Are common childhood or adolescent infections risk factors for schizophrenia and other psychotic disorders?

Ian B Hickie, Richard Banati, Claire H Stewart and Andrew R Lloyd

ABSTRACT

- Postnatal infection may represent a preventable risk factor for onset of psychotic disorders in adolescence and early adulthood.
- The mechanism of action is likely to involve site-directed triggering of the brain's innate immune system, mediated principally through localised activation of microglial cells. This triggering may occur in response to systemic inflammatory stimuli, without direct involvement of the central nervous system.
- Microglial activation can represent a primary response or a secondary phenomenon at sites made vulnerable by prior injury; that is, areas containing previously activated microglia will respond more strongly to a new stimulus.
- The presence of activated microglia is indicative of a recent insult or active disease. It is not characteristic of long-established neurodevelopmental abnormalities.
- Activated microglia, acting through a variety of cytokine and other signal systems, have the capacity to significantly interfere with synaptic turnover and thus, over time, alter synaptic architecture and function.
- This pathophysiological path should be investigated more systematically as it may explain a novel "neuroprotective" mode of action for some existing antipsychotic compounds.

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Simple genetic theories of schizophrenia and other psychotic disorders are now being challenged by more complex models of gene–environment interactions.[1] These gene–environment models strive not only to identify significant environmental risks, but also to assess their relationship with the onset of these disorders in adolescence (see Hickie and McGorry,[2] *page S5*; McGorry and colleagues,[3] *page S33* in this supplement).[1,4] Critically, gene–environment models shift the focus of preventive and early-intervention research away from a narrow neurodevelopmental focus, towards potential reduction of major environmental risks.[1]

Traditionally, the postpubertal onset of schizophrenia, psychotic disorders and major mood disorders has been thought to result from the effect of normal developmental factors (eg, hormonal factors, frontal lobe maturation, synaptic pruning) on those who already carry some pre-existing genetic, environmental (eg, intra-uterine infection) or neurodevelopmental vulnerability.[5] More recently, this view has been challenged by the concept of a "double hit", whereby exposure to one or more additional risk factors in adolescence (eg, misuse of cannabis or amphetamines and other stimulants [see Hermens and colleagues,[6] *page S22*; Wood and colleagues,[7] *page S10*], head injury, brain infection, emotional trauma) precipitates the progression from being "at risk" to an active illness state.

In this article, we focus on the possible role of postnatal or postpubertal infections (or other inflammatory stimuli) as discrete risk factors. We do not assume that such infective agents are rare, neurotropic or neurotoxic. Indeed, such infections are not necessarily directly involved with the central nervous system (CNS) or associated with clinical evidence of CNS involvement. The way in which systemic infections or inflammation can give rise to a wide range of CNS-related symptoms,[8] and that these phenomena persist beyond the acute illness phase, is increasingly recognised.[9]

Our focus on exposure to infective stimuli is driven by:

- epidemiological studies linking major psychiatric disorders with infective exposures (albeit often dependent on host genotype; see Box 1);
- altered immune function in people with schizophrenia that may indicate an ongoing inflammatory process;[22-24]
- evidence that common infective stimuli outside the CNS modify the responses of the brain's innate immune system (eg, microglial activation occurs in the presence of peripheral immune activation[25-27]);
- clinical evidence that recent infective stimuli are correlated with a range of short- or longer-term neurological, cognitive and other neuropsychiatric syndromes;[9] and
- neuroimaging data indicative of microglial activation (MA) in persons with schizophrenia (see Banati and Hickie,[28] *page S26*).[29]

Microglial response to peripheral inflammation or infection

Microglia, unlike other glial cells, are not of neuroectodermal origin. They are derived from circulating monocytes, and are continuously recruited into the brain (at a low rate), where they undergo differentiation in situ. When activated by one of a range of insults,[30-32] microglia release pro-inflammatory cytokines and nitric oxide (NO). MA has been reported across a broad range of neuroinflammatory and neurodegenerative disorders.[33-36] Importantly, microglial dysfunction has been proposed as a mechanism linking in-utero viral exposure with increased risk of schizophrenia.[37]

We offer a different interpretation of the importance of detection of MA in adults with schizophrenia or other psychotic disorders. Key additional observations include that MA is transient, not present in old gliotic scars, and does not occur in response to stable neurodevelopmental abnormalities.[33-36] That is, MA implies a recent, active or ongoing pathophysiology and is, therefore, unlikely to represent a response to an in-utero exposure alone. After cessation of a pathological stimulus, activated microglia persist and continue to affect synaptic function. In animal models, the minimal period for MA is 1 month. In the adult human brain, the disappearance of activated microglia may be significantly slower because of a protracted pathological stimulus or the effects of other adaptive processes, such as glial cell regeneration.[38,39]

In addition to their immunomodulatory role, it has recently emerged that microglia are vital members of the "quadpartite synapse", which also includes presynaptic and postsynaptic neur-

1 Infections implicated in psychiatric aetiology

Infection	Outcome
CNS infection at age < 14 years*	Schizophrenia[10]
Meningitis at age < 11 years	Schizophrenia;[11] affective psychosis[11]
Tuberculosis at age < 11 years	Schizophrenia;[11] affective psychosis[11]
Viral CNS infection in childhood (0–12 years)	Schizophrenia;[12] non-affective psychosis[13]
Meningitis at age 0–4 years	Schizophrenia[14]
Specific pathogen	
Toxoplasma gondii	Psychosis[15,16]
Human herpesviruses	Psychosis;[15,16] schizophrenia[15,16]
Herpes simplex virus 1	Bipolar disorder;[17] cognitive deficits in schizophrenia[18]
Herpes simplex virus 6	Schizophrenia[16]
Herpes simplex virus 2	Psychosis[19]
Cytomegalovirus (serum IgG at diagnosis)	Schizophrenia[16,20]
Human endogenous retroviruses (timing unknown)	Schizophrenia[21]

CNS = central nervous system. * Infective agents recorded: Cocksackie B5; adenovirus 7; mumps encephalitis; *Haemophilus influenzae* meningitis; *Neisseria meningitidis* meningitis. ◆

ones, and astrocytes.[40] Their release of pro-inflammatory cytokines (interleukin [IL]-1β, IL-6 and tumour necrosis factor [TNF]-α) influences neurotransmission, potentially in the long term, through positive feedback loops. This bridging role of MA that links immune response and altered neurotransmission suggests a plausible pathway from infection to persistent neuropsychiatric disorders. Of particular interest is the observation that MA may be triggered by a single exposure to pathogen-associated molecular patterns, such as the lipopolysaccharide component of the cell wall of gram-negative bacteria.[25] These stimuli interact with pattern recognition receptors, such as toll-like receptors, to induce TNF-α production and associated neuronal injury. These adverse effects may then be sustained for many months in the absence of systemic inflammation.[25]

Communication between microglia is coordinated by purinergic signalling, including the ionotropic ATP receptor, P2X7. Polymorphisms of this receptor (eg, $gln^{460}arg$) have recently been associated with depression and bipolar disorder.[41,42] Such receptor polymorphisms may confer dysfunctional signalling, influencing long-term potentiation,[43] and thereby alter synaptic communication. We do not suggest that immune activation alone induces psychotic symptomatology. Instead, we propose that exposure to infection is a potential priming event for the longer-term development of abnormal signalling patterns that underpin such symptoms.

The tentative findings of MA in schizophrenia[28,29] are consistent with previous structural imaging studies demonstrating active brain changes during the period of onset of psychotic symptoms.[44,45] Calprotectin, a novel inflammatory marker protein, was found to be localised to microglia and elevated in postmortem frontal cortex tissue from people with schizophrenia and other psychotic disorders.[46] Further, a relationship between the degree of MA and the extent of neurophysiological impairment (as measured by changes in cortical evoked potentials) implies that MA is linked to the course of structural brain change and illness progression in people with schizophrenia.[28] It has also been suggested recently that suicidal behaviour in people with schizophrenia or depression may be linked with MA.[47]

Site-directed vulnerability within the CNS

Central to our postnatal infective hypothesis is evidence that brain tissue containing activated microglia will be a preferred site for recruitment of other bloodborne immunological cells, such as activated T lymphocytes. This site-directed homing of peripheral leucocytes into brain regions containing activated microglia has been demonstrated in models of optic nerve transaction[48] and in the facial nucleus after injury to the peripheral facial nerve.[49,50] In these models, T lymphocytes infiltrate the CNS through an intact blood–brain barrier and interact with microglia to modulate the brain's neural response.[51,52]

Consequently, we propose a model for the development of major psychiatric disorders in which activated microglia represent a key link between postnatal infection and later psychopathological events (Box 2). In this model, changes in the state of the brain's innate immune system (notably microglia):

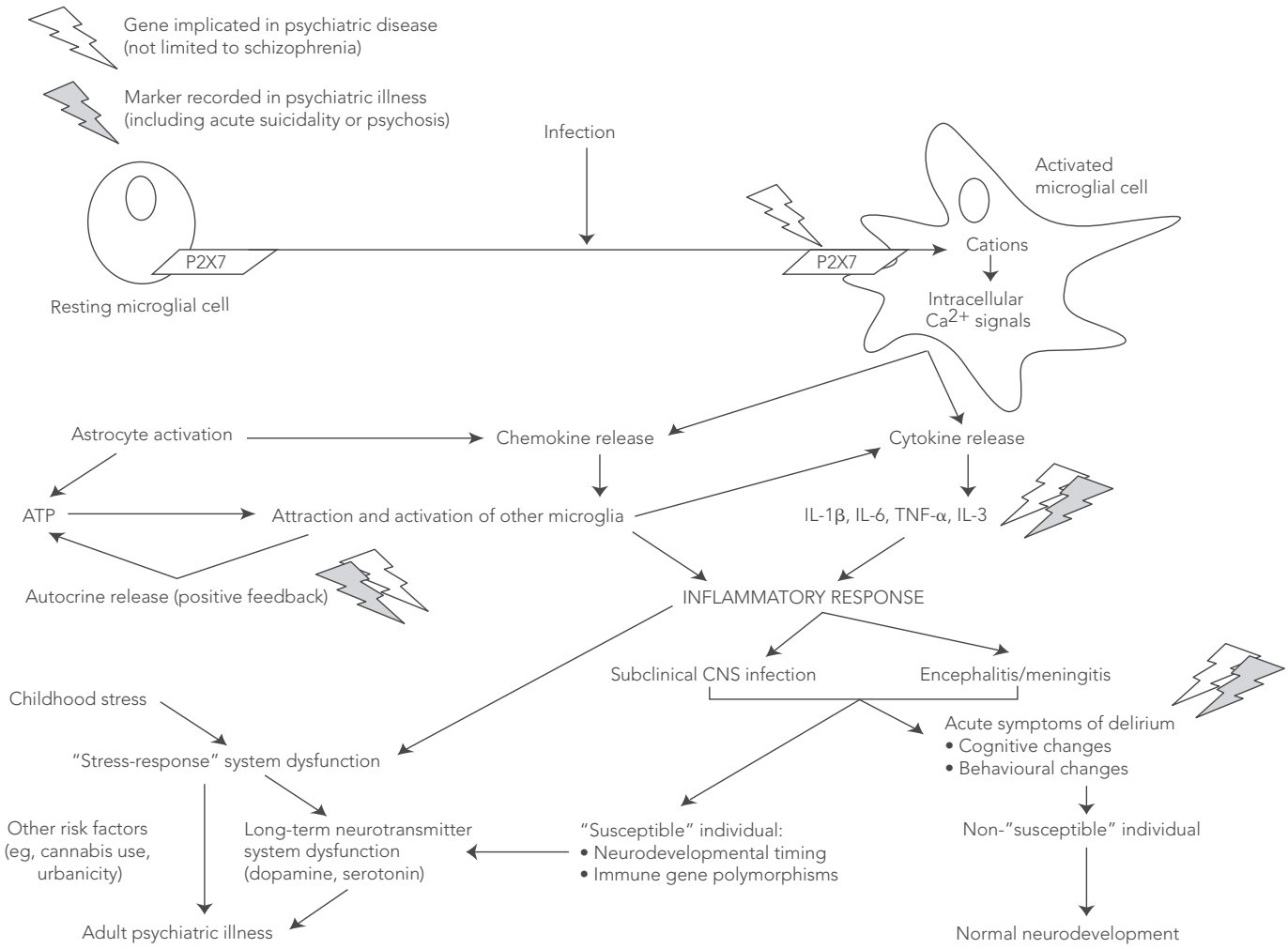
- alter normal neuroglial interactions and, thus, ongoing synaptic functioning;
- lead to structural (but localised) changes in brain circuitry; and
- create specific sites that are vulnerable to later injury in the face of another minor infective or inflammatory stimulus (ie, double-hit hypothesis).

Timing of infective exposures

To date, the most plausible evidence for infection as a major risk factor for schizophrenia has been obtained from epidemiological studies[53] and animal models of intrauterine exposure.[54] These models are consistent with epidemiological evidence linking prenatal infection with increased risks of most major neurological and psychiatric disorders, including (but not limited to) schizophrenia and other psychotic disorders.[55] In our view, however, the plausibility of infective stimuli as important risk factors has also been constrained by a preoccupation with fetal development. Although neurogenesis occurs largely before birth, other key developmental mechanisms such as synaptogenesis, synaptic pruning and myelination continue throughout childhood and adolescence. Hence, the potential adverse impacts of infective or inflammatory stimuli continue up to and include the typical age of onset of these disorders — between 15 and 25 years.

A range of childhood infections have been linked to adult psychotic disorders.[10,56] As early childhood is associated with the highest rates of gastroenteritis and common respiratory infections, these exposures may be relevant in those predisposed to the CNS consequences of peripheral infection or inflammation. Adolescence is again an important time for infectious exposures, as it is a high-risk period for exposure to both neurotropic and systemic viral pathogens, including herpes simplex virus type 1 (HSV1) and HSV2, Epstein–Barr virus and cytomegalovirus.

2 Proposed mechanism whereby activated microglial cells, in response to infection or other inflammatory stimuli, increase risk of major psychiatric illness



CNS = central nervous system. IL = interleukin. TNF = tumour necrosis factor. ◆

The role of genes and viral exposures in risk of illness and clinical phenotypes

Preliminary evidence of interactions between at-risk genes, infective risk factors, phenotypes and biological correlates of psychotic disorders has recently appeared. Although presence of the *val*^{158}*met* catechol-*O*-methyltransferase polymorphism and HSV1 exposure both increase the risk of cognitive changes, the combination of these two factors is associated with an 85-fold increased risk of cognitive impairment in patients with bipolar disorder.[17] Prasad and colleagues reported reduced prefrontal grey matter among HSV1-exposed first-episode patients with schizophrenia.[57] Prasad and colleagues also examined the impact of a polymorphism of major histocompatibility complex class I polypeptide-related sequence B (MICB) on grey matter changes.[58] Critically, and suggestive of a genuine gene–environment interaction, they reported that MICB genotype and HSV1 exposure both contributed to greater grey matter differences between patient and control subjects. Shirts and colleagues have also suggested that, not only are there specific associations between genes that regulate IL-18 pathways and schizophrenia, but that some specific single-nucleotide polymorphisms are also associated with elevated HSV1 antibody titres.[24] It is also becoming increasingly evident that the severity of acute sickness phenomena (presumably reflecting both degree of immune activation and CNS-related phenomena) after common infective stimuli is itself dependent on host genotype.[59]

Ongoing immune dysfunction in patients with schizophrenia

These speculative views are supported by findings that adult patients with schizophrenia demonstrate evidence of altered immune function (eg, in-vivo increases in IL-1RA [receptor agonist], soluble IL-2R and IL-6 production and an in-vitro decrease in IL-2 production) that is consistent with ongoing inflammatory responses.[60,61] Similar findings of ongoing immune disturbance have been noted in other major psychiatric disorders, particularly affective disorders.[62-64] Evidence that genetic variations in immune response are also susceptibility factors for major psychiatric disorders (eg, P2X7 and risk to bipolar disorder and unipolar depression) suggests that progress in our understanding of these complex relationships may also depend on more sophisticated human and

animal model designs that capture relevant gene–environment interactions.

Immunomodulatory effects of treatments

Recently, there has been some interest in two novel therapeutic strategies. First, some antipsychotic agents may have immunomodulatory properties — perospirone, quetiapine, aripiprazole, risperidone and, to some extent, ziprasidone have been shown to inhibit release of pro-inflammatory cytokines or NO from activated microglia.[65,66] Further, olanzapine (but not clozapine or haloperidol) has been shown to inhibit NO release from mouse microglia.[67] Second, anti-infective agents that have anti-inflammatory properties (eg, minocycline) may be used to treat psychotic disorders.[68]

Although these approaches may be consistent with the hypotheses we have outlined in this article, they are clearly highly speculative. In fact, a common element of many recently proposed adjunctive "neuroprotective" strategies (eg, lithium carbonate, omega-3 fatty acids) may be their capacity to moderate MA that occurs in response to a wide range of pathological stimuli.[3]

Conclusion

This article has focused on the potential role of common postnatal infections as risk factors for the adolescent onset of schizophrenia and other psychotic disorders. Mechanistically, this is assumed to depend on MA as part of an augmented and site-specific reaction of the brain's innate immune system. This could be in response to a single severe infection (presumably rarely) or, more commonly, through aggravation of pre-existing and localised microglial reaction. Importantly, persistent MA is associated with disrupted neural circuits and, consequently, dysfunctional neurochemistry. Specifically, we also propose that the adverse effects of common postnatal infections depend on interactions with key immunomodulatory genes (eg, *P2X7*, *MICB*), priming infections or other earlier CNS insults. This line of research opens new pathways for both preventive and early intervention strategies that utilise either existing or novel pharmacological strategies.

Competing interests

None identified.

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