A consideration of the increased risk of schizophrenia due to prenatal maternal stress, and the possible role of microglia

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Abstract

Schizophrenia is caused by interaction of a combination of genetic and environmental factors. Of the latter, prenatal exposure to maternal stress is reportedly associated with elevated disease risk. The main orchestrators of inflammatory processes within the brain are microglia, and aberrant microglial activation/function has been proposed to contribute to the aetiology of schizophrenia. Here, we evaluate the epidemiological and preclinical evidence connecting prenatal stress to schizophrenia risk, and consider the possible mediating role of microglia in the prenatal stress-schizophrenia relationship. Epidemiological findings are rather consistent in supporting the association, albeit they are mitigated by effects of sex and gestational timing, while the evidence for microglial activation is more variable. Rodent models of prenatal stress generally report lasting effects on offspring neurobiology. However, many uncertainties remain as to the mechanisms underlying the influence of maternal stress on the developing foetal brain. Future studies should aim to characterise the exact processes mediating this aspect of schizophrenia risk, as well as focussing on how prenatal stress may interact with other risk factors.

Key words:

Schizophrenia; maternal stress; prenatal stress; environmental risk; microglia

Introduction

Schizophrenia is a highly debilitating illness characterised by a pattern of positive (e.g., hallucinations and delusions), negative (e.g., depression), and cognitive (e.g., memory, concentration and attention deficits) symptoms (Haro et al., 2003), with a lifetime prevalence of around 1% (Insel, 2010). Antipsychotic drugs are somewhat effective in the treatment of psychotic symptoms, but a considerable level of non-responsiveness remains, and such drugs can exert significant side effects (Haddad and Correll, 2018). Furthermore, there has been little success in developing effective treatments for negative and cognitive symptoms of schizophrenia, despite their considerable impact on patients (Maas et al., 2017). Hence, in order to improve treatment prospects, it is crucial that a greater understanding of the underlying mechanisms of the disorder is gained.

It has long been known that persistent stress exerts deleterious effects on the body. Exposure to chronic stress in adulthood is associated with increased risk for both physical and psychological pathologies (Faraji et al., 2011; Greenwood et al., 1996; Peña-Bautista et al., 2020). However, exposure to stress during the very earliest stages of development can also lead to negative effects. Various forms of prenatal stress (PS) such as maternal exposure to natural disaster (Dancause et al., 2015, 2011; King and Laplante, 2005; Kinney et al., 2008; Laplante et al., 2008; Torche and Kleinhaus, 2012), war (Kertes et al., 2016; Khan et al., 2015), poverty (Lefmann and Combs-Orme, 2014; Lobel et al., 1992; Perkins et al., 2013), and familial problems (Chisholm et al., 2017; Li et al., 2010a, 2010b, 2009; Radtke et al., 2011; Udo et al., 2016) appear to be associated with worsened developmental outcomes in a variety of neurological domains, including schizophrenia. Alongside such epidemiological findings, various animal model paradigms such as maternal restraint stress (Diz-Chaves et al., 2012; Lemaire et al., 2006; Leuner et al., 2014; Peña et al., 2012; Schmitz et al., 2002), and repeated variable stress (utilising multiple stress paradigms in conjunction with one another) (Koenig et al., 2005; Markham et al., 2010; Neeley et al., 2011; Ratajczak et al., 2015; Wilson et al., 2013) have provided further support for these associations. However, our understanding of the underlying mediating mechanisms remains incomplete.

Recent evidence, however, is beginning to suggest that microglia, a key cell type in the brain, may be implicated in these associations (Calcia et al., 2016). Microglia are the brain's resident macrophages and carry out an array of functions such as the clearance of tissue debris and damaged cells, and protection against pathogens (Kettenmann et al., 2011). They also play a key role in the developing brain in synaptic removal and pruning in both prenatal and postnatal life (Paolicelli et al., 2011; Thion and Garel, 2017). An array of findings have implicated these cells in the pathophysiology of schizophrenia, and as exposure to stress has known consequences for inflammatory systems (Rohleder, 2019), the question has arisen as to whether alterations to microglial functioning may mediate the association between PS exposure and subsequent schizophrenia development. However, this line of enquiry is still in its infancy. Hence, the aim of this review is to provide an overview of the evidence linking prenatal maternal stress to schizophrenia risk, and to outline and evaluate the evidence implicating microglia in the association between PS and schizophrenia, as well as to highlight critical areas for future research consideration.

Pathophysiology of Schizophrenia

Schizophrenia has a complex pathophysiology, involving several brain systems and regions. Structurally, varying degrees of cortical atrophy and ventricular enlargement are commonly observed and are particularly correlated with negative and cognitive symptoms (Coyle et al., 2016), alongside reductions in neuronal spine density and complexity, particularly in areas such as the dorsolateral prefrontal cortex (dlPFC), sensory cortex and hippocampus (HC), and particularly at glutamatergic synapses (Coyle, 2017). Other findings from studies employing imaging methods have also demonstrated impairments in the default mode network in schizophrenia patients, particularly in inhibiting this network when engaging in other cognitive tasks (Hu et al., 2017).

Dysregulation of dopaminergic (Howes and Kapur, 2009) and glutamatergic (Dawson et al., 2014; Morris et al., 2005; Pratt et al., 2018; Pratt and Morris, 2015) signalling, especially with respect to NMDA receptor-mediated transmission, is strongly implicated in schizophrenia aetiology. Decreases in brain-derived neurotrophic factor (BDNF) may also play a role in the propagation of schizophrenia symptoms (Jindal et al., 2010; Pillai et al., 2010; Ray et al., 2014, 2011; Tan et al., 2005; Xiu et al., 2009) (although see exception: (Jockers-Scherübl et al., 2004)). Studies have also found that BDNF levels may vary over time course of illness and may be linked to symptom severity (Palomino et al., 2006). Based on these and other findings, it has been hypothesised that deficits in BDNF levels during development may lead to abnormal regulation and organisation of neurotransmitter systems such as dopaminergic transmission in the striatum, as well as deficits in synaptic plasticity that may underpin the cognitive deficits observed in the disorder (Angelucci et al., 2005).

Prenatal Stress and Schizophrenia

Epidemiological Studies

Numerous studies have assessed the relationship between PS and schizophrenia, often utilising quasi-experimental designs that assess the impact of maternal exposure to a naturally occurring stressor on schizophrenia incidence rates. 33 studies were found that have implemented such designs and are summarised in Table 1. Findings generally support the hypothesis of an association between PS exposure and schizophrenia, with 26 studies producing predominantly positive findings (see Table 1). However, the evidence is not unequivocal, and studies investigating the same stressor type have not always concurred with one another. Mixed findings have been observed, especially in relation to stressors such as maternal exposure to bereavement, general stress, with more consistency with respect to war, terrorism and famine (see Table 1). In the ten studies assessing the impact of natural disaster, two studies investigated The Great Tangshan Earthquake of 1976 and produced findings in support of an association (Guo et al., 2019; Song et al., 2019), and Selten and colleagues' (1999) assessment of the impact of the Dutch Flood Disaster observed evidence of increased risk although their statistical power was insufficient to reach a p value <0.05. Effect sizes between the studies were remarkably similar. In some cases reporting negative findings, it may be that low statistical power resulted in a failure to reject the null hypothesis. However, in other studies, limited effect sizes have been found (Debost et al., 2015; Selten et al., 2003).

Studies assessing the moderating role of gestational age at the time of stress generally concur that earlier gestational exposure is associated with greater risk for later schizophrenia development (Davies et al., 2020; Dorrington et al., 2014; Guo et al., 2019; Khashan et al., 2008; St Clair et al., 2005; van Os and Selten, 1998). Hence, the first trimester may be a particularly vulnerable time for the development of brain processes implicated in schizophrenia, and studies that do not differentiate between gestational timing of exposure may be clouded by an insufficient proportion of their sample having been exposed at the crucial early time point, and thus statistical power may be too low to detect an effect. Other analytical shortcomings may explain the discrepancies, as the majority of studies implement relatively simple linear modelling techniques such as ANOVA or simple non-parametric tests such as Mann-Whitney U comparisons, when more refined methods such as bootstrapping (Field and Wilcox, 2017) and generalized linear models (Dunn and Smyth, 2018) are capable of detecting smaller and more nuanced effects.

Sexual dimorphisms of foetal CNS development may also underpin inconsistencies between findings. The incidence of schizophrenia is slightly higher in males, with females also generally demonstrating better outcomes (Abel et al., 2010), and there are known sex differences in the stress response (Bekhbat and Neigh, 2018; Heck and Handa, 2019; Oyola and Handa, 2017). Of the studies reported here, three reported sex differences in the relationship between maternal exposure to PS and schizophrenia development in offspring, but with opposing findings. Malaspina and colleagues

(2008) reported that the relationship between maternal exposure to the Arab-Israeli war of 1967 and schizophrenia development was stronger in female offspring than males. Similar findings in relation to exposure to war were reported by He et al (2019). However, Fineberg et al. (2016) in fact observed a negative effect in females, in that they were less likely to develop schizophrenia after PS exposure to schizophrenia, whereas males showed the opposite pattern. Unpicking the moderating role of sex on the association between PS exposure and schizophrenia is challenging, as PS is one among many risk factors for schizophrenia, they all may interact differentially with the sexually dimorphic neurobiological systems implicated in the disorder to produce more complex alterations than simply an increased severity of an effect in one sex than another.

Disentangling effects of other risk factors that may co-vary with PS has also proven difficult. Although certain studies have included confounding factors such as maternal education and socioeconomic status in their models and have still found notable relationships between PS and schizophrenia (Guo et al., 2019; Weinstein et al., 2018), not all variables can easily be modelled. Events such as natural disasters and war each occur within a specific geographic and socioeconomic context. For instance, the effect of a natural disaster may be moderated by factors such as governmental responses, provision of replacement housing, and access to necessities such as supermarkets and pharmacies, among others. Similarly, one of the most robust epidemiological predictors of schizophrenia cited in Table 1 is famine, a risk factor further complicated by the effects of nutritional deficiencies on foetal brain development. A further confounding variable, as is the case in most psychological studies, is sample size. The incidence rate of schizophrenia is around 1%. Hence if a sample size for live births in both an exposed and unexposed cohort is 1,000, only around 10 individuals would be expected to develop schizophrenia under typical circumstances. Thus, even if the effect size resulted in a doubling of incidence, the number of individuals in the study with schizophrenia would still remain relatively small, resulting in low statistical power. However, despite these confounding issues, the literature in this area generally supports an association between PS and subsequent schizophrenia development, with effects more apparent when stress occurs during earlier gestational periods and with possibly differing outcomes between sexes, and many of the studies report similar effect sizes of around a one-and-a-half to two-fold increase in risk (see Table 1).

Table 1. A summary of the findings from 33 studies that have been published assessing the relationship between prenatal maternal stress and subsequent schizophrenia development using human participants.

Natural Disaster			
Study	**Predictor Variable**	**No. of Cases Exposed**	**Key Findings**
Davies et al., 2020	Exposure to any Catastrophic Event	Meta-analysis	Increased likelihood (not statistically significant) of SCZ development – odds ratio 1.15 (0.98 – 1.36; $p = 0.087$) with effects most apparent in 1st trimester.
Guo et al., 2019	Great Tangshan Earthquake (1976)	100	Increased likelihood of SCZ development – odds ratio 3.38 (1.43 – 8.00) with effects most apparent in 1st trimester – odds ratio 7.45 (2.83 – 19.59).
Song et al., 2019	Great Tangshan Earthquake (1976)	9	Increased likelihood of SCZ development - $\chi^2 = 10.273, p = 0.006.$
St Clair et al., 2005	Chinese Famine (1959 – 1961)	383	Increased likelihood of SCZ development – relative risk: 2.30 (1.99 – 2.65) for those born in 1960 and 1.93 (1.68 – 2.23) for those born in 1961.
He et al., 2018	Chinese Famine (1959 – 1961)	~ 1800	Increased likelihood of SCZ development – relative risk: 1.82 (1.11 – 2.98) for those born in 1960 and 1.93 (1.68 – 2.23) for those born in 1961.
Wang and Zhang, 2017	Chinese Famine (1959 – 1961)	~ 650	Increased likelihood of SCZ development – relative risk not specified directly.
Xu et al., 2009	Chinese Famine (1959 – 1961)	1751	Increased likelihood of SCZ development – relative risk: up to 2.05 (1.86 – 2.27) for those born in 1961.
Susser et al., 1996	Netherlands hunger winter (1945)	27	Increased likelihood of SCZ development – relative risk: 2.0 (1.2 - 3.4), similar for men and women.
Susser and Lin, 1992	Netherlands hunger winter (1945)	~ 32	Increased likelihood of SCZ development – relative risk: 1.40 (0.73 - 2.69) (not statistically significant) for men, 2.56 (1.41 - 4.65) for women, for 1st trimester exposure. No increased incidence for 3rd trimester exposure.

Selten et al., 1999	Dutch Flood Disaster (1953)	4	Indicative of increased likelihood of non-affective psychosis development – relative risk: 1.80 (0.90 – 3.5). However, not statistically significant.
War/Terrorism			
Study	**Predictor Variable**	**No. of Cases Exposed**	**Key Findings**
He et al., 2019	Sino-Japanese War (1939 – 1945)	~ 700	Increased likelihood of SCZ development, in females only – adjusted relative risk: 1.16 (1.01, 1.33).
Weinstein et al., 2018	Terror attacks in Israel (1975 – 1995)	21	Increased likelihood of SCZ development – adjusted relative risk: 2.53 (1.63 – 3.91).
Levine et al., 2016	Holocaust exposure (1928 – 1945)	101	Increased likelihood of SCZ development (not statistically significant), but findings suggestive – adjusted relative risk: 1.32, (0.95 – 1.83).
Levine et al., 2014	Residing in Nazi-dominated Europe (1933 – 1945)	584	Poorer course of schizophrenia measured by rehospitalisations – adjusted relative risk: 2.28, (2.00 – 2.60).
Malaspina et al., 2008	Arab-Israeli War (1967)	37	Increased likelihood of SCZ of those exposed in 2nd gestational month – relative risk: 2.3 (1.1 – 4.7); females: 4.3 (1.7 – 10.7); males: 1.2 (0.4 – 3.8) (not statistically significant), but no notable findings were observed for other months.
Selten et al., 2003	Arab-Israeli War (1967)	253	No notable change in SCZ risk – relative risk: 0.98 (0.85 – 1.13). No difference between trimesters.
	Yom Kippur War (1973)	214	No notable change in SCZ risk – relative risk: 1.00 (0.86 – 1.16). No difference between trimesters.
van Os and Selten, 1998	Nazi invasion of the Netherlands (1940)	419	Increased likelihood of SCZ development – relative risk: 1.15 (1.03 – 1.28). 2nd Trimester sex difference: M: 1.35 (1.05 – 1.74); F: 0.83 (0.61 – 1.12).

Bereavement			
Study	**Predictor Variable**	**No. of Cases Exposed**	**Key Findings**
Davies et al., 2020	Death or severe illness of a close relative	Meta-analysis	No notable effect of stressor on SCZ. Odds ratio: 0.84 (0.61 – 1.17; p = 0.31).
Debost et al., 2015	Death or severe illness of a close relative	29	No notable effect of stressor on SCZ. Relative risk: 0.96 (0.78 – 1.19).
Abel et al., 2014	Death of first degree relative	92	No notable effect of stressor on SCZ. Odds ratio: 1st trimester – 0.95 (0.58 – 1.56); 2nd trimester – 0.79 (0.46 – 1.33); 3rd trimester – 1.14 (0.78 – 1.66).
Class et al., 2014	Death of a first degree relative	24	No notable effect of stressor on SCZ development. Adjusted hazard ratio: across pregnancy – 0.78 (0.49 – 1.24); 1st trimester – 0.16 (0.02 – 1.10); 2nd trimester – 1.13 (0.56 – 2.26); 3rd trimester – 0.94 (0.49 – 1.80).
Khashan et al., 2008	Death of a relative	66	Increased likelihood of SCZ development, but only when bereavement occurred during first trimester. Adjusted relative risk: 1.67 (1.02 – 2.73).
Huttunen and Niskanen, 1978	Death of child's father	6	Increased likelihood of SCZ development. χ^2 = 3.87, p < 0.05.
General Stress			
Study	**Predictor Variable**	**No. of Cases Exposed**	**Key Findings**
Davies et al., 2020	Stress not otherwise specified	Meta-analysis	Increased likelihood of SCZ – odds ratio: 2.40 (1.15 – 5.01; p = 0.019).
Pugliese et al., 2019	Self-reported stress	23	Increased likelihood of SCZ – odds ratio: 2.16 (1.087 – 4.291), p = 0.028.

Brannigan et al., 2019	Self-reported stress	56	Increased likelihood of SCZ – Odds ratio: 1.47 (0.83 – 2.62). However, not statistically significant.
Fineberg et al., 2016	Self-reported stress	79	Increased likelihood of SCZ in males but decreased likelihood in females. Male odds ratio: 1.995 (1.061 – 3.750), $p = 0.032$. Female odds ratio: 0.393 (0.178 – 1.073), $p = 0.071$ (not statistically significant).
Other			
Study	**Predictor Variable**	**No. of Exposed Cases**	**Key Findings**
Ellman et al., 2019	Maternal cortisol	Not reported	No notable effect of maternal cortisol on SCZ development. Odds ratio: 1st trimester – 0.977 (0.974 – 1.091), $p = 0.679$; 2nd trimester – 0.971 (0.927 – 1.018), $p = 0.223$; 3rd trimester – 0.980 (0.953 – 1.008), $p = 0.158$.
Betts et al., 2014	Stressful life events	Not reported	Increased incidence of general psychotic experiences – standardised parameter estimate: 0.08, $p = 0.030$. No notable difference in experience of paranoia – SPE: -0.03, $p = 0.871$; or thought interference: SPE -0.03, $p = 0.722$. Odds ratio: 1.09 (1.05, 1.34).
Dorrington et al., 2014	Severe life events	665	No notable effect of stressor on SCZ – odds ratio: 1.01 (0.93 – 1.10), but subjects assessed when only 12 years old. Life-long incidence will be dramatically under-estimated.
Kimhy et al., 2006	Crowded housing	45	Increased likelihood of SCZ – relative risk: 1.47 (0.99 – 2.16), $p = 0.05$. However, no longer significant after adjusting for paternal age – relative risk: 1.18 (0.76 – 1.84), $p = 0.46$.
Herman et al., 2006	Unwanted pregnancy	16	Increased likelihood of SCZ – hazard ratio: 1.75 (0.97 – 3.17), $p = 0.06$. However, not statistically significant.
Myhrman et al., 1996	Unwanted pregnancy	19	Increased likelihood of SCZ – odds ratio: 2.4 (1.2 – 4.8).

Microglia as potential mediators of prenatal stress effects on the developing brain

Alongside PS, prenatal exposure to infection has been robustly associated with schizophrenia (Boksa, 2008; Brown and Patterson, 2011; Cheslack-Postava et al., 2015; Khandaker et al., 2013; Zhou et al., 2021). The maternal immune activation (MIA) hypothesis of schizophrenia posits that the immune response triggered by infection affects foetal brain development. The exact mechanisms of this effect remain unclear; however, several hypotheses have been developed. For instance, alterations in levels of inflammatory signalling molecules have been shown to affect key developmental processes such as neuronal differentiation and neurogenesis (Canetta and Brown, 2012). However, animal model findings of inflammatory marker concentration in the foetal brain after exposure to pathogen or viral mimetic are not wholly consistent and factors such as gestational timing may moderate effects (Boksa, 2010). Other hypotheses suggest that inflammatory markers may affect placental functioning which may in turn affect foetal development (Hsiao and Patterson, 2011) with a possible involvement of oxidative stress toxicity (Oskvig et al., 2012; Talukdar et al., 2020). It is worth noting that the elevated schizophrenia risk due to prenatal infection is also associated with exposure in the first and second, but not third trimester (Howes and Kapur, 2009; Khan et al., 2015; Lefmann and Combs-Orme, 2014; Perkins et al., 2013), just as appears to be the case for PS. Hence there is value in exploring possible commonalities of mechanism.

Microglia are the brain's resident macrophages and are responsible for orchestrating an immune response in the presence of pathogens (Kettenmann et al., 2011) as well as a range of regulatory functions such as apoptosis and synaptic pruning (Paolicelli et al., 2011; Thion and Garel, 2017). During their 'surveillance' state, microglia are highly ramified with motile processes which work to scan their surroundings for tissue damage, debris and pathogens. However, highly complex signalling mechanisms can trigger transformation to an 'activated' state in which cells develop an amoeboid appearance and the ability to migrate to sites of injury or pathogen, release a variety of cytotoxic substances, phagocytose and self-proliferate (Kettenmann et al., 2011). This neuroinflammatory response is a key mechanism for the protection of the brain from tissue injury or pathogen invasion. However, an excessive inflammatory response in the brain can lead to acute cellular and synaptic impairment and death (Lyman et al., 2014) and has been implicated in several neurological and psychiatric disorders (Heneka et al., 2015; Naegele and Martin, 2014), including schizophrenia (Meyer, 2013).

A number of studies have reported increased microglial activity in MIA offspring (Chamera et al., 2021; Hadar et al., 2017; van den Eynde et al., 2014; Zhao et al., 2019). However, these findings are not without exception (Smolders et al., 2015), further indicating that the effects on microglial functioning are nuanced and may be affected by several other factors, such as astroglial activity (Bernstein et al., 2016). Ozaki et al. (2020) noted alterations in the motility of foetal microglia that persisted postnatally, but only if infection occurred in earlier gestational periods, further supporting the hypothesis of gestational timing as a key moderator. Purves-Tyson et al. (2021) produced mixed findings: while they did observe an increase in microglial gene transcription, they did not find evidence for increases in cell density or alterations in morphology of these cells. Sex differences have also been observed, with greater increases in microglial activity in MIA-exposed females than males (Hui et al., 2020; Zhang et al., 2019).

The MIA model does not in itself directly provide support for the mediating role of microglia in the relationship between prenatal stress and schizophrenia. However, it does demonstrate the impact of inflammatory stressors on microglia and related signalling pathways during foetal brain development. A key question is therefore the extent to which the effects of maternal stress can resemble an inflammatory response. The traditional view of stress exposure, and consequently elevated circulating glucocorticoid (GC) levels, is that this functions to suppress the innate immune

response and the ensuing inflammation. However, it seems that this may not always be the case, particularly in CNS tissue (Sorrells and Sapolsky, 2007). Stress is a known risk factor for a variety of inflammatory disorders (Faraji et al., 2011; Peña-Bautista et al., 2020; Tafet and Bernardini, 2003) and evolutionary neurobiologists have posited that for the majority of human history, stressors (e.g., predator exposure) were a strong predictor of pathogen exposure and infection (e.g., wounds), and an inflammatory response associated with stress would be advantageous in protecting against infection. However, in modern society, psychosocial stressors can last over periods of months or years, and subsequently may result in chronic inflammation (Slavich and Irwin, 2014). The inflammatory response induced by stress also extends to the brain and inflammatory molecules such as nitric oxide (NO) and pro-oxidants can induce neurotoxicity via numerous mechanisms, including oxidative and nitrosative stress (Munhoz et al., 2008), and a chronic neuroinflammatory response has been implicated in neurodegenerative disorders (Heneka et al., 2015).

Stress has been linked with increased microglial activity in numerous brain regions (Calcia et al., 2016), particularly HC (Brevet et al., 2010; Delpech et al., 2016; Espinosa-Oliva et al., 2011), PFC (Bollinger et al., 2020, 2016; Hinwood et al., 2013, 2012; Kopp et al., 2013) and NAc (McGrath and Briand, 2019; Rodríguez-Arias et al., 2018; Tynan et al., 2010). PS specifically has also been shown to affect microglial activity in the hippocampus, with prenatally stressed mice showing a higher density of microglia, increased inflammatory marker presence, as well as heightened microglial responses to peripheral inflammation induced by lipopolysaccharide, a potent microglia activator (Diz-Chaves et al., 2013, 2012; Ślusarczyk et al., 2015). However, in PS-exposed rats, increased numbers of ramified microglia have been observed in numerous cortical and subcortical areas, alongside a reduction in amoeboid microglia at birth, with these differences disappearing by postnatal day ten (Gómez-González and Escobar, 2010). In their 2017 study, Gumusoglu et al. investigated the mediating role of the inflammatory cytokine interleukin-6 (IL-6) in the relationship between prenatal stress and microglia aberrations. Both prenatal stress and IL-6 administration resulted in increased density of multivacuolated microglia at embryonic day 14. However, IL-6 blockade inhibited the effects of prenatal stress on microglia morphology. An increased density of multivacuolated microglia may indicate a shift between states of inflammatory activation (Bittle and Stevens, 2018). The same study also found increased microglial ramification in adulthood after prenatal stress. These findings are noteworthy as they demonstrate that the microglial numbers are not simply increased in prenatally stressed animals, but that their morphology and state of activation during the earliest stages of postnatal development may be altered. So, while there is not complete agreement on the nature of the microglial changes, the preclinical findings overall are consistent with the neurodevelopmental account of schizophrenia.

Experimental animal models utilising stress paradigms in pregnant rodents can be particularly useful as rats and mice have short developmental timescales (Sengupta, 2013) as well as demonstrating the capacity for complex cognitive and behavioural processes (Alves et al., 2020; Pontecorvo et al., 1996; Rennie et al., 2013; Zhou and Crystal, 2009). Biochemical and behavioural changes in rodents that are putatively analogous to those observed in schizophrenia patients have been found in several studies (e.g. Koenig et al., 2005; Markham et al., 2010; Ratajczak et al., 2015; Wilson et al., 2013) . Evidence specifically implicating microglia in these effects of stress are more limited. Niu and colleagues (2020) found that the expression of BDNF and inflammatory markers such as CD68 were differentially altered between males and females, with levels showing distinct patterns of change from adolescence to adulthood between the sexes, but with both deviating from controls. As there are slight suggestions that the progress of the disorder is not simply less severe in human females, but shows severity differences over the course of illness (Abel et al., 2010), these findings perhaps suggest that the underlying cellular and molecular aberrant mechanisms may differ between the sexes, as opposed to a single disease pathway manifesting with greater severity in males. Another report suggests upregulation of inflammation-associated miRNAs in offspring brain after prenatal stress (Zucchi et al., 2013). However, in rats, Neeley et al (2011) observed (strain-dependent)

decreases in offspring hippocampal TNFα. Overall, the extent of offspring microglial activation due to gestational maternal stress exposure remains under-investigated, with most studies to date either employing prenatal maternal immune activation (which complicates interpretation), or post-natal stressors. For a more comprehensive review of the animal model literature of the effects of early developmental stress on microglia see Carloni et al. (2021).

Current research is attempting to decipher the specific molecular pathways whereby microglia may mediate the relationship between PS and schizophrenia. The hypothalamic-pituitary-adrenal axis orchestrates increases in circulating GCs in the stress response. GCs influence bodily systems to respond to environmental stressor(s) by binding with GC receptors (GRs) expressed on cells throughout the body to prioritise immediately essential processes such as cardiovascular and respiratory activity, and inhibit non-essential processes such as digestion and growth (Smith and Vale, 2006). Microglia also express GRs and are thus susceptible to the effects of this endocrinological response to stress. Microglia isolated from adult male rats exposed to an acute stressor (inescapable tail-shock) have been shown to be sensitized in their cytokine response to a pro-inflammatory stimulus, with this effect blocked in rats who had been administered with the GR antagonist mifepristone, indicating that the effects of stress on microglia are occurring via GC signalling (Frank et al., 2014). However, others have found that NMDA receptor antagonism as well as GR blockage inhibited the increased microglial proliferation that had occurred after acute stress exposure (Nair and Bonneau, 2006), indicating that increased glutamatergic signalling may also play a role in the effects of stress on microglia. In their 2018 study, Bittle and Stevens found that the administration of GCs alongside the pro-inflammatory cytokine IL-1β to foetal microglia, could not fully replicate the effects of PS in terms of morphological changes, indicating that the effects of PS on microglia are highly complex and involve multiple molecular pathways.

Microglia and Schizophrenia

Table 2 summarises the literature that has investigated differences in microglial functioning between schizophrenia patients and healthy controls. A variety of sources, such as post-mortem tissue, patient-derived cell cultures and CSF or plasma concentrations of inflammatory markers have been assessed in order to better understand the role of microglia in the pathophysiology of schizophrenia. Similarly, several different outcome measures that relate to microglial functioning have been investigated, such as microglial density, inflammatory marker concentration, and microglial lateralisation. Microglial density has been assessed in five studies, and has produced mixed findings, with two studies failing to observe any notable effects (see Table 3). Other studies have looked specifically at the densities of microglia expressing HLA-DR, a marker of microglial activation that can be detected via immunohistological methods, and thus allow the densities of activated microglia to be quantified. HLA-DR+ microglia were found to be in higher numbers in schizophrenia samples in two studies (see Table 2). However, other work has suggested that other factors may mitigate the findings of increased activated microglial density in schizophrenia. Specifically, one study found that the density of HLA-DR+ cells was not increased, but differences in the lateralisation of these cells was observed between patients and controls (Steiner et al., 2006). Similarly, other studies have observed this finding in only certain sub-groups of patients, particularly those with higher suicidality (Steiner et al., 2008), as well as those with greater paranoid tendencies (Busse et al., 2012).

Another method that has utilised inflammatory marker expression is TSPO PET imaging. Translocator protein (TSPO) is expressed on the mitochondrial outer membrane and its upregulation has been implicated in neuroinflammatory processes and has thus been utilised as a biomarker for microglial activity. Several studies have found differences in TSPO binding in schizophrenia patients or patient-derived cell cultures compared with controls, however increases, decreases and lack of change have all been reported (see Table 2). Several factors may mitigate this disparity. For instance, certain studies have noted associations between levels of TSPO binding and symptom severity, even if a

notable difference in TSPO binding between patients and controls was not observed (Bloomfield et al., 2016; Hafizi et al., 2017b). Similarly, regional differences have also been noted, with effects predominantly observed in sub-cortical rather than cortical regions (De Picker et al., 2019; Doorduin et al., 2009; Hafizi et al., 2017b; Ottoy et al., 2018; Plavén-Sigray et al., 2018). Specific methodological issues may also lead to inconsistencies, as different radiotracers and quantification methods are implemented between studies and samples vary in their duration of illness and treatment histories (Notter and Meyer, 2017). Similarly, outcomes may vary based on whether binding potential or volume distribution are used as outcome measures (Marques et al., 2019). It should also be noted that, as a mitochondrial marker, TSPO is present in all cell types in the brain, and may not in retrospect be a sensitive probe for altered microglial numbers; rather having utility for detecting instances of local cellular proliferation (e.g., astrocytosis) in diseases with more overt pathologies.

It has been hypothesised that aberrant activation of microglia cells during critical neurodevelopmental periods may lead to deleterious effects via increased rates of synaptic pruning (Notter and Meyer, 2017), a process first implicated in the pathophysiology of schizophrenia by Irwin Feinberg in 1982. Supporting evidence has come from Sellgren and colleagues (2019), who utilised a schizophrenia patient-derived *in vitro* model whereby neurons were cultured both with and without microglia (also patient-derived). They observed increased synaptic elimination in those cultured with microglia, but not those without, indicating that the synaptic reduction observed in schizophrenia is resultant of altered microglial activity. The specific time points during which this hyper-pruning activity occurs have not yet been elucidated. Extensive synaptic pruning is a key feature of neurodevelopment throughout childhood and adolescence and this time period would coincide with the typical age of schizophrenia onset (Germann et al., 2021), but whether the changes in microglia that facilitate this aberrant pruning occur even earlier, and possibly prenatally, has not yet been confirmed.

Table 2. A summary of the 52 studies assessing the alterations in microglial and wider neuroinflammatory functioning in schizophrenia patients.

PET Imaging		
Study	**Source**	**Key Findings**
Conen et al., 2021	Recent-onset and chronic SCZ patients.	Higher TSPO binding was found in older patients and controls but did not differ between groups, apart from unmedicated recent-onset SCZ patients showing lower binding than medicated, chronic or control participants. In chronic patients, binding was negatively associated with positive symptoms and positively associated with negative symptoms.
De Picker et al., 2019	Psychosis patients.	Age-dependent change in TSPO binding between groups (increased with age). Binding was also associated with positive symptom scores.
Marques et al., 2019	SCZ patients.	Increased TSPO binding potential but no notable difference in volume of distribution.
Ottoy et al., 2018	SCZ patients during psychotic phase.	Increased TSPO binding in HC, amygdala and brain stem, but no notable differences in any other regions of interest.
Plavén-Sigray et al., 2018	Metanalysis of 5 studies including first episode psychosis (FEP) or SCZ patients.	Lower TSPO binding in all brain regions: FC, TC and HC.
Selvaraj et al., 2018	Ultra-high risk for psychosis (UHRP) and SCZ patients.	Reductions in grey matter volume in SCZ but not UHRP. Negative association between TSPO binding and grey matter volume in SPZ patients, most notably in right superior PC.
Collste et al., 2017	Untreated FEP.	Reduction in TSPO binding in gray matter areas. No notable associations between binding and clinical or cognitive measures.
Di Biase et al., 2017	Recent-onset and chronic SCZ patients.	No notable differences were found in TSPO binding in any area between any groups.
Hafizi et al., 2017a	Untreated clinically high-risk sample.	No notable differences were found in TSPO binding in either dlPFC or HC. However, binding was associated with apathy and state anxiety.

Hafizi et al., 2017b	Untreated FEP	No notable differences were observed between groups in dlPFC or HC. No associations between TSPO binding and duration of illness or clinical presentation.
Bloomfield et al., 2016	UHRP and SCZ patients.	Elevated TSPO binding in gray matter which was positively correlated with symptom severity in UHRP sample. Increased binding was also observed in SCZ sample.
Coughlin et al., 2016	Recent-onset SCZ patients.	No notable differences in TSPO binding between groups in cortical or subcortical regions.
Holmes et al., 2016	Medicated and unmedicated moderate-to-severely symptomatic SCZ patients.	No notable differences in TSPO binding between unmedicated patients and controls, but elevations were found in PFC, cingulate cortex and PC regions between medicated patients and controls.
van der Doef et al., 2016	Recent-onset SCZ patients.	No notable differences in TSPO binding between groups in cortical or subcortical regions.
Kenk et al., 2015	SCZ patients during psychotic phase.	No notable differences in TSPO binding between groups in grey matter or white matter were observed.
Takano et al., 2010	Chronic SCZ patients.	No notable difference in [^{11}C]DAA1106 binding between groups, however a positive correlation was seen between cortical activation and positive symptoms and duration of illness.
Doorduin et al., 2009	SCZ patients during psychotic phase.	Increased ^{11}C-(*R*)-PK11195 binding in hippocampus as well as whole grey matter to a lesser extent, indicative of increased inflammation.
van Berckel et al., 2008	Recent-onset SCZ patients.	*(R)*-[^{11}C]PK11195 PET imaging indicates increased density of activated microglia in grey matter of SCZ patients.
Microglial Density/Morphology		
Study	**Source**	**Key Findings**
Gober et al., 2022	Chronic SCZ patients.	Iba-1 staining showed increased microglial density in all cortical gray matter and frontal/temporal sub-cortical white matter regions in SCZ patients.

Snijders et al., 2021	Metanalysis of 38 studies.	No notable changes in microglial density or morphology. However, there was reduced expression of several microglial-specific genes.
Uranova et al., 2021	Chronic SCZ patients.	Increased microglial density (as measured by transmission electron microscopy and morphometry) in SCZ patients compared to controls.
Laurikainen et al., 2020	FEP patients.	Decreased distribution volume but with no regionally specific effects. Distribution volume was also inversely associated with serum CCL22 and CCL17.
Petrasch-Parwez et al., 2020	Chronic SCZ patients.	No notable difference in Iba-1$^+$ cells in anterior midcingulate cortex (aMCC) between groups. However, density was lateralised towards the right aMCC in patients which was not found in controls.
Uranova et al., 2020	SCZ patients during psychotic phase.	Alterations in the mitochondrial morphology of microglia and adjacent oligodendrocytes indicative of dystrophy.
Uranova et al., 2018	Post-mortem tissue of chronic SCZ patients.	Increased amoeboid and dystrophic microglia adjacent to oligodendrocytes, but no notable differences were found in level of oligodendrocyte dystrophy.
van Kesteren et al., 2017	Metanalysis of 41 studies including SCZ patients.	Increased density of microglial cells, most consistently found in temporal cortex.
Gos et al., 2014	Chronic SCZ patients.	No notable differences in HLA-DR$^+$ microglial density between groups. Fewer activated microglial cells were observed in CA1 of HC compared with controls and no notable changes in CA2/CA3/DG regions.
Fillman et al., 2013	SCZ patients.	Increased microglia density of microglia and increased expression of inflammatory mRNA in dlPFC.
Busse et al., 2012	Chronic SCZ patients.	Increased density of HLA-DR$^+$ microglia in paranoid SCZ compared with residual SCZ and controls.

Steiner et al., 2008	Chronic SCZ patients.	No notable differences in HLA-DR$^+$ microglial density between groups. However, increases in HLA-DR$^+$ microglial density in DLPFC, ACC and md-Thalamus were found in SCZ patients who had completed suicide.
Steiner et al., 2006	Chronic SCZ patients.	No notable differences in HLA-DR$^+$ microglial density between groups. However, lateralisation of amoeboid microglia found in controls was not shown in SCZ patient tissue. HLA-DR$^+$ microglial density was elevated in two patients who had completed suicide.
Radewicz et al., 2000	Chronic SCZ patients.	Increased density of HLA-DR$^+$ microglia in TC and FC.
Microglial Markers in Post-mortem Tissue		
Study	**Source**	**Key Findings**
De Picker et al., 2021	Chronic SCZ patients.	Increased cortical expression of Fcγ receptors (CD64 and CD64/HLA-DR ratio). In patients with psychotic symptoms present at death, age-dependent increased Iba-1 expression and increased CD64/HLA-DR ratios relative to patients without psychotic symptoms at death.
Hill et al., 2021	Chronic SCZ patients.	Decreased fractalkine (a neuron-microglia signalling molecule) protein levels in SCZ patients compared with controls.
North et al., 2021	SCZ patients.	Increased SCZ patients compared to controls in high-inflammatory sub-group. No difference in Iba-1 expression between SCZ patients and controls but decreased phagocytotic microglial markers (*PRPY12/PRPY13*) and increased expression of macrophage (*CD163*), monocyte (*CD14*), natural killer cell (*FCGR3A*) and adhesion molecule (*ICAM1*) markers.
Shimamoto-Mitsuyama et al., 2021	SCZ patients.	Reduced gene expression of microglial markers, inflammatory cytokines and *CSF1R* (a regulator of microglial density) in the corpus callosum.
Tzioras et al., 2021	Chronic SCZ patients.	No notable difference in Iba1 CD68, synapsin-1 in dlPFC, nor in colocalization of the markers, or in synaptic engulfment by microglia.

Karpiński et al., 2020	Meta-analysis of seven datasets of gene expression in post-mortem SCZ patients.	Increased microglial marker expression in dlPFC and decreased expression in PC.
Ormel et al., 2020	SCZ patient-derived microglia-like cell culture.	Increased expression of several microglial and inflammatory markers.
Purves-Tyson et al., 2020	SCZ patients.	Positive associations between complement protein transcription and microglial markers across groups, but specific associations between CD163 and C1qA in the high-inflammatory SCZ sub-group only.
Zhang et al., 2020	Chronic SCZ patients.	Reduced mRNA expression of microglial associated genes (CX3CR1) in SCZ patients who completed suicide compared with controls with increases in others (P2RY12).
López-González et al., 2019	Elderly chronic SCZ patients.	Downregulation of several inflammatory markers, all of which correlated with expression of *CD68* (microglial-specific inflammatory marker).
Ormel et al., 2017	SCZ-patient derived macrophage culture.	Increased expression of *P2RX7* in response to pro-inflammatory stimulus, but no other differences in the 23 genes studied between groups.
Yoshino et al., 2016	SCZ patients.	Increased expression of *TREM2* mRNA.
Marco et al., 2015	SCZ patients.	Enrichment of SNPs associated with increased HLA-C and HLA-DRA expression in SCZ patients.
Hercher et al., 2014	Chronic SCZ patients.	No notable difference in IBA-1-stained microglia between groups.
Foster et al., 2006	Chronic SCZ patients.	Calprotectin (nonspecific inflammatory marker) was found to be elevated in PFC tissue and was localized to microglia.
Other		
Study	**Source**	**Key Findings**
Sellgren et al., 2019	Patient-derived neural cultures with and without	Increased synaptic pruning mediated by microglia.

	patient-derived microglial co-culturing.	

Limitations of Current Research

Evidence is at least consistent with the involvement of microglia in the relationship between PS and schizophrenia. However, unresolved questions still remain. Firstly, schizophrenia is highly heterogenous in numerous aspects, such as responsivity to treatment (Case et al., 2011; Gillespie et al., 2017; Kinon, 2019), degree of cognitive impairment (Bora, 2016; Bruder et al., 2011; Joyce et al., 2005; van Rheenen et al., 2017), structural pathology (Arnone et al., 2009; Brugger and Howes, 2017; Nenadic et al., 2015; Wolfers et al., 2018), and psychosis presentation (Jones and Luhrmann, 2016; van Os, 2016). Schizophrenia shows overlap with bipolar disorder and schizoaffective disorder in terms of shared genetic risk (Berrettini, 2000; Cardno and Owen, 2014; Carroll and Owen, 2009; Schulze et al., 2014) and symptom profile (Pearlson, 2015; Rosen et al., 2012). Hence, some have argued that our conceptualisation of schizophrenia as a singular disease may not be well founded, and instead should be considered as a multi-faceted syndrome with no singular cause or pattern of pathology (Bentall et al., 1988; Jablensky, 2010). Regarding the PS hypothesis, it is also important to acknowledge that not all individuals with schizophrenia were subject to experiences of PS, and conversely, the majority of those who experience PS do not go on to develop schizophrenia. Thus, it may not be wise to expect unequivocal microglial involvement in schizophrenia, but instead alterations in microglial morphology and activity could be reliable biological markers in those with a history of PS exposure. It may be that other risk factors confer their effects via differing mechanisms, or with aberrant microglial activity only playing a partial role.

It also must be questioned whether animal model paradigms such as foot shocks or repeated restraint can authentically simulate human psychosocial stress. Variable stress paradigms have been developed to address the issue on animals habituating to a singular stressor (Koenig et al., 2005), as they are less predictable and more complex. However, when an event such as an earthquake occurs, several forms of stressor occur that ripple out over an extended period of time, for instance, bereavement (Sveen et al., 2018), loss of secure housing (Comerio, 1997), long-standing economic recessions (Coffman and Noy, 2012; Pelling et al., 2002), and other psychiatric confounds such as posttraumatic stress disorder (Kar, 2006). Thus, it is challenging to simulate such drastic and highly interactive forms of stress that occur in the context of a wider society in an animal model. Biological measures of stress such as salivary cortisol concentration can be used to assess the similarities between the stress responses of animal models and human experiences of stress (Egliston et al., 2007). However, the biological processes of stress are not limited to a neuroendocrine response but involve many systems, such as alterations in the gut microbiome, and epigenetic and other hormonal responses which are not always assessed in conjunction with one another (Beijers et al., 2014).

Furthermore, it is impossible to make assessments about an animal's conscious experience and perception of stress. The notion of meta-cognition has been highly implicated in psychopathological effects of stress (Capobianco et al., 2018; Hosseini Ramaghani et al., 2019) but is naturally challenging to assess in animals. It has been argued that animal models should only ever be considered as reconstructions rather than replications of human experience, and animal model findings alone are only direct evidence for the model animal itself, and inferences regarding human functioning are only ever indirect (Sjoberg, 2017). However, that is not to say that animal model research is not a highly valuable tool to generate detailed mechanistic accounts of causal relationships that are less feasible in human research, but they cannot prove or disprove a hypothesis regarding human pathology alone.

Conclusion

Evidence supports the idea that PS constitutes a schizophrenia risk factor, albeit with sex and gestational timing as mitigators. Similarly, evidence supports a complex array of inflammatory alterations in the disorder including aberrant microglial activity. The investigations attempting to assess the relationships between these factors are far from complete, with future work required to better understand the specific cellular and molecular pathways whereby these effects occur. Specifically, future work ought to focus on understanding whether high and low inflammatory subtypes of schizophrenia may exist, and how PS incidence may differ between such groups. Furthermore, a better understanding of how dysfunctional microglial activity affects the systems implicated in schizophrenia, such as glutamatergic, GABAergic and dopaminergic pathways, as well as BDNF signalling, and again how these effects may differ between the sexes. Naturally, risk factors do not occur in isolation, hence, questions still remain as to how PS may work in conjunction with other risk factors such as prenatal infection and genetic determinants. However, despite this remaining uncertainty, the continuing research in this area offers hope for improved treatment possibilities and outcomes for patients.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

The authors have no competing interests to declare.

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