The neurodevelopmental hypothesis of schizophrenia – convergent clues from epidemiology and neuropathology

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Synopsis

The neurodevelopmental hypothesis of schizophrenia suggests that the disruption of early brain development increases the risk of later developing schizophrenia. While lacking in precise details, this hypothesis focuses attention on critical periods of early brain development. From an epidemiological perspective, various pre- and peri-natal risk factors have been linked to schizophrenia – these include exposures related to infection, nutrition and obstetric complications. From a genetic perspective, candidate genes have also been linked to altered brain development. In recent decades evidence from neuropathology has provided support for the neurodevelopmental hypothesis. In particular, there is evidence implicating disruption of GABA-ergic interneurons in schizophrenia. Animal models involving early life exposures have been linked to changes in these same brain systems, providing convergent evidence for this long-standing hypothesis.

Keywords: schizophrenia, epidemiology, neuropathology, animal models

Conflicts of interest

Michael Piper, Monica Beneyto, Darryl Eyles and Thomas Burne report no competing interests. David A. Lewis currently receives investigator-initiated research support from Bristol-Myers Squibb, Curridium Ltd and Pfizer and in 2009-2011 served as a consultant in the areas of target identification and validation and new compound development to BioLine RX, Bristol-Myers Squibb, Merck and SK Life Science. Monica Beneyto reports no competing interests. John J McGrath has received conference travel support from Janssen and Eli Lilly.

Introduction

In the field of schizophrenia research, it is unusual to find a theory, like the neurodevelopmental hypothesis, that has grown stronger over two to three decades. This hypothesis, presented in its current formulation nearly a quarter of a century ago, proposes that genetic and/or environmental factors during critical early periods of brain development, adversely impact on adult mental health[1, 2]. Early formulations of this hypothesis proposed that after the developmental insult, the 'lesion' was clinically dormant ('silent') until after puberty, after which maturational events (or other environmental factors, such as cannabis use) were postulated to lead to the emergence of the characteristic psychotic features of schizophrenia. Whether such early exposures produce static (allostasis) or dynamic alterations in brain ontogeny remains an important research question[3].

The neurodevelopmental hypothesis provided a degree of coherence to a wide range of findings associated with schizophrenia. Several epidemiological clues had implicated early life exposures (e.g. season of birth, obstetric complications). People with schizophrenia have more minor physical anomalies, suggestive of prenatal disruptions[4-6], as well as subtle changes in cognitive and psychological function in early childhood, predating the onset of schizophrenia[7].

In some respects, the initial formulation of the neurodevelopmental hypothesis was an unsatisfactory guide for research – it lacked a precise form that predicted a particular causal factor or even a particular category of risk factors (e.g., genetic versus nongenetic). Nevertheless, it did provide guidance as to the timing of the key events – it proposed that disruptive events during early brain development (e.g. pre-

or peri-natal period, or during the first few years of life), contribute to the risk architecture of schizophrenia. The use of the label 'neurodevelopmental' has led to some debate about static versus progressive encephalopathies[3, 8, 9]. This issue has come into sharper focus in recent years as the MRI evidence has accumulated indicating that schizophrenia is associated with changes in brain volume that predate the onset of the clinical syndrome and continue to change after onset[10, 11]. It is feasible that early disruption of brain development can alter the trajectory of both brain growth and involution across the lifespan.

Clearly, genetic factors are also implicated in the neurodevelopmental hypothesis[12] - major advances have occurred in this field in recent years. In particular, it is now clear that both common single nucleotide polymorphisms (SNPs) and rarer structural variants are associated with an unexpectedly wide range of neuropsychiatric disorders[13]. For example, a large study recently implicated MIR137, a short, noncoding RNA molecule known to regulated dendritic development and the maturation of neurons[14]. Many of these clues have been subsequently investigated in transgenic animal models. However, this topic will not be covered in this review. Here we will examine evidence for the neurodevelopmental hypothesis from two perspectives; (a) modifiable risk factors from the field of observational epidemiology, and (b) recent developments from neuropathology at the molecular and cellular levels.

Modifiable risk factors for schizophrenia that impact during early life

INSERT BOX 1 ABOUT HERE

Nutrition

Catastrophic prenatal famine has been linked to an increased risk of schizophrenia. Individuals who were *in utero* during the Dutch famine during World War II showed an increased risk of schizophrenia and schizophrenia spectrum personality disorders[15]. The finding has been replicated in studies based on a catastrophic famine in China during the Cultural Revolution[16-18]

With respect to the association between risk of schizophrenia and specific maternal micronutrients, elevated homocysteine (a marker of impaired folate metabolism) from maternal third trimester sera has been linked to an increased risk of schizophrenia[19]. Based on clues from season of birth, low prenatal vitamin D has also been proposed as a risk factor for schizophrenia[20]. A recent case-control study lends weight to this candidate[21]. There is now robust evidence from rodent models demonstrating that transient prenatal vitamin D deficiency results in persistent changes in adult brain structure, neurochemistry and behavior[22-27]. Maternal iron deficiency has also been linked to an increased risk of schizophrenia[28]. Even if altered prenatal nutrition contributes to only a small fraction of those with schizophrenia, the potential to use safe and cheap interventions in at-risk groups makes these candidate exposures attractive from a public health perspective[29].

Infection

Evidence linking prenatal infection with an increased risk of schizophrenia has accumulated over recent decades[30]. The association was initially mostly based on ecological studies (e.g. examining the rate of schizophrenia in cohorts who were *in utero* during influenza epidemics[31]). More recent studies have been able to access biobanks in order to test these hypotheses in stronger, analytic settings. To date,

some evidence suggests that the risk of schizophrenia is elevated in those with prenatal exposure to influenza[32], rubella[33], or Toxoplasmosis gondii[34, 35], with mixed evidence for herpes simplex virus type 2 (HSV2)[36, 37]. Evidence from animal models suggests that the prenatal infection may impact on brain development via features of the maternal immune response rather than the direct impact of infectious agents [38].

Pregnancy and birth complications

Two meta-analyses have examined the association between pregnancy and birth complications and the risk of schizophrenia[39, 40]. Both have found that a diverse range of pregnancy and birth complications are associated with a significant but modest increased risk of later schizophrenia. Based on prospective population-based studies, Cannon and colleagues[40] reported that the following specific exposures were associated with increased risk of schizophrenia; antepartum haemorrhage, gestational diabetes, rhesus incompatibility, preeclampsia, low birth weight, congenital malformations, reduced head circumference, uterine atony, asphyxia, and emergency caesarean section. Animal models based on these exposure have been informative for schizophrenia research[41, 42].

Advanced paternal age

The offspring of older fathers have an increased risk of a range of neurodevelopmental disorders, including schizophrenia[43-45], autism[46] and epilepsy[47]. The offspring of older fathers have slightly impaired neurocognitive development during early childhood[48, 49]. With respect to schizophrenia, a meta-analysis[50] reported that the offspring of fathers aged 30 years or older had a significantly increased risk of schizophrenia compared to fathers aged 29 years or younger. The

greatest increased risk was found in fathers who were 50 years or older. These findings raise the possibility that an age-related accumulation of *de novo* mutations in paternal sperm contributes to the risk of schizophrenia. A recent animal model based on advanced paternal age confirmed that the offspring of older male mice had a significantly increased risk of de novo copy number variants[51]. While paternal age may impact on health outcomes via genetic factors, this risk factor is potentially modifiable with public health education (much as has happened with the risks associated with advanced maternal age).

Other risk factors that may impact on early brain development

There is now robust evidence showing that migrant groups in some countries have an increased risk of schizophrenia[52, 53]. Meta-analysis of the primary studies shows that both first and second generation migrants have an increased risk of developing schizophrenia, and that the effect is most pronounced in dark-skinned migrants[53]. Veling and colleagues[54] have recently examined age-at-migration and risk of schizophrenia in first generation migrants. They found that migrants who arrive as babies or infants had the highest risk of schizophrenia, with risk decreasing with age at migration thereafter, such that those who migrated aged 29 years or older had no greater risk of psychotic disorder than the indigenous population. They conclude that the critical window of exposure is during early life.

There is also evidence linking an increased risk of schizophrenia in those who are born and grow up in urban, more densely populated settings (e.g., in population-based studies from Holland[55] and Denmark [56]). The evidence suggests that urbanicity of place of birth is a proxy marker for a yet-to-be-identified risk-modifying variable operating at or before birth[57]. However, because most people who are born

in a city are also brought up there, it is difficult to disentangle pre- and perinatal effects from those operating later in childhood. Early life stress has also been proposed as a risk factor for schizophrenia[58, 59].

While this review focuses on early life exposures, it should be noted that puberty is also a critical for brain development and maturation, and exposures during this period have also been linked to risk of schizophrenia. In particular, cannabis use during early teenage years increased the risk of psychotic-related outcomes[60, 61]. There is also evidence linking exposure to trauma and an increased risk of psychotic-related outcomes[62-64].

Neuropathological correlates of schizophrenia – clues related to the neurodevelopmental hypothesis

Findings from morphological and molecular postmortem studies support the hypothesis that schizophrenia is a consequence of a developmental process, and not a degenerative process, affecting the cellular connectivity and network plasticity of the cerebral cortex. Macroscopic morphological studies of postmortem tissue show a reduction in the normal brain asymmetry (or 'torque')[65] in subjects with schizophrenia which, given that brain asymmetries are first apparent prenatally, is consistent with a neurodevelopmental disruption in brain development[66]. The absence of prominent gliotic or other neurodegenerative changes in schizophrenia makes adult-onset brain insults unlikely (e.g. as would be expected from the neuropathology associated with adult-onset infection or autoimmune or other degenerative processes)[67].

At the cellular level, there is evidence to suggest that schizophrenia is associated with subtle abnormalities in cytoarchitecture of different brain regions; for

example, certain populations of cortical neurons are smaller and the density of white matter neurons just below the cortex is greater in schizophrenia[68]. Recent studies have demonstrated that schizophrenia pathology is not only characterized by macroscopic or cytoarchitectural alterations, but also by molecular disturbances in circuits that are substantially remodelled during developmental periods critical for the cognitive functions that are impaired in schizophrenia. In fact, when examined at the level of individual types of neurons, molecular alterations in schizophrenia can be quite robust[69].

INSERT BOX 2 ABOUT

Disturbances in certain cognitive processes, such as attention, context representation, and working memory, appear to form part of the core clinical landscape of schizophrenia[1, 70]. These cognitive deficits seem to correlate with abnormal activation of the dorsolateral prefrontal cortex (DLPFC) in patients with schizophrenia[71-73]. At the cellular level, working memory performance requires the precise timing and coordination of activity in subsets of pyramidal neurons in the DLPFC[74]. This “tuning” of pyramidal cells is accomplished by inhibitory inputs from gamma-aminobutyric acid (GABA) interneurons[75, 76].

Developmental refinements in the connectivity between GABA neurons and pyramidal cells are thought to provide the neural substrate for age-related improvement in working memory performance[77-79]. Recent findings suggest that working memory impairments in schizophrenia might reflect disturbances in the developmental trajectories of DLPFC synaptic circuitry[80]. Given the protracted nature of these circuitry refinements, a number of different environmental risk factors, acting

at different stages of development, could converge on a common pathology. Such alterations, even if minor initially, could become progressively more detrimental as they lead to a diversion from the normal developmental trajectory. In addition, inflection points in these trajectories may delineate periods of increased risk for specific components of cortical circuits.

The ontogeny of cortical GABA interneurons

Interneurons comprise a suite of neurons that display a diverse range of cellular mophologies, laminar distributions, patterns of connectivity and electrophysiologiocal properties. Within the cortex, interneurons contribute approximately 20% of the total neuronal complement. Cortical GABA-ergic interneurons are born in the ganglionic eminence, migrate tangentially into the cortical plate following well-defined pathways[81-85], and then vertically into specific cortical layers[86, 87]. In recent years, much work has focused on defining the signalling systems that may influence the migration of these cells – these include such well-known agents as Slit/Robo, Neuregulin/Erb4, semaphorin/neuropilin and BDNF and NT4 via TrkB receptors. Microarray experiments have also discovered specific genes that are differentially expressed in these cells during migration[88]. Curiously, several of the genes expressed by these cells during migration are of broad interest to schizophrenia. These include ErbB4[89], Pcdhh8, Nr4a1 (also known as Nur77), Rora, and several genes involved in calcium channels.

Inhibitory GABA neurons in the cerebral cortex can be categorized into different neuronal subtypes defined by the presence of specific molecular, electrophysiological, and/or anatomical properties. Cell type/input- and lamina-specific alterations of pre- and postsynaptic markers of specific circuits formed by

certain of these cell types have been found in the DLPFC of subjects with schizophrenia. Early post-mortem studies in patients with schizophrenia revealed an apparent reduction in inhibitory GABA neurons. These findings were largely in the cortex with the most robust changes seen in the calcium-binding protein parvalbumin (PV) containing neurons. However, it was never certain whether such reductions indicated a loss of cells or a down-regulation of the PV marker protein[90]. In particular, widely replicated findings of a reduced expression of GAD67, an enzyme required for the synthesis of GABA at inhibitory synapses, and GAT-1, the protein responsible for the reuptake of GABA at the presynaptic site, suggest alterations in both the synthesis and reuptake of GABA in a subset of DLPFC inhibitory interneurons in schizophrenia[91-93]. The affected GABA neurons include those that contain PV, and the postsynaptic $GABA_A$ receptors that receive inputs from PV neurons are also altered in schizophrenia[69]. Interestingly, both PV neurons and their postsynaptic $GABA_A$ receptors have a protracted period of development[94], providing a broad window during which environmental events could disrupt their developmental trajectories.

It is the complex nature of interneuron development, migration, maturation and synapse formation that makes these interneuons of specific interest to the field of schizophrenia research. Research is now focussing on understanding how changes to the trajectory of interneuron specification, migration and/or maturation might contribute to the etiopathogenesis of schizophrenia.

INSERT BOX 3 ABOUT HERE

Integrating epidemiology and neuropathology – what can we learn from animal models?

Several of the animal models related to schizophrenia have shown abnormalitiies in GABA-ergic interneurons. Post-natal exposure to various psychopharmacological probes have been associated with altered GAD67 and/or PV expression in regions of interest. Agents used include: MK-801[95],amphetamine [96], phencyclidine (PCP)[95] and picrotoxin (a non-competitive antagonist of the GABA-A receptor)[97].

Altered GAD67 and/or PV expression has also been noted in transgenic animals of interest to schizophrenia research, including the heterozygous Reeler mouse[98] and DISC1 mutant mice[99]. An interesting recent approach has been to selectively target the function of these GABA-ergic interneurons directly. In one study when the expression of the NR1 subunit of the NMDA receptor was reduced selectively within inhibitory GABA neurons in mice, this appeared to confer a schizophrenia-like phenotype[100]. Impaired GABAergic function in schizophrenia could also be secondary to alterations in the striatal DA system. For example, Kellendonk and colleagues who developed a model in which increased striatal dopamine signalling has been linked with diminished prefrontal cortical inhibition, presumably due to diminished GABA function[101].

Meyer and Feldon have recently published a comprehensive assessment of epidemiologically-informed animal models related to schizophrenia[102]. To date, animal models have tried to emulate a range of exposures related to the neurodevelopmental hypothesis. These included obstetric complications[103, 104], immune activation[105-107], low maternal vitamin D[23, 108], advanced paternal age[51, 109, 110], and early life stress[111, 112]. These models express surprisingly high face and

predictive validity for schizophrenia. For example, maternal immune activation with the viral mimic Poly-IC leads to a reduction in both Reelin and PV positive interneurons and GABA content in the prefrontal cortex of adult offspring[113, 114]. Similarly, when pregnant rats were exposed to the bacterial membrane component lipopolysaccharide (LPS) a reduction in both reelin and GAD67 interneurons in the hippocampus of their offspring was revealed[115]. Finally in models of post-adolescent stress, such as social isolation, similar reductions in hippocampal or prefrontal cortical GABAergic neuron structure or content have been found[116, 117]. In summary, there is evidence from animal models to suggest that disruption to GABA interneurons is a *shared phenotype associated with diverse genetic and environmental stressors*. As such, the orderly development of these cells may be a marker of early brain disruption.

Conclusions

We have previously argued that it is critical that schizophrenia epidemiology is firmly anchored to a neurobiologically-informed framework[118]. While clinical research is clearly important, animal models can play a key role in unravelling the biological mechanisms linking early life disruptions to later neuropsychiatric disorders. Moreover, animal models provide an experimental platform that allows researchers to focus on more substrate-pure neurobiological correlates of clinical syndromes[119].

Research inspired by the epidemiological clues such as prenatal nutrition and prenatal infection is likely to lead to the identification of informative pathways. However, on its own, epidemiology will never be able to address the biocomplexity underpinning a poorly understood group of disorders like schizophrenia. The best returns will come from linking schizophrenia epidemiology with molecular, cellular

and behavioural neuroscience. Cross-disciplinary projects related to candidate genetic or nongenetic risk factors can address the biological plausibility of these factors, and can also provide a road to new discoveries in neuroscience. We need to build shared discovery platforms that encourage greater cross-fertilization between schizophrenia epidemiology and basic neuroscience research. We are confident that the neurodevelopmental hypothesis will continue to inspire research in both epidemiology, and neuroscience, and that this journey will continue to provide clues to the neurobiological correlates of schizophrenia.

BOX 1

Clues from Epidemiology that implicate the neurodevelopmental hypothesis

Excess risk of schizophrenia associated with exposures and proxy markers that could impact on early brain development;

- Winter-spring birth
- Born and/or raised in urban areas
- Prenatal infection
- Prenatal famine
- Prenatal micronutrient deficiency (e.g. vitamin D, iron, folate)
- Pregnancy and birth complications
- Early life motor and cognitive antecedents in cohort studies
- Increased prevalence of minor physical anomalies

BOX 2

Clues from neuropathology that implicate the neurodevelopmental hypothesis

Schizophrenia is associated with findings suggestive of altered early brain development;

- Loss of normal cerebral asymmetry
- Lack of prominent gliosis or related markers of adult-onset neuropathology
- Subtle alterations in cytoarchitecture.
    a. smaller neurons
    b. shorter dendrites
    c. increased density of neurons in the subcortical white matter.
- Altered expression of markers of genes/proteins implicated in brain development

BOX 3

Cortical GABA neurons in schizophrenia

- Multiple markers of GABA inhibitory neurons are altered but the number of neurons in the cerebral cortex does not appear to be reduced.
- A subset of GABA neurons exhibit decreased GABA synthesis and uptake; these changes are best characterized in the parvalbumin-containing subset.
- Postsynaptic GABA receptors are also altered; these changes appear to be specific for different subunits and thus types of $GABA_A$ receptors.
- Lower expression levels of the gene for GAD67, which is responsible for most GABA synthesis, are found in multiple cortical regions.

References

1. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;44(7):660-669.
2. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed) 1987;295(6600):681-682.
3. Thompson BL, Levitt P. Now you see it, now you don't--closing in on allostasis and developmental basis of psychiatric disorders. Neuron 2010;65(4):437-439.
4. McGrath JJ, van Os J, Hoyos C, et al. Minor physical anomalies in psychoses: associations with clinical and putative aetiological variables. Schizophr Res 1995;18(1):9-20.
5. Buckley PF, Dean D, Bookstein FL, et al. A three-dimensional morphometric study of craniofacial shape in schizophrenia. Am J Psychiatry 2005;162(3):606-608.
6. Compton MT, Chan RC, Walker EF, et al. Minor physical anomalies: potentially informative vestiges of fetal developmental disruptions in schizophrenia. Int J Dev Neurosci 2011;29(3):245-250.
7. Welham J, Isohanni M, Jones P, et al. The antecedents of schizophrenia: a review of birth cohort studies. Schizophr Bull 2009;35(3):603-623.
8. McGrath J, Feron F, Burne THJ, et al. The neurodevelopmental hypothesis of schizophrenia; a review of recent developments. Annals of Medicine 2003;35(2):86-93.
9. Velakoulis D, Wood SJ, McGorry PD, et al. Evidence for progression of brain structural abnormalities in schizophrenia: beyond the neurodevelopmental model. Aust N Z J Psychiatry 2000;34 Suppl:S113-126.
10. Pantelis C, Yucel M, Wood SJ, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 2005;31(3):672-696.
11. Pantelis C, Velakoulis D, McGorry PD, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 2003;361(9354):281-288.

12. Jones P, Murray RM. The genetics of schizophrenia is the genetics of neurodevelopment. BrJPsychiatry 1991;158:615-623.
13. Owen MJ, O'Donovan MC, Thapar A, et al. Neurodevelopmental hypothesis of schizophrenia. Br J Psychiatry 2011;198(3):173-175.
14. Ripke S, Sanders AR, Kendler KS, et al. Genome-wide association study identifies five new schizophrenia loci. Nat Genet 2011;43(10):969-976.
15. Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch hunger winter of 1944-1945. Archives of General Psychiatry 1992;49:938-988.
16. St Clair D, Xu M, Wang P, et al. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961. JAMA 2005;294(5):557-562.
17. Xu MQ, Sun WS, Liu BX, et al. Prenatal malnutrition and adult schizophrenia: further evidence from the 1959-1961 Chinese famine. Schizophr Bull 2009;35(3):568-576.
18. Brown AS, Susser ES. Prenatal nutritional deficiency and risk of adult schizophrenia. Schizophr Bull 2008;34(6):1054-1063.
19. Brown AS, Bottiglieri T, Schaefer CA, et al. Elevated prenatal homocysteine levels as a risk factor for schizophrenia. Arch Gen Psychiatry 2007;64(1):31-39.
20. McGrath J. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophr Res 1999;40(3):173-177.
21. McGrath JJ, Eyles DW, Pedersen CB, et al. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. Arch Gen Psychiatry 2010;67(9):889-894.
22. Kesby JP, Eyles DW, Burne TH, et al. The effects of vitamin D on brain development and adult brain function. Mol Cell Endocrinol 2011;347(1-2):121-127.
23. Kesby JP, Cui X, O'Loan J, et al. Developmental vitamin D deficiency alters dopamine-mediated behaviors and dopamine transporter function in adult female rats. Psychopharmacology (Berl) 2010;208(1):159-168.
24. McGrath J, Iwazaki T, Eyles D, et al. Protein expression in the nucleus accumbens of rats exposed to developmental vitamin D deficiency. PLoS ONE 2008;3(6):e2383.

25. Kesby JP, Burne TH, McGrath JJ, et al. Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: An animal model of schizophrenia. Biol Psychiatry 2006;60(6):591-596.
26. Feron F, Burne TH, Brown J, et al. Developmental Vitamin D3 deficiency alters the adult rat brain. Brain Res Bull 2005;65(2):141-148.
27. Eyles D, Brown J, Mackay-Sim A, et al. Vitamin D3 and brain development. Neuroscience 2003;118(3):641-653.
28. Insel BJ, Schaefer CA, McKeague IW, et al. Maternal iron deficiency and the risk of schizophrenia in offspring. Arch Gen Psychiatry 2008;65(10):1136-1144.
29. McGrath J, Brown A, St Clair D. Prevention and schizophrenia--the role of dietary factors. Schizophr Bull 2011;37(2):272-283.
30. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry 2010;167(3):261-280.
31. McGrath J, Castle D. Does influenza cause schizophrenia? A five year review. AustNZJPsychiatry 1995;29(1):23-31.
32. Brown AS, Begg MD, Gravenstein S, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 2004;61(8):774-780.
33. Brown AS, Cohen P, Greenwald S, et al. Nonaffective psychosis after prenatal exposure to rubella. Am J Psychiatry 2000;157(3):438-443.
34. Brown AS, Schaefer CA, Quesenberry CP, Jr., et al. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. Am J Psychiatry 2005;162(4):767-773.
35. Mortensen PB, Norgaard-Pedersen B, Waltoft BL, et al. Early infections of Toxoplasma gondii and the later development of schizophrenia. Schizophr Bull 2007;33(3):741-744.
36. Buka SL, Tsuang MT, Torrey EF, et al. Maternal Infections and Subsequent Psychosis Among Offspring. ArchGen Psychiatry 2001;58:1032-1037.
37. Brown AS, Schaefer CA, Quesenberry CP, Jr., et al. No evidence of relation between maternal exposure to herpes simplex virus type 2 and risk of schizophrenia? Am J Psychiatry 2006;163(12):2178-2180.

38. Patterson PH. Immune involvement in schizophrenia and autism: etiology, pathology and animal models. Behav Brain Res 2009;204(2):313-321.
39. Geddes JR, Verdoux H, Takei N, et al. Schizophrenia and complications of pregnancy and labor: an individual patient data meta-analysis. Schizophr Bull 1999;25(3):413-423.
40. Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry 2002;159(7):1080-1092.
41. Rehn AE, Van Den Buuse M, Copolov D, et al. An animal model of chronic placental insufficiency: relevance to neurodevelopmental disorders including schizophrenia. Neuroscience 2004;129(2):381-391.
42. Boksa P. Animal models of obstetric complications in relation to schizophrenia. Brain Res Brain Res Rev 2004;45(1):1-17.
43. Malaspina D, Harlap S, Fennig S, et al. Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry 2001;58(4):361-367.
44. El-Saadi O, Pedersen CB, McNeil TF, et al. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. Schizophr Res 2004;67(2-3):227-236.
45. Sipos A, Rasmussen F, Harrison G, et al. Paternal age and schizophrenia: a population based cohort study. BMJ 2004;329(7474):1070.
46. Hultman CM, Sandin S, Levine SZ, et al. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. Mol Psychiatry 2011;16(12):1203-1212.
47. Vestergaard M, Mork A, Madsen KM, et al. Paternal age and epilepsy in the offspring. Eur J Epidemiol 2005;20(12):1003-1005.
48. Saha S, Barnett AG, Buka SL, et al. Maternal age and paternal age are associated with distinct childhood behavioural outcomes in a general population birth cohort. Schizophr Res 2009;115(2-3):130-135.
49. Saha S, Barnett AG, Foldi C, et al. Advanced paternal age is associated with impaired neurocognitive outcomes during infancy and childhood. PLoS Med 2009;6(3):e40.
50. Miller B, Messias E, Miettunen J, et al. Meta-analysis of Paternal Age and Schizophrenia Risk in Male Versus Female Offspring. Schizophr Bull 2010.
51. Flatscher-Bader T, Foldi CJ, Chong S, et al. Increased de novo copy number variants in the offspring of older males. Translational Psychiatry 2011;1(e34).

52. McGrath J, Saha S, Welham J, et al. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004;2(1):13.
53. Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. Am J Psychiatry 2005;162(1):12-24.
54. Veling W, Hoek HW, Selten J, et al. Age at Migration and Future Risk of Psychotic Disorders Among Immigrants in the Netherlands: A 7-Year Incidence Study. American Journal of Psychiatry 2011;168:1278-1285.
55. Marcelis M, Navarro-Mateu F, Murray R, et al. Urbanization and psychosis: a study of 1942-1978 birth cohorts in The Netherlands. Psychological Medicine 1998;28:871-879.
56. Mortensen PB, Pedersen CB, Westergaard T, et al. Effects of family history and place and season of birth on the risk of schizophrenia. New England Journal of Medicine 1999;340:603-608.
57. McGrath J, Scott J. Urban birth and risk of schizophrenia: a worrying example of epidemiology where the data are stronger than the hypotheses. Epidemiol Psichiatr Soc 2006;15(4):243-246.
58. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. Nature 2010;468(7321):203-212.
59. Scott J, Varghese D, McGrath J. As the twig is bent, the tree inclines: adult mental health consequences of childhood adversity. Arch Gen Psychiatry 2010;67(2):111-112.
60. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007;370(9584):319-328.
61. McGrath J, Welham J, Scott J, et al. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. Arch Gen Psychiatry 2010;67(5):440-447.
62. Saha S, Varghese D, Slade T, et al. The association between trauma and delusional-like experiences. Psychiatry Res 2011;189(2):259-264.
63. Scott J, Chant D, Andrews G, et al. Association between trauma exposure and delusional experiences in a large community-based sample. Br J Psychiatry 2007;190:339-343.

64. Read J, van Os J, Morrison AP, et al. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. Acta Psychiatr Scand 2005;112(5):330-350.
65. Guerguerian R, Lewine RR. Brain torque and sex differences in schizophrenia. SchizophrRes 1998;30(2):175-181.
66. Harrison PJ. Schizophrenia: a disorder of neurodevelopment? CurrOpinNeurobiol 1997;7(2):285-289.
67. Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 1999;122 (Pt 4):593-624.
68. Harrison PJ, Lewis DA, Kleinman JE. Neuropathology of schizophrenia. *Schizophrneia*. Third Edition ed. Oxford: Blackwell; 2001:372-392.
69. Lewis DA, Curley AA, Glausier JR, et al. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci 2011.
70. Goldman-Rakic PS. Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci 1994;6(4):348-357.
71. Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. Arch Gen Psychiatry 1986;43(2):114-124.
72. Perlstein WM, Carter CS, Noll DC, et al. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am J Psychiatry 2001;158(7):1105-1113.
73. Callicott JH, Mattay VS, Verchinski BA, et al. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. Am J Psychiatry 2003;160(12):2209-2215.
74. Goldman-Rakic PS. Cellular basis of working memory. Neuron 1995;14(3):477-485.
75. Sawaguchi T, Matsumura M, Kubota K. Depth distribution of neuronal activity related to a visual reaction time task in the monkey prefrontal cortex. J Neurophysiol 1989;61(2):435-446.
76. Rao SG, Williams GV, Goldman-Rakic PS. Destruction and creation of spatial tuning by disinhibition: GABA(A) blockade of prefrontal cortical neurons engaged by working memory. J Neurosci 2000;20(1):485-494.

77. Alexander GE, Goldman PS. Functional development of the dorsolateral prefrontal cortex: an analysis utlizing reversible cryogenic depression. Brain Res 1978;143(2):233-249.
78. Luna B, Garver KE, Urban TA, et al. Maturation of cognitive processes from late childhood to adulthood. Child Dev 2004;75(5):1357-1372.
79. Crone EA, Wendelken C, Donohue S, et al. Neurocognitive development of the ability to manipulate information in working memory. Proc Natl Acad Sci U S A 2006;103(24):9315-9320.
80. Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci 2002;25:409-432.
81. Marin O, Rubenstein JL. A long, remarkable journey: tangential migration in the telencephalon. Nat Rev Neurosci 2001;2(11):780-790.
82. Marin O, Yaron A, Bagri A, et al. Sorting of striatal and cortical interneurons regulated by semaphorin-neuropilin interactions. Science 2001;293(5531):872-875.
83. Pleasure SJ, Anderson S, Hevner R, et al. Cell migration from the ganglionic eminences is required for the development of hippocampal GABAergic interneurons. Neuron 2000;28(3):727-740.
84. McKenna IM, Ramakrishna G, Diwan BA, et al. K-ras mutations in mouse lung tumors of extreme age: independent of paternal preconceptional exposure to chromium(III) but significantly more frequent in carcinomas than adenomas. Mutation Research 2001;490(1):57-65.
85. Marin O, Anderson SA, Rubenstein JL. Origin and molecular specification of striatal interneurons. J Neurosci 2000;20(16):6063-6076.
86. Tanaka DH, Yanagida M, Zhu Y, et al. Random walk behavior of migrating cortical interneurons in the marginal zone: time-lapse analysis in flat-mount cortex. J Neurosci 2009;29(5):1300-1311.
87. Murakami F, Tanaka D, Yanagida M, et al. Intracortical multidirectional migration of cortical interneurons. Novartis Foundation Symposium 2007;288:116-125; discussion 125-119, 276-181.
88. Faux C, Rakic S, Andrews W, et al. Differential gene expression in migrating cortical interneurons during mouse forebrain development. J Comp Neurol;518(8):1232-1248.

89. Chen PL, Avramopoulos D, Lasseter VK, et al. Fine mapping on chromosome 10q22-q23 implicates Neuregulin 3 in schizophrenia. Am J Hum Genet 2009;84(1):21-34.
90. Eyles DW, McGrath JJ, Reynolds GP. Neuronal calcium-binding proteins and schizophrenia. Schizophr Res 2002;57(1):27-34.
91. Beneyto M, Morris HM, Rovensky KC, et al. Lamina- and cell-specific alterations in cortical somatostatin receptor 2 mRNA expression in schizophrenia. Neuropharmacology 2011.
92. Beneyto M, Abbott A, Hashimoto T, et al. Lamina-specific alterations in cortical GABAA receptor subunit expression in schizophrenia. Cereb Cortex 2011;21(5):999-1011.
93. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 2005;6(4):312-324.
94. Beneyto M, Lewis DA. Insights into the neurodevelopmental origin of schizophrenia from postmortem studies of prefrontal cortical circuitry. Int J Dev Neurosci 2011;29(3):295-304.
95. Turner CP, DeBenedetto D, Ware E, et al. Postnatal exposure to MK801 induces selective changes in GAD67 or parvalbumin. Exp Brain Res 2010;201(3):479-488.
96. Peleg-Raibstein D, Knuesel I, Feldon J. Amphetamine sensitization in rats as an animal model of schizophrenia. Behav Brain Res 2008;191(2):190-201.
97. Berretta S, Gisabella B, Benes FM. A rodent model of schizophrenia derived from postmortem studies. Behav Brain Res 2009;204(2):363-368.
98. Pillai A, Mahadik SP. Increased truncated TrkB receptor expression and decreased BDNF/TrkB signaling in the frontal cortex of reeler mouse model of schizophrenia. Schizophr Res 2008;100(1-3):325-333.
99. Shen S, Lang B, Nakamoto C, et al. Schizophrenia-related neural and behavioral phenotypes in transgenic mice expressing truncated Disc1. J Neurosci 2008;28(43):10893-10904.
100. Belforte JE, Zsiros V, Sklar ER, et al. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. Nat Neurosci;13(1):76-83.
101. Li YC, Kellendonk C, Simpson EH, et al. D2 receptor overexpression in the striatum leads to a deficit in inhibitory transmission and dopamine sensitivity in

mouse prefrontal cortex. Proc Natl Acad Sci U S A 2011;108(29):12107-12112.

102. Meyer U, Feldon J. Epidemiology-driven neurodevelopmental animal models of schizophrenia. Prog Neurobiol 2010;90(3):285-326.
103. Mallard EC, Rehn A, Rees S, et al. Ventriculomegaly and reduced hippocampal volume following intrauterine growth-restriction: implications for the aetiology of schizophrenia. Schizophr Res 1999;40(1):11-21.
104. Boksa P, El-Khodor BF. Birth insult interacts with stress at adulthood to alter dopaminergic function in animal models: possible implications for schizophrenia and other disorders. Neurosci Biobehav Rev 2003;27(1-2):91-101.
105. Meyer U, Yee BK, Feldon J. The neurodevelopmental impact of prenatal infections at different times of pregnancy: the earlier the worse? Neuroscientist 2007;13(3):241-256.
106. Patterson PH. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. Curr Opin Neurobiol 2002;12(1):115-118.
107. Zuckerman L, Rehavi M, Nachman R, et al. Immune activation during pregnancy in rats leads to a postpubertal emergence of disrupted latent inhibition, dopaminergic hyperfunction, and altered limbic morphology in the offspring: a novel neurodevelopmental model of schizophrenia. Neuropsychopharmacology 2003;28(10):1778-1789.
108. Eyles DW, Feron F, Cui X, et al. Developmental vitamin D deficiency causes abnormal brain development. Psychoneuroendocrinology 2009;34 Suppl 1:S247-257.
109. Foldi CJ, Eyles DW, McGrath JJ, et al. Advanced paternal age is associated with alterations in discrete behavioural domains and cortical neuroanatomy of C57BL/6J mice. Eur J Neurosci 2010;31(3):556-564.
110. Smith RG, Kember RL, Mill J, et al. Advancing paternal age is associated with deficits in social and exploratory behaviors in the offspring: a mouse model. PLoS ONE 2009;4(12):e8456.
111. Rilling JK, Winslow JT, O'Brien D, et al. Neural correlates of maternal separation in rhesus monkeys. Biol Psychiatry 2001;49(2):146-157.

112. Ellenbroek BA, van den Kroonenberg PT, Cools AR. The effects of an early stressful life event on sensorimotor gating in adult rats. Schizophr Res 1998;30(3):251-260.
113. Meyer U, Nyffeler M, Yee BK, et al. Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice. Brain Behav Immun 2008;22(4):469-486.
114. Bitanihirwe BK, Peleg-Raibstein D, Mouttet F, et al. Late prenatal immune activation in mice leads to behavioral and neurochemical abnormalities relevant to the negative symptoms of schizophrenia. Neuropsychopharmacology 2010;35(12):2462-2478.
115. Nouel D, Burt M, Zhang Y, et al. Prenatal exposure to bacterial endotoxin reduces the number of GAD67- and reelin-immunoreactive neurons in the hippocampus of rat offspring. Eur Neuropsychopharmacol 2011.
116. Bloomfield C, French SJ, Jones DN, et al. Chandelier cartridges in the prefrontal cortex are reduced in isolation reared rats. Synapse 2008;62(8):628-631.
117. Harte MK, Powell SB, Swerdlow NR, et al. Deficits in parvalbumin and calbindin immunoreactive cells in the hippocampus of isolation reared rats. J Neural Transm 2007;114(7):893-898.
118. McGrath JJ, Richards LJ. Why schizophrenia epidemiology needs neurobiology--and vice versa. Schizophr Bull 2009;35(3):577-581.
119. Arguello PA, Gogos JA. Modeling madness in mice: one piece at a time. Neuron 2006;52(1):179-196.