lateral geniculate nucleus. It should be noted that although Bogerts et al. failed to detect a difference in glial cell density in schizophrenia, they did report a significant reduction in glial size in schizophrenia patients. Galloxyalin, another staining technique, also did not detect an effect of schizophrenia on glial cell density in the dorsolateral prefrontal cortex of 13 male schizophrenic patients. Similarly, Beckmann and Lauer did not find any significant differences in glial density in several brain regions including the striatum, caudate, putamen and nucleus accumbens. Crow et al. also did not detect a difference in glialis in the temporal horn and in the periventricular region using Holzer’s technique between schizophrenia patients and controls. This was confirmed using diazepam inhibitor binding to evaluate gliosis. In another study, Nasrallah et al. found no differences in glial cell density in the corpus callosum in schizophrenia compared with healthy controls using hematoxylin and eosin staining. The authors did note that gliosis rating scores were higher in late onset schizophrenia compared with early onset and control patients.

### CYTOKINES AND CHEMOKINES

Ten studies evaluated cytokine and chemokine expression in postmortem brains of schizophrenic patients (Table 4). Two studies reported no difference in IL-1β mRNA in the prefrontal cortex, despite measuring increases IL-1RA, IL-6 (ref. 86) and IL-8 mRNA. INF-γ, measured by enzyme-linked immunosorbent assay, was reported to be increased in the prefrontal cortex of 35 schizophrenia patients compared to unaffected controls. However, Rao et al. reported 150% and 3.9 fold increases in IL-1β protein and mRNA respectively in the frontal cortex of schizophrenics. TNF-α protein and mRNA concentrations were also increased, 76% and 2.3-fold respectively, in schizophrenic patients. In a study of 19 schizophrenics, TNF-α receptor 1 mRNA was increased in the dorsolateral prefrontal and cingulate cortices compared to controls, whereas soluble TNF-α protein, transmembrane TNF-α protein and TNF-α receptor 2 mRNA concentrations were unchanged.

A microarray analysis, followed by qPCR validation, found a decrease in IL-8 and IL-1α mRNA expression in the temporal cortex of 10 schizophrenic patients as compared with healthy control patients. However, increases detected in the microarray were not

### Table 4. Cytokine and chemokine expression in postmortem schizophrenia brain

| Author | Brain region | Technique | Inflammatory markers | Results |
|--------|--------------|-----------|----------------------|---------|
| Dean et al. | DLPFC, ACC | PCR, WB | TNF-α, CCL2 | ↑, ↔, # |
| Fillman et al. | DLPFC, ACC | PCR, WB | IL-8*, IL-6*, IL-1β | ↑, ↔, # |
| Harris et al. | BA10 | ELISA | IFN-γ | ↑, ↔, # |
| Nakatani et al. | FC | PCR, WB | IFN-γ | ↑, ↔, # |
| Schmitt et al. | FC | PCR | TNF-α, IL-1β | ↑, ↔, # |
| Toyooka et al. | FC | PCR | IL-6, IL-1β | ↑, ↔, # |

Abbreviations: ACC, anterior cingulate cortex; BA, BAOME, Allegheny County Office of the Medical Examiner; BAOCME, Allegheny County Office of the Medical Examiner; BBDPOG, Brain Bank for Psychiatric Disorders at the Göttingen University CCL3, CCL3 chemokine (c-c motif) ligand; CCR, chemokine (c-c motif) receptor; CCL2, CCL2 chemokine (c-c motif) ligand; DLPFC, dorsolateral prefrontal cortex; ELISA, enzyme-linked immunosorbent assay; FC, frontal cortex; HBM, Harvard Brain Museum; IL-1, IL-1α, IL-1β, IL-1 receptor antagonist; INF-γ, interferon-γ; IHC, immunohistochemistry; PCR, polymerase chain reaction; PK11195, [3H]PK11195; WB, western blot; VIFM, Victorian Institute of Forensic Medicine; VMM, Victorian Medical School; WB, western blot.
reproduced by qPCR for cytokines and chemokines such as IL-1β and CCL2. Another study also found a decrease in IL-8 mRNA in the middle frontal gyrus in schizophrenia, whereas IL-1β, TNF-α, IL-18 and IL-6 were not changed. Two more microarray studies also found decreases in expression, with CCL3 being reduced ninefold in the prefrontal cortex and IL-13RA reduced in the temporal lobe.

**ARACHIDONIC ACID CASCADE**

Seven studies have evaluated the arachidonic acid cascade in postmortem schizophrenic brains (Table 5). Regional differences in concentration of cytosolic prostaglandin E synthase (PGES) protein were reported in schizophrenia compared with healthy controls. In schizophrenia, cytosolic PGES was elevated in the prefrontal cortex, but no changes were observed in the temporal and occipital cortices. COX-1 and 2, enzymes regulating the production of prostaglandin E₂, were not altered in the brains of schizophrenics. No changes in COX-2 mRNA expression were also observed in the dorsolateral prefrontal cortex and middle frontal gyrus, whereas COX-1 mRNA expression was unchanged in the dorsolateral prefrontal cortex. Similarly, immunohistochemical analysis of the hippocampus shows no differences in COX-2-positive cell density between schizophrenia and healthy controls. It should be noted that age did affect COX-1 and COX-2 mRNA expression in schizophrenia, with older schizophrenia patients having increased COX-1 and decreased COX-2 mRNA expression. ALOX5AP, a protein regulating 5-lipoxygenase (LOX) activity, was found to have lower mRNA expression in the temporal lobe of 66 schizophrenia patients compared with control patients.

In contrast, Rao et al. observed no changes in cytosolic PGES mRNA and protein in the frontal cortex in schizophrenia. They also reported no changes in other arachidonic cascade enzymes, such as calcium-independent phospholipase (PLA)2, LOX5, LOX12, LOX15 and microsomal PGES. They did, however, find COX-2 to be increased in schizophrenia, along with cPLA2 and sPLA2.

**SUBSTANCE P**

Substance P has been measured in postmortem brains of patients with schizophrenia in 11 studies (Table 6). One study evaluated preprotachykinin A, a precursor to substance P, and reported that mRNA measured by in situ hybridization is decreased in the basal and lateral nuclei of the amygdala, whereas no changes were measured in the temporal cortex. Similarly, the density of cells containing preprotachykinin A mRNA measured by in situ hybridization is also not changed in the caudate and putamen in schizophrenia. Substance P density in multiple brain regions, including substantia nigra, caudate nucleus, frontal cortex, basal ganglia and hypothalamus, detected by radioimmunoassay, is not different in schizophrenia compared with healthy controls. Psychosis without schizophrenia, such as affective disorder and unspecified functional psychosis, did exhibit higher substance P protein concentrations. An immunohistochemical study also did not detect any changes in substance P in the basal ganglia of six schizophrenia patients compared with control patients.

Two studies, however, have reported differences in substance P concentration in schizophrenia. Toru et al. found a significant increase in substance P detected by radioimmunoassay in the orbitofrontal cortex and hippocampus, and in antipsychotic medication users in the thalamus, substantia nigra and temporal cortex. Similarly, Roberts et al. found increased hippocampal substance P, but no changes were seen in multiple brain regions including the amygdala, thalamus, basal ganglia, and temporal, frontal, parietal and cingulate cortices.
Five studies evaluated substance P binding to substance P neurokinin 1 receptor. Autoradiography found no changes in neurokinin 1 receptor density in the putamen,150 anterior cingulate cortex,151 and temporal cortex.143 There was, however, an increase in receptor density in the caudate150 and nucleus accumbens.150 Immunohistochemical analysis found similar increases in substance P receptor in the prefrontal cortex in schizophrenia,152 but not in the amygdala.153 This lack of change in the amygdala cell density expressing substance P receptor was consistent with mRNA expression.153

**OTHER MARKERS**

Multiple other markers associated with inflammation that do not fit the categories mentioned above have also been measured in postmortem brains of schizophrenic patients to evaluate a potential link between neuroinflammation and schizophrenia. We identified 16 studies evaluating miscellaneous markers in postmortem brains in schizophrenia (Table 7).

ICAM-1 is a marker of neuroinflammation, associated with blood–brain barrier disruption. Thomas et al.154 found no differences in ICAM-1 labeled cells in both the dorsolateral prefrontal cortex and anterior cingulate cortex of 15 schizophrenia patients of the Stanley Foundation Neuropathology Consortium compared to healthy controls.

Four studies investigated the NF-κB pathway in postmortem schizophrenic brains. Rao et al.152 measured increases in both NF-κB p50 and p65 subunits mRNA expression in the BA10 of schizophrenia patients. A second study evaluating the prefrontal cortex of schizophrenics reported increased NF-κB1 and 2 mRNA expression.155 However, 2 separate studies could not detect any differences in NF-κB2 expression in the frontal cortex156 and NF-κB in the dorsolateral prefrontal cortex157 between schizophrenics and healthy controls. Schnurri-2, a NF-κB site binding protein inhibiting downstream transcription, has been reported to be decreased in the prefrontal cortex of schizophrenia patients.155

Microarray analyses followed by qPCR have proposed markers associated with the immune system or inflammatory response being associated with schizophrenia. One such marker, which was reported in four microarray analyses, is SERPINA3, a protease inhibitor that is involved in inflammatory processes and connective tissue turnover. In the dorsolateral prefrontal cortex, SERPINA3 mRNA expression was significantly higher in the brains of schizophrenics compared with healthy controls.86 The same group confirmed this finding in a second cohort, finding increased SERPINA3 mRNA expression in the medial frontal gyrus in schizophrenia, whereas changes in IL-1R1L1 expression were not detected.139 Similar increases of SERPINA3 mRNA expression were reported in two other microarray studies in the frontal cortices of 55 (ref. 93) and 14 (ref. 157) schizophrenia patients and were confirmed by qPCR.

These two microarray studies also found elevated interferon-induced transmembrane protein (IFITM1), 2 and 3, proteins involved in regulation of the immune response; mRNA expression in the prefrontal cortex in schizophrenia.93,157 A third study confirmed the increased IFITM3 mRNA expression in the prefrontal cortex.158 Similar overexpression of IFITM1, 2 and 3 was observed by microarray and confirmed by qPCR in the hippocampus of schizophrenic patients.77 A fifth study targeted IFITM1 and 2/3 expression in a separate cohort of prefrontal cortices of schizophrenic and healthy controls.86 The same group confirmed this finding in a second cohort, finding increased IFITM3 mRNA expression in the medial frontal gyrus in schizophrenia, whereas changes in IL-1R1L1 expression were not detected.139 Similar increases of SERPINA3 mRNA expression were reported in two other microarray studies in the frontal cortices of 55 (ref. 93) and 14 (ref. 157) schizophrenia patients and were confirmed by qPCR.

Other markers that either increased or decreased in microarrays include CD163 and S100a8 and 9 in the hippocampus,77 CH3L1 (ref. 157) and GBP1 (ref. 93) in the prefrontal cortex, TTNFSF8, 10, and 13 (although 8 and 13 were not significant in PCR validation) in the dorsolateral prefrontal cortex,166,167 and TIMP1, TYROB and
| Author             | Brain bank                  | n   | Sex (m/f) | Age | Death from suicide | Brain region | Technique | Inflammatory markers | Results |
|--------------------|-----------------------------|-----|-----------|-----|--------------------|--------------|-----------|---------------------|---------|
| Arion et al.       | UPCNMDBB                    | 157 | scz 14    | ctr 14 | scz 12/2           | PFC (BA9)    | PCR       | SERPINA3, IFITM1, IFITM3, CHI3L1, HSPB1, MT2A | ↑       |
| Catts and Weickert | SMRIAC, NSWTRC              | 72  | ctr 27    | scz 37 | scz 50/22          | DLPFC*, OFC# | PCR       | TNFSF13             | ↑, ↔ #  |
| Durrenberger et al.| BBPDGU                      | 10  | ctr 10    | scz 37 | scz 5/5            | TL (BA22)    | PCR       | TIMP1, TNFSF1A, TYROBP | ↓       |
| Fillman et al.     | NSWRGC                      | 35  | ctr 35    | scz 35 | scz 24/13          | DLPFC (BA46) | PCR       | NFXb#, SERPINA3*, IL6ST# | ↑, ↔ #  |
| Fillman et al.     | SMRIAC                      | 35  | ctr 35    | scz 35 | scz 26/9           | Middle frontal gyrus | PCR     | SERPINA3*, IL-1 Rl# | ↔ #    |
| Harris et al.      | SMRIAC                      | 33  | ctr 33    | scz 33 | scz 26/9           | BA10         | ELISA     | TIMP1              | ↔       |
| Hwang et al.       | SNFC, SMRIAC                | 34  | scz 34    | scz 34 | scz 23/10          | PFC (BA10)   | PCR       | IL-1Rb, NFXb50*, NFXb65*, INOS# | ↑, ↔ #  |
| Fillman et al.     | SMRIAC                      | 37  | scz 37    | scz 37 | scz 24/13          | FC (BA10)    | PCR, WB    | IFITM2, IFITM3, SERPINA3, GPB1 | ↑       |
| Hwang et al.       | SFNC, HBTRC, MBB            | 55  | NA        | NA    | NA                 | FC (BA9 and 9), superior frontal gyrus | PCR   | ↑       |
| Schmitt et al.     | BBPDGU                      | 10  | scz 10    | scz 5  | scz 5/5            | TC (BA22)    | PCR       | LPL*, CFD*, PTGER4*, EDG3* ITGA1#, LCP1#, LISC4B*, MTHFD2#, SOD2#, CR1R1, IL1RAP#, IFI16p, IFNAR2*, CD8#, GPX# | ↓, ↔ #  |
| Siegel et al.      | ACOME                       | 57  | scz 57    | scz 57 | scz 23/9           | DLPFC (BA46) | PCR       | TNFSF8, TNFSF10 | ↔       |
| Shao and Vawter    | SMRIAC                      | 27  | scz 27    | scz 27 | scz 23/9           | DLPFC (BA9)  | PCR       | IFITM1, IFITM2/3 | ↑       |
| Thomas et al.      | SFNC                        | 15  | NA        | NA    | NA                 | FC (BA9,46), ACC | PCR | NFXb2 | ↔       |
| Volk et al.        | ACOME                       | 62  | scz 62    | scz 62 | scz 24/15          | PFC (BA9)    | PCR       | NFXb19, NFXb20, Shn-2* | ↑†#     |

**Abbreviations:** ACC, anterior cingulate cortex; ACOME, Allegheny County Office of the Medical Examiner; APOL, apolipoprotein L; BA, Brodmann area; BBPDGU, Brain Bank for Psychiatric Diseases at theGottingen University; CCR, chemokine (c-c motif) receptor; CD, cluster of differentiation; CFD, complement factor D; CHI3L1, chitinase-3 like protein 1; ctr, control; DLPFC, dorsolateral prefrontal cortex; EDG3, endothelial differentiation, sphingolipid g-coupled-receptor; FC, frontal cortex; GPX, glutathione peroxidase; GPB, guanylate binding protein; HBTRC, Harvard Brain Tissue Resource Centre; HPC, hippocampus; HSPB, heat shock protein beta; ICAM, intercellular adhesion molecule; IFL, interferon gamma-inducible; IFITM, interferon-induced transmembrane; IFNAR, interferon (alpha, beta and omega) receptor; IHC, immunohistochemistry; IL1RAP, interleukin 1 receptor accessory protein; IL1RL, interleukin 1 receptor like; IL6ST, glycoprotein 130; ITGA, integrin alpha; INOS, inducible nitric oxide; LCP, lymphocyte cytosolic protein; LPL, lipoprotein lipase; LTC4S, leukotriene C4 synthase; MBB, Maudsley Brain Bank; MT2A, metallothionein 2A; MTHFD, methylenetetrahydrofolate dehydrogenase; NA, not available; NFXb, nuclear factor kappa-light-chain-enhancer of activated B cells; NSWRGC, New South Wales Tissue Resource Centre; OFC, orbitofrontal cortex; PCR, polymerase chain reaction; scz, schizophrenia; PFC, prefrontal cortex; PTGER, prostaglandin E receptor 4; SERPIN, serine protease inhibitor; SNFC, Stanford Foundation Neuropathology Consortium; Shn-2, Schnurri-2; SMRIAC, Stanley Medical Research Institute Array Collection; SOD, superoxide dismutase; TC, temporal cortex; TIMP, tissue inhibitor of metalloproteinases; TL, Temporal lobe; TNFSF, tumor necrosis factor superfamily; TYROBP, TYRO protein tyrosine kinase binding protein; UPCNMDBB, University of Pittsburgh's center for the neuroscience of mental disorder brain bank.

*# indicate which variables results are representing.
TNFSRF1A in the temporal lobe. However, unlike the decrease in TIMP1 mRNA expression measured in the temporal lobe, TIMP1 protein concentration, measured by enzyme-linked immunosorbent assay, was not changed in the prefrontal cortex in another study. Schmitt et al. reported 6 out of 23 immune-related genes are downregulated in the superior temporal cortex in schizophrenia. The 23 immune-related genes include cytokines and microglial markers, discussed above, and other markers including LPL, CFD, PTGER4 and EDG3 being downregulated and ITGA1, LCP1, LTC4S, MTHFD2, CD84, GPX, IFI16 and SOD2 being unchanged.

**DISCUSSION**

Schizophrenia has been linked to neuroinflammation. Schizophrenic patients have been shown to have elevated cytokines measured by PET analysis in some but not all reports. This patients.

The paper systematically reviewed the literature covering neuroinflammatory analyses in postmortem brains from schizophrenic patients.

Multiple studies evaluating neuroinflammation in postmortem brain samples found evidence of neuroinflammation in schizophrenia. However, a definitive statement cannot be made on whether neuroinflammation is present in schizophrenic postmortem brain samples due to the number of null studies. For example, out of 33 studies evaluating GFAP, 21 studies did not find any effect of schizophrenia on GFAP expression, whereas 6 studies found a decrease in GFAP and 6 studies had elevated GFAP expression. Similarly, out of 34 studies that evaluated glial cell density, 25 studies found no effect of schizophrenia, whereas 7 studies found a decrease in glial cells and 2 studies found an increase. Variability is also observed for four microglial markers (HLA, CD11b, CD68 and calprotectin), where 11 studies had elevated expression of microglial markers, 8 studies found no differences and 3 found a decrease. SERPIN3, a protease inhibitor that is involved in inflammatory processes and connective tissue turnover, however, was elevated in the 4 studies, which have reported on its mRNA expression. IFITM, a viral restriction factor, was also reported elevated in four microarrays, and confirmed in one targeted study.

These discrepancies may be explained, at least partly, by the heterogeneity in study designs across studies. One of the heterogeneous variable across studies is brain region analyzed. For example, studies evaluating GFAP expression have analyzed 34 brain regions, including the hippocampus, prefrontal cortex, entorhinal cortex, orbitofrontal cortex and cingulate cortex among others. Whereas all five studies analyzing GFAP expression in the entorhinal cortex found no differences in schizophrenia, 4 of the 13 studies evaluating GFAP expression in the frontal cortex, prefrontal cortex or dorsolateral prefrontal cortex (BA9, 10 or 46) identified differences between schizophrenia and healthy controls. However, classification of the frontal cortices varied between studies and may explain differing results. Moreover, four out of six studies examining the cingulate cortex, subgenual cingulate cortex or anterior cingulate cortex found significant changes in GFAP in schizophrenia. It is possible that certain brain regions, such as the cingulate cortex, are more susceptible to change in schizophrenia compared to other regions such as the entorhinal cortex. Nevertheless, despite more studies pointing to a decrease in GFAP expression in the cingulate cortex in schizophrenia, not all studies show decreases despite evaluating the same brain region and marker.

Consideration of the cortical layer in which the markers are measured may be needed in order to tease out the differences across studies. Many studies found layer-specific effects in various brain regions and markers. For example, in two studies, GFAP expression was increased solely in layer V of the dorsolateral prefrontal cortex and layer I in subgenual cingulate cortex. This could explain differences across studies measuring GFAP in the whole prefrontal cortex mentioned above. Similarly, layer-specific effects of schizophrenia on glial cell density measured by cresyl violet were observed in several studies evaluating the motor cortex (layer III), planum temporale (layer IV), cingulate cortex (layer IV) and dorsolateral prefrontal cortex (layer V).

Differences in methodological approaches also warrant consideration when evaluating the results of the studies mentioned above. Stereological analysis, an unbiased cell counting method, was applied to approximately half of the studies measuring glial cells. Only one study utilizing stereology measured differences in glial cell density, whereas seven studies using other methods reported differences. However, the use of stereology is not always clear in the methods section and therefore the results above should be considered with caution. Similarly, double labeling could be utilized to detect different subtypes of cells. However, few studies in this review utilized double labeling, which should be considered when no differences in cell densities are detected. Thus, the lack of changes in cell densities may not reflect changes in subtypes of cells.

Another variable that may contribute to the heterogeneous results is the stage of the disorder. By separating paranoid schizophrenia from residual schizophrenia, differences in S100b-positive cells were observed. Microglia are also elevated in paranoid schizophrenia, where HLA-DR-positive cell density is higher in paranoid schizophrenia compared to residual schizophrenia. Moreover, differences in gliosis score are seen between early onset and late onset schizophrenia. Similarly, the three patients with microgliosis in the study by Bayer et al. were all defined to have late onset schizophrenia.

Suicide is common in schizophrenia. This is important to consider as postmortem brains from suicide victims may present elevated pro-inflammatory cytokines. This is in agreement with Steiner and colleagues where the two schizophrenia patients that committed suicide had the highest HLA-DR-positive cell density. When accounting for suicide victims, the same group found no differences between diagnosis groups. They did, however, find a relation between suicide and HLA-DR-positive cells. Similarily, GFAP cell density is elevated in the dorsolateral prefrontal cortex of suicide victims compared with non-suicide schizophrenic patients. This effect on GFAP, in the dorsolateral prefrontal cortex of suicide victims, however, was not found in another study measuring GFAP in the western blot. No effect of suicide was also observed for ICAM-1 expression. This is also an important consideration for control group selection. Tooney et al. found an effect of schizophrenia on neurokinin 1 receptor compared with a control group that contained suicide victims, which may potentially confound the results. Although a few studies considered the effect of suicide on their measurements, many studies do not report this data or include it in their statistical analysis, making it a limitation and should be considered in future studies.

Several other confounding factors have been associated with potential effects on neuroinflammatory markers in schizophrenia in postmortem brains. Antipsychotics have been associated with modulation of inflammation. Typical antipsychotics generally reduce pro-inflammatory markers while atypical antipsychotics generally increase them. In our systematic review, antipsychotics were reported to raise GFAP, substance P and HLA. No effect of medication, however, was seen on IL-1β. This is important to note, as not all studies measured antipsychotic levels at time of death or corrected for this potential confounder. Moreover, even when measured, separation of typical and atypical antipsychotics was not considered in the statistical analysis. Also, control subjects would not have been exposed to antipsychotic medication, potentially creating a confounding effect between controls and the experimental group. Similarly, age is
positively correlated to the expression of GFAP66 S100β and substance P receptor binding.151 Lifestyle choices, such as smoking and alcohol abuse, may also contribute to neuroinflammation. In one study, decreases in MHC I observed in the dorsolateral prefrontal cortex of non-smoking schizophrenia patients were no longer apparent in the smoking population.100 Interestingly, lifestyle choices and antipsychotic use are also risk factors for the development of type II diabetes,106 which is more prevalent in schizophrenia107 and has been associated with neuroinflammation.168,169 Although not reported in the studies in this review, it would be of interest for future studies to investigate a potential link between diabetes in schizophrenia and neuroinflammation.

The source of the brains also needs consideration. Several brain banks produced multiple studies utilizing several different brain regions from the same brains. Brain banks may have different diagnosis methods, inclusion and exclusion criteria, storage, and demographics among many other variables. Thus, it is possible that the results may be biased by where the brains samples used were provided from. For example, the 33 studies on GFAP reported in this paper were generated from brains from 15 separate brain banks. Of those 33 studies, 6 studies reported a decrease in GFAP. Of those 6 studies, 2 studies utilized the Stanley Foundation Neuropathology Consortium whereas 3 other studies used theCorsellis Brain Collection.

Despite the heterogeneity across studies, the expression of both SERPINA3 and IFITM was repeatedly found to be increased in microarray studies. SERPINA3, a member of the serine protein inhibitor family, is an acute-phase protein which increases during inflammatory episodes170 and is expressed in reactive astrocytes.171 SERPINA3 has previously been linked with decreased age of onset of Alzheimer’s symptoms.172 Moreover, SERPINA3 expression is correlated with GFAP positive cells in Alzheimer’s disease.173 Patients with multiple sclerosis have elevated SERPINA3 CFS concentration.174 In depression, no association was reported between blood levels of SERPINA3 and symptoms.175 IFITM, on the other hand, is an immune-related protein involved in viral replication. In animal models of inflammation, IFITM1 is increased in the cortex of mice lacking the NF-κB site binding protein Schnurri-2.176 Similarly, IFITM1 and 3 expression is upregulated in the hippocampus following centrally administered lipopolysaccharide injection,177 suggesting its involvement in neuroinflammatory processes.

In conclusion, although the majority of studies note a lack of change in neuroinflammatory markers in postmortem brain samples of patients with schizophrenia, there are still multiple studies indicating either increases or decreases in neuroinflammatory markers. Although ~70% of studies evaluating astrocytes or glial cells in schizophrenia found no change, there were still ~30% of studies showing either an increase or decrease in astrocytic markers and glial cell density. The changes in microglial markers in schizophrenia is more variable across studies, with ~45% of studies showing an increase and 40% of studies showing no change. Similarly, pro-inflammatory cytokine concentration in the postmortem schizophrenia brain is also variable across studies, with studies showing both elevated and decreased cytokine levels in schizophrenia. The cause of this heterogeneity in results is not clear at the moment, but may be due to several factors including brain region measured, stage of disorder, source of the brain and medication. Despite this heterogeneity, microarray analyses have consistently indicated markers such as SERPINA3 and IFITM to be elevated in schizophrenia. Future studies should consider these potential sources of heterogeneity when measuring neuroinflammatory markers in postmortem brain samples of schizophrenia patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

MOT holds a studentship from the Natural Sciences and Engineering Research Council of Canada (PGSD-442373-2013). RPB acknowledges funding from the Canadian Institutes of Health Research (#303157) and holds a Canada Research Chair in Brain Lipid Metabolism. The authors would also acknowledge Dr. JL Sievenpiper for the helpful discussion on systematic reviews.

REFERENCES

1 Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, ‘just the facts’ what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 2008; 102: 1–18.
2 van Os J, Kapur S. Schizophrenia. Lancet 2009; 374: 635–645.
3 Insel TR. Rethinking schizophrenia. Nature 2010; 468: 187–193.
4 Rouspos P, Haroutunian V. Schizophrenia: susceptibility genes and oligodendroglial and myelin related abnormalities. Front Cell Neurosci 2014; 8: 5.
5 Karoutzou G, Enrich HM, Dietrich DE. The myelin-pathogenesis puzzle in schizophrenia: a literature review. Mol Psychiatry 2008; 13: 245–260.
6 Stephan KE, Friston KJ, Frith CD. Dysfunction in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 2009; 35: 509–527.
7 Abi-Dargham A. Schizophrenia: overview and dopamine dysfunction. J Clin Psychiatry 2014; 75: e31.
8 Leza JC, Garcia-Bueno B, Bloque M, Arango C, Parelada M, Do K et al. Inflammation in schizophrenia: a question of balance. Neurosci Biobehav Rev 2015; 55: 612–626.
9 Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. J Neuroinflammation 2013; 10: 43.
10 Reus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. Neuroscience 2015; 300: 141–154.
11 Muller N, Weidinger E, Leitner B, Schwarz MJ. The role of inflammation in schizophrenia. Front Neurol Sci 2015; 9: 372.
12 Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC. CNS immune privilege: hiding in plain sight. Immunol Rev 2006; 213: 48–65.
13 Cherry JD, Olshchowa J, O'Banion MK. Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. J Neuroinflammation 2014; 11: 98.
14 Rapoport SI. Lithium and the other mood stabilizers effective in bipolar disorder target the rat brain arachidonic acid cascade. ACS Chem Neurosci 2014; 5: 459–467.
15 van Neerven S, Nemes A, Imholz P, Regen T, Denecke B, Johann S et al. Inflammatory cytokine release of astrocytes in vitro is reduced by all-trans retinoic acid. J Neuroinmunol 2010; 229: 169–179.
16 Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL et al. Neuroinflammation in Alzheimer’s disease. Lancet Neurol 2015; 14: 388–405.
17 Potvin S, Stip E, Sepehy AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 2008; 63: 801–808.
18 Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011; 70: 663–671.
19 Barman M, Wood J, Chorover K, Watson AM, Celik C, Mansour H et al. Evaluation of HLA polymorphisms in relation to schizophrenia risk and infectious exposure. Schizophr Bull 2012; 38: 1149–1154.
20 Yue WH, Wang HF, Sun LD, Tang FL, Liu ZH, Zhang HX et al. Genome-wide association study identifies a susceptibility locus for schizophrenia inHan Chinese at 11p11.2. J Med Genet 2011; 48: 1226–1231.
21 Pasterk M, Kubicki M, Shenton ME. In vivo imaging of neuroinflammation in schizophrenia. Schizophr Res 2015; 41: 85–93.
22 van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitemaker A, Caspers E et al. Microglia activation in recent-onset schizophrenia: a quantitative [(11)C]PK11195 positron emission tomography study. Biol Psychiatry 2008; 64: 820–822.
23 Dooı̈dmun D, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC. Neu­roinflammation in schizophrenia-related psychosis: a PET study. J Nucl Med 2009; 50: 1801–1807.
24 Bloomfield PS, Selvaraj S, Veronese M, Rizzo G, Bertoldo A, Owen DR et al. Microglial activity in people at ultra high risk of psychosis and in schizo­phrenia: an [(11)C]PBR28 PET brain imaging study. Am J Psychiatry 2016; 173: 44–52.
25 Kenk M, Selvanathan T, Rao N, Surdian J, Rusjan P, Remington G et al. Imaging neuroinflammation in gray and white matter in schizophrenia: an in vivo PET study with [(18)F]FEPPA. Schizophr Bull 2015; 41: 85–93.
26 Takano A, Arakawa R, Ito H, Tateno A, Takahashi H, Matsumoto R et al. Peripheral benzodiazepine receptors in patients with chronic schizophrenia: a PET study with [(11)C]JDA1106. Int J Neuropsychopharmacol 2010; 13: 943–950.

Molecular Psychiatry (2016), 1009 – 1026 © 2016 Macmillan Publishers Limited
Buntinx M, Moreels M, Vandenabeele F, Lambrichts I, Raus J, Steels P et al.

Emsley R, Chiliza B, Asmal L, du Plessis S, Phahladira L, van Niekerk E

Roberts GW, Colter N, Lofthouse R, Bogerts B, Zech M, Crow TJ. Gliosis in schizophrenia.

Downen M, Amaral TD, Hua LL, Zhao ML, Lee SC. Neuronal death in cytokine-induced

Monje ML, Toda H, Palmer TD. Intraocular inflammatory glial abnormalities in the

Rapaport MH, Delrham KH, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D. Absence of

Akhondzadeh S, Tabatabaei M, Amini H, Ahmadi Abhari SA, Abbasi SH, Behnham B. Cerebrospinal fluid in patients with schizophrenia.

Falke E, Han LY, Arnold SE. Evidence for morphological alternations in bipolar disorder, but not schizophrenia. Brain Behav Immun 2001; 15: 611–618.

Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 2003; 362: 798–805.

Katsel P, Byne W, Roussos P, Tan W, Siever L, Haroutunian V. Astrocyte and glutamate markers in the superficial, deep, and white matter layers of the anterior cingulate gyrus in schizophrenia. Neuropsychopharmacology 2011; 36: 1171–1177.

Beasley CL, Dwork AJ, Rosoklija G, Mann JJ, Mancsok B, Jakovljević Z. Metabolic abnormalities in fronto-striatal-thalamic white matter tracts in schizophrenia. Schizophr Res 2009; 109: 159–166.

Pateni SJ, Laurence JA, Azaghi-Niknam M, Stary JM, Schulz SC, Lee S et al. Glial fibrillary acidic protein is reduced in cerebellum of subjects with major depression, but not schizophrenia. Schizophr Res 2004; 69: 317–323.

Kasen CS, Canavoa MF, Kleinman JE, Griffen WS. Choline acetyltransferase in schizophrenia. J Psychiatry 1993; 150: 454–459.

Dean B, Gray L, Scantlebury C. Regionally specific changes in cortical S100beta in bipolar disorder but not schizophrenia. Aust N Z J Psychiatry 2006; 40: 217–224.

Kasen CS, Mank RE, Schluter KA, Stumer WQ, Sheng JG, Griffen WS. Alterations in synaptic proteins and their encoding mRNAs in prefrontal cortex in schizophrenia: a possible neurochemical basis for ‘hypofrontality’. Mol Psychiatry 1999; 4: 39–45.

Perrone-Bizzozero NI, Mostoni FM, Goldberg Y, Velayudhan T, Koenigsknecht A, Schalling M. Altered expression of glial fibrillary acidic protein in prefrontal cortex in psychiatric illness. Schizophr Res 2013; 150: 252–257.

Steffek AE, McCullumsmith RE, Haroutunian V, Meyer-Woodford JH. Cortical expression of glial fibrillary acidic protein and glutamine synthetase is decreased in schizophrenia. Schizophr Res 2008; 103: 71–82.

Williams MR, Hampton T, Pearce RK, Hirsch SR, Ansorge O, Thom M et al. Astrocyte decrease in the subgenual cingulate and callosal genu in schizophrenia. Eur Arch Psychiatry Clin Neurosci 2013; 263: 41–52.

Williams M, Pearce RK, Hirsch SR, Ansorge O, Thom M, Maier M. Fibrillary astrocytes are decreased in the subgenual cingulate in schizophrenia. Eur Arch Psychiatry Clin Neurosci 2014; 264: 357–362.

Williams MR, Kool D, O’Dell J, MacDonald CD, Ching EW, Turkheimer F et al. Neuropathological changes in the substantia nigra in schizophrenia but not depression. Eur Arch Psychiatry Clin Neurosci 2014; 264: 285–296.

Rajkowska G, Miguel-Hidalgo JI, Makkos Z, Melletz H, Overholser J, Stockmeier C. Layer-specific reductions in GFAP-reactive astroglia in the dorsolateral prefrontal cortex in schizophrenia. Schizophr Res 2002; 57: 127–138.

Tordesillas CT, Hallak JE, Dunham JS, Deakin JF. Gliarial fibrillary acidic protein and glutamine synthetase in subregions of prefrontal cortex in schizophrenia and mood disorder. Neurosci Lett 2006; 404: 276–281.

Markova E, Markov I, Revishchik A, Ohkotin V, Sulimov G. 3-D Golgi and image analysis of the optical tubercle in schizophrenia. Annu Quant Cytool Histol 2002; 18: 178–182.

Rao JS, Kim HW, Harvey GJ, Rapoport SI, Reeve EA. Increased neuroinflammation and arachidonic acid cascade markers, and reduced synaptic proteins, in the posterior frontal cortex from schizophrenia patients. Schizophr Res 2013; 147: 24–31.

Barley K, Dracheva S, Byne W. Subcortical oligodendrocyte and astrocyte-associated gene expression in subjects with schizophrenia, major depression and bipolar disorder. Schizophr Res 2009; 112: 54–64.
84 Uranova NA, Zimina IS, Vikhreva OV, Krukov NO, Rachmanova VI, Orlovskaya DD. Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. *Transl Psychiatry* 2013; 3: 1–9.

85 Steiner J, Schmitt A, Steyskal C, Bernstein HG, Schneider-Axmann T, Parlapani E, Pakkenberg B. Regional differences in human ependymal and blood vessels. *J Neural Transm (Vienna)* 2015; 122: 1055–1068.

86 Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T. Regulation of immune-modulatory genes in left temporal cortex in schizophrenia. *Schizophr Res* 2015; 161: 208–216.

87 Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP. Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb Cortex* 2012; 22: 386–394.

88 Cotter D, Mackay D, Landau S, Kerwin R, Everall I. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry* 2001; 58: 545–553.

89 Benes FM, Davidson J, Bird ED. Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. *Arch Gen Psychiatry* 1986; 43: 31–35.

90 Kurumaji A, Waki T, Toru M. Decreases in peripheral-type benzodiazepine receptors in postmortem brains of chronic schizophrenics. *J Neurotransm* 2009; 116: 247–252.

91 Comte I, Kotagiri P, Szele FG. Regional differences in human ependymal and subventricular zone cytoarchitecture are unchanged in neuropsychiatric disease. *Dev Neurosci* 2012; 34: 299–309.

92 Nakatani N, Hattori E, Chihni S, Dean B, Iwayama Y, Matsumoto I et al. Gene-expression analysis detects eight genes with robust alterations specific to bipolar I disorder: relevance to neuronal network perturbation. *Hum Mol Genet* 2006; 15: 1517–1523.

93 Connor CM, Guo Y, Akbarian S. Cingulate white matter neurons in schizophrenia and bipolar disorder. *J Neurol Sci* 2009; 286: 486–493.

94 Durrenberger PF, Fernando FS, Kashefi SN, Bonnert TP, Seilhean D, Nait-Oumesmar B et al. Common mechanisms in neurodegeneration and neuroinflammation: a BrainNet Europe gene expression microarray study. *J Neural Transm (Vienna)* 2015; 122: 1055–1068.

95 Sinkus ML, Adams CE, Logel J, Freedman R, Leonard S. Expression of immune-related genes on chromosome 6p21.3–22.1 in schizophrenia. *Brain Behav Immun* 2013; 32: 51–62.

96 Busse S, Busse M, Schiltz K, Bielau H, Gos T, Brisch R. Deletion of lymphocytes and microglia in the hippocampus of patients with psychiatric illnesses. *J Psychiatr Res* 2006; 40: 3561–3566.

97 Cotter D, Mackay D, Landau S, Kerwin R, Everall I. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry* 2001; 58: 545–553.

98 Benes FM, Davidson J, Bird ED. Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. *Arch Gen Psychiatry* 1986; 43: 31–35.

99 Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex of nonsmoker patients with schizophrenia. *Neurosci Lett* 2009; 46: 282–292.

100 Stein et al. Postmortem evidence of cerebral inflammation in schizophrenia. *MO Trépanier et al.* 2010; 1009–1026.
bipolar disorder, and schizophrenia: evidence for decreased neuronal somal size and increased neuronal density. *Brain Research* 2003; 103: 1086–1098.

125 Benes FM, McSparran J, Bird ED, SanGiovanni JP, Vincent SL. Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. *Arch Gen Psychiatry* 1991; 48: 996–1001.

126 Pennington K, Dicker P, Hudson L, Cotter DR. Evidence for reduced neuronal somal size within the insular cortex in schizophrenia, but not in affective disorders. *Schizophrenia Research* 2008; 106: 164–171.

127 Cotter D, Hudson L, Landau S. Evidence for orbitalfrontal pathology in bipolar disorder and major depression, but not in schizophrenia. *Bipolar Disorder* 2005; 7: 358–369.

128 Jonsson SA, Luts A, Guldberg-Kjaer N, Brun A. Hippocampal pyramidial cell disinharmony correlates negatively to cell number: implications for the pathogenesis of schizophrenia. *Eur Psychiatry* 2012; 27: 124–127.

129 Beasley CL, Chana G, Honavar M, Landau S, Everall IP, Cotter D. Evidence for altered neuronal organisation within the planum temporale in major psychiatric disorders. *Schizophrenia Research* 2005; 73: 69–78.

130 Bogerts B, Hantsch J, Herzer M. A morphometric study of the dopamine-containing cell groups in the mesencephalon of normals, Parkinson patients, and schizophrenics. *Biological Psychiatry* 1983; 18: 951–969.

131 Selimom LD, Begovic A. Stereological analysis of the lateral geniculate nucleus of the thalamus in normal and schizophrenic subjects. *Psychiatry Research* 2007; 151: 1–10.

132 Hoistad M, Heinsen H, Wicinski B, Schmitz C, Hof PR. Stereological assessment of the dorsal anterior cingulate cortex in schizophrenia: absence of changes in neuronal and glial densities. *Neuropathol Appl Neurobiol* 2013; 39: 348–361.

133 Beckmann H, Laue M. The human striatum in schizophrenia. II. Increased number of striatal neurons in schizophrenics. *Psychiatry Research* 1997; 68: 99–109.

134 Crow TJ, Ball J, Bloom SR, Brown R, Bruton CJ, Colter N et al. Schizophrenia as an anomaly of development of cerebral asymmetry. A postmortem study and a proposal concerning the genetic basis of the disease. *Arch Gen Psychiatry* 1989; 46: 1145–1150.

135 Nasraiah HA, McCalley-Whitters M, Bigelow LB, Rauscher FP. A histological study of the corpus callosum in chronic schizophrenia. *Psychiatry Research* 1983; 8: 251–260.

136 Toyooka K, Watanabe Y, Iritani S, Shimizu E, Iyo M, Nakamura R et al. A decrease in interleukin-1 receptor antagonist expression in the prefrontal cortex of schizophrenic patients. *Neurosci Res* 2003; 46: 299–307.

137 Harris LW, Pietsch S, Cheng TM, Schwarz E, Guest PC, Bahn S. Comparison of peripheral and central schizophrenia biomarker profiles. *PLoS ONE* 2012; 7: e46368.

138 Dean B, Gibbons AS, Taywood N, Brooks L, Everall IP, Sear D. Different changes in cortical tumor necrosis factor-alpha-related pathways in schizophrenia and mood disorders. *Mol Psychiatry* 2013; 18: 767–773.

139 Fillman SG, Sinclair D, Fung SJ, Webster MJ, Shannon Weckert C. Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. *Translational Psychiatry* 2014; 4: e365.

140 Maida ME, Hurley SD, Daeschner JA, Moore AH, O’Malley K, Lichtenstein P et al. Expression of cyclooxygenase-2, a pro-inflammatory factor, is increased in interleukin-1 receptor antagonist expression in the prefrontal cortex of schizophrenia. *Biological Psychiatry* 2007; 62: 711–721.

141 Ivanamoto K, Kikuchi C, Bundo M, Ikeda K, Kato T. Molecular characterization of bipolar disorder by comparing gene expression profiles of postmortem brains of major mental disorders. *Mol Psychiatry* 2004; 9: 406–416.

142 Siegel BI, Sengupta EJ, Edelson JR, Lewis DA, Volk DW. Elevated viral restriction factor levels in cortical blood vessels in schizophrenia. *Biological Psychiatry* 2014; 76: 160–167.

143 Shao L, Vawter MP. Shared gene expression alterations in schizophrenia and bipolar disorder. *Biological Psychiatry* 2008; 64: 89–97.

144 Catts VS, Weckert CS. Gene expression analysis implicates a death receptor pathway in schizophrenia pathology. *PLoS ONE* 2012; 7: e35511.

145 Pandey GR, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC et al. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatry Research* 2012; 46: 57–63.

146 Tonelli LH, Stiller J, Rujescu D, Giegling I, Schneider B, Maurer K et al. Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. *Acta Psychiatrica Scand* 2008; 117: 198–206.

147 Na KS, Jung HY, Kim YK. The role of pro-inflammatory cytokines in the neuro-inflammation and neurogenesis of schizophrenia. *Prog Neuropsychopharmacology and Biological Psychiatry* 2014; 48: 277–286.

148 Dryzga Z, Obuchowicz E, Marcinowksa A, Herman ZS. Cytokines in schizophrenia and the effects of antipsychotic drugs. *Brain Behav Immun* 2006; 20: 532–545.

149 Ventriglio A, Gentile A, Stella E, Bellomo A. Metabolic issues in patients affected by schizophrenia: clinical characteristics and medical management. *Front Neuropsychiatry* 2015; 7: 297.

150 Suviasaar J, Perala J, Saarini S, Harkank T, Pirikka S, Joukamaa M et al. Type 2 diabetes among persons with schizophrenia and other psychotic disorders in a general population survey. *Eur Arch Psychiatry Clin Neurosci* 2008; 258: 129–136.

151 Purkayastha S, Cai D. Neuroinflammation basis of metabolic syndrome. *Mol Metab* 2013; 2: 356–363.

152 Van Dijk G, van Heijningen S, Reijne AC, Nyakas C, van der Zee EA, Eisel UL. Integrative neurobiology of metabolic diseases, neuroinflammation, and neurodegeneration. *Front Neurosci* 2015; 9: 173.

153 Kalsheker NA. Alpha 1-antichymotrypsin. *Int J Biochem Cell Biol* 1996; 28: 961–964.

154 Gopalan SM, Wilczynska KM, Konik BS, Bryan L, Kordula T. Astrocyte-specific expression of the alpha1-antichymotrypsin and glial fibrillary acidic protein genes requires activator protein-1. *J Biol Chem* 2006; 281: 1956–1963.

155 Kamboh MI, Minster RL, Kenney M, Ozturk A, Desai PP, Kammerer CM et al. Alpha-1-antichymotrypsin (ACT or SERPINA3) polymorphism may affect age-at-onset and disease duration of Alzheimer’s disease. *Neurobiol Aging* 2006; 27: 1435–1439.

156 Licastro F, Mallory M, Hansen LA, Masliah E. Increased levels of alpha-1-antichymotrypsin in brains of patients with Alzheimer’s disease correlate with activated astrocytes and are affected by AP0E 4 genotype. *J Neuroinmunol* 1998; 88: 105–110.
Multiple sclerosis: identification and clinical evaluation of novel CSF biomarkers. *J Proteomics* 2010; **73**: 1117–1132.

Zalli A, Jovanova O, Hoogendijk WJ, Tiemeier H, Carvalho LA. Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology* 2015.

Takao K, Kobayashi K, Hagihara H, Ohira K, Shoji H, Hattori S et al. Deficiency of schnurri-2, an MHC enhancer binding protein, induces mild chronic inflammation in the brain and confers molecular, neuronal, and behavioral phenotypes related to schizophrenia. *Neuropsychopharmacology* 2013; **38**: 1409–1425.

Bonow RH, Aid S, Zhang Y, Becker KG, Bosetti F. The brain expression of genes involved in inflammatory response, the ribosome, and learning and memory is altered by centrally injected lipopolysaccharide in mice. *Pharmacogenomics J* 2009; **9**: 116–126.

Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)