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Evaluating negative-symptom-like behavioural changes in developmental models of schizophrenia ☆

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Abstract
Many lines of evidence suggest that schizophrenia has a major developmental component and that environmental factors that disrupt key stages of development, such as maternal stress during pregnancy as a result of infection or malnutrition, can increase the risk of developing schizophrenia in later life. This review examines how non-clinical neurodevelopmental models pertinent to schizophrenia have been evaluated for their ability to reproduce behavioural deficits related to the negative symptoms of schizophrenia. The more frequently used are the prenatal application of the mitotoxic agent methylazoxymethanol, prenatal immune challenge and the neonatal ventral hippocampus lesion model. In general they have been extensively evaluated in models considered relevant to positive symptoms of schizophrenia. In contrast, very few studies have examined tests related to negative symptoms and, when they have, it has almost exclusively been a social interaction model. Other aspects related to negative symptoms such as anhedonia, affective flattening and avolition have almost never been studied. Further studies examining other components of negative symptomatology are needed to more clearly associate these deficits with a schizophrenia-like profile as social withdrawal is a hallmark of many disorders. Although there are no truly effective treatments for negative symptoms, better characterisation with a broader range of drugs used in schizophrenia will be necessary to better evaluate the utility of these models. In summary, developmental models of schizophrenia have been extensively studied as models of positive symptoms but, given the unmet need in the clinic, the same effort now needs to be made with regard to negative symptoms.

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1. Introduction

Numerous lines of evidence suggest that schizophrenia has a neurodevelopmental component (for recent reviews see Fatemi and Folsom, 2009; Murray et al., 2008; Rapoport et al., 2012). The presence of minor anatomical anomalies such as low-set ears and wider than normal gaps between first and second toes in patients with schizophrenia, reports of premorbid neurological signs and impairments in attention, social integration etc. (Fatemi and Folsom, 2009) all suggest abnormal development. There are also changes in cortical thickness and a disorganisation of cortical neuronal layering (reviewed in Meyer and Feldon, 2010), which, in the absence of gliosis suggest a developmental origin (Harrison, 1999). Finally there are the epidemiological observations that various insults during pregnancy such as infection and malnutrition, as well as obstetric complications can all increase the risk of developing schizophrenia. Indeed, it is the evidence linking these perinatal insults to schizophrenia that has been the basis for the models discussed in this review in the following sections.

This review will concentrate on perinatal environmental factors and how they have been studied in relation to behavioural correlates of schizophrenia. Clinical data suggests that prenatal malnutrition, maternal infection during pregnancy, birth complications etc. all lead to a small but measurable increase in the incidence of schizophrenia in later life (Tandon et al., 2008; Meyer and Feldon, 2010). With such a weight of evidence in favour of the neurodevelopmental hypothesis of schizophrenia and in the absence of other models with compelling construct validity, it is natural that researchers have tried to reproduce some of these findings in animals. The aim is to better understand how these early insults can affect brain development and the appearance of schizophrenia-like symptoms and also to serve as a model for testing putative antipsychotic treatments. Many of these models are very ambitious – not everyone who is subjected to infectious diseases or famine while *in utero* gets schizophrenia and there is no *a priori* reason to think that rats or mice have the necessary genetic predisposition to schizophrenia. Nevertheless these experimental paradigms represent interesting approaches for studying the processes that might increase the risk for developing schizophrenia. In this review, the objective is not to critically evaluate the relevance of the various models to schizophrenia but to specifically evaluate each one for their ability to induce behavioural changes that can be considered analogous to negative symptomatology in schizophrenic patients.

If we take negative symptoms to include affective flattening, anhedonia, avolition, poverty of speech and asociality, then it is largely, if not exclusively, the latter that has been assessed in proposed models of neurodevelopmental aspects of schizophrenia (see Table 1 for summary). One of the reasons for this is the difficulty of assessing some of the other symptoms in animals which may not have a suitable animal parallel. Poverty of speech is probably the most difficult symptom to model in animals although possibilities are being explored (e.g. Chabout et al., 2012). Other symptoms such as anhedonia, asociality and avolition have more established counterparts in animal tests (Castagné et al., 2009; Der-Avakian and Markou, 2012; Ellenbroek and Cools, 2000; O'Tuathaigh et al., 2010). To what extent this limited evaluation of the full range of negative symptoms impacts our understanding of the relevance of these models to schizophrenia is unclear: for example some of these approaches may be equally pertinent to other developmental disorders that feature social deficits, with autism being a prime example (i.e. pre- and perinatal insults have also been suggested as risk factors for autism, e.g. Grabrucker, 2012). In compiling this review, only those models where a developmental disorder has been induced at a particular time have been included. This has excluded many of the models that might be more pertinent to autism which are typically mutant or transgenic animals where the modification that led to the observable phenotype is still present at adulthood.

The developmental insults that have been studied are numerous and many of these are based on epidemiological observations such as the increased incidence of schizophrenia after influenza epidemics or after periods of famine (for review see Meyer and Feldon, 2010). The actual type of insult may be less important than its timing. For example, prenatal insults are typically applied during the third quarter of gestation in rats and mice, between GD9.5 and GD17 (Table 1). This corresponds approximately to the end of the first trimester in human pregnancy as far as cortical neurogenesis is concerned (which peaks around GD15 in the rat) but earlier for many others such as limbic system development (Workman et al., 2013). The end of the first trimester appears to be the most sensitive period in humans for the impact of famine and maternal infections on the incidence of schizophrenia (e.g. Tandon et al., 2008; Fatemi and Folsom, 2009). Later events in human brain development, such as pruning of synapses which occur towards the end of gestation, do not occur until about 3 weeks after birth in the rat (Workman et al., 2013). Most post-natal insults such as the ventral hippocampus lesion or post-natal polyI:C are typically given about a week after birth (Table 1) and so probably impact synaptic pruning rather than neurogenesis. The same is probably true of social isolation which although starting much later, around PD21 (Table 1), has been shown to affect synaptic plasticity and cortical thickness (for review see Fone and Porkess, 2008). All of these models are of value in exploring how disruption of critical phases in brain development might lead to psychiatric disease.

2. Prenatal insults

2.1. Methylazoxymethanol

Application of mitotoxic agents that interfere with cell proliferation during specific phases of development is a widely used procedure to induce developmental deficits of specific neuronal populations (Cattabeni and Di Luca, 1997). The most commonly used such agent is methylazoxymethanol (MAM). Administration of MAM to pregnant rats on gestational day 17 (GD17) induces neurodevelopmental deficits in the cortex and hippocampus of the offspring that are considered to resemble those in patients diagnosed with schizophrenia, including reduced cortical thickness and disorganisation of pyramidal cells in the hippocampus