Adolescent environmental enrichment prevents the emergence of schizophrenia-like abnormalities in a neurodevelopmental model of schizophrenia

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Abstract
In the present study, we investigated whether exposure to an enriched environment (EE) during adolescence might affect the behavioural dysfunction (sensorimotor gating deficit, memory and social interaction impairments) and neurochemical changes (GAD67 expression, histone methylation) induced by methylazoxymethanol (MAM) in the MAM-E17 rat model of schizophrenia. EE was introduced for 7 days in early adolescence (days 23-29), and behavioural and biochemical studies were performed on adult rats at postnatal day 70. The results showed that exposure to EE prevented the development of adult behavioural deficits induced by prenatal MAM administration. EE also prevented the decrease in GAD67 mRNA and protein levels induced by MAM in the medial prefrontal cortex (mPFC). Moreover, EE inhibited the reductions in the amount of Gad1 bound to H3K4me3 and in the total H3K4me3 protein level induced by prenatal MAM administration in the adult mPFC. However, there was no effect of EE on behaviour or levels of the various neurochemical markers in adult rats prenatally treated with vehicle. Thus, these results indicate that EE exposure during early adolescence may inhibit the development of schizophrenia related symptoms through epigenetic mechanisms that regulate the expression of genes (e.g., Gad1) that are impaired in schizophrenia.

1. Introduction
Several epidemiological studies indicate that schizophrenia is a neurodevelopmental disorder related to a genetic predisposition and environmental factors that lead to
abnormal brain development (Burrows and Hannan, 2016; van Os et al., 2008). Psychosis is a core symptom of schizophrenia, starting in adolescence during the ultrahigh risk (UHR) period, when prodromal symptoms are observed, and progressing to the first psychotic episode in young adulthood. However, cognitive and social dysfunction develop long before the UHR phase and evolve to become the most disabling symptoms (Sommer et al., 2016). Several clinical findings suggest that the risk of transition to psychosis in UHR subjects may be decreased by active interventions, i.e., omega-3 polyunsaturated fatty acid (PUFA) treatment, antipsychotic medication, antipsychotics with cognitive-behavioural therapy, or psychotherapy (Fusar-Poli et al., 2012; Millan et al., 2016). Moreover, some recent works also indicate that intervention strategies during childhood or early adolescence in the population with a high risk of schizophrenia may represent a chance to prevent the emergence of cognitive and social deficits (Sommer et al., 2016). Preclinical studies with animal models of schizophrenia also confirmed clinical and epidemiological findings that adolescent interventions, i.e., pharmacological, behavioural or environmental manipulations, might alter the course of schizophrenia (Millan et al., 2016). However, early-life pharmacotherapy strategies might have some ethical and diagnostic limitations (non-specific, prodromal symptoms) (Fusar-Poli et al., 2012; Millan et al., 2016; Sommer et al., 2016); thus, the development of non-pharmacological and non-invasive course-altering strategies might be the best choice of early intervention in groups at risk of schizophrenia (Sommer et al., 2016). The first epidemiological study on this topic suggested that environmental interventions (i.e., nutritional, educational and physical exercise enrichment programmes) for a period of only 2 years during early childhood might protect against the onset of schizophrenia (Raine et al., 2003), which suggests that positive early life experiences during the critical period of brain development might contribute to the prevention of schizophrenia (Schmitt et al., 2014). The positive effect of exposure to an enriched environment (EE) during adolescence in the prevention of schizophrenia symptoms has also been supported by findings from neurodevelopmental models of schizophrenia based on pharmacological (Koseki et al., 2012; Nozari et al., 2015) and genetic modifications (Ishihama et al., 2010; McOmish et al., 2008; Santos et al., 2016). In addition, cognitive training during adolescence also prevented cognitive deficits in adult rats with neonatal ventral hippocampus lesions (Lee et al., 2012).

The adolescent brain has a high capacity for experience-dependent neuroplasticity (Spear, 2013); however, the effect of environmental stimulation on the trajectory of brain development might be age-dependent (Renner and Rosenzweig, 1986). Moreover, findings from animal studies also suggest that environmental factors during the early stages of development might be more effective in altering the course of schizophrenia (Ishihama et al., 2010); however, most of these animal studies examined EE exposure during the entire adolescent period, i.e., 4 or more weeks (Ishihama et al., 2010; Koseki et al., 2012; McOmish et al., 2008; Melik et al., 2014; Nozari et al., 2015; Santos et al., 2016), at different stages of postnatal development, i.e., at birth (Nozari et al., 2015), at the age of 3 weeks (Koseki et al., 2012; McOmish et al., 2008; Melik et al., 2014), or at the age of 4 or 8 weeks (Ishihama et al., 2010). Thus, whether shorter exposures to EE during a specific developmental window of early adolescence might affect the emergence of schizophrenia is not known, even though there is some evidence for deterioration of cognitive and social function at this age (Sommer et al., 2016).

The present study aimed to investigate the effect of a shorter EE exposure during early adolescence on the development of schizophrenia-like symptoms induced by the antimitotic agent methylazoxymethanol (MAM) (Kisby et al., 2013). Prenatal administration of MAM at embryonic day 17 (E17) is an environmental manipulation that induces certain behaviour (e.g., reduced social interaction, sensorimotor gating and memory deficits), anatomic (e.g., a decrease in cerebral cortical volume) and neurophysiological (e.g., alteration in cortico-cortical synaptic transmission) abnormalities in adult rats like those observed in patients with schizophrenia (Modinos et al., 2015). Moreover, environmental manipulation (until 5 months of age) and additional training can improve cognition in this model of schizophrenia (Jenks et al., 2013), but this appears to be dependent upon the dose of the mitotin (Wallace et al., 2003). We investigated the impact of EE on MAM-induced behavioural dysfunction, such as cognitive deficits, i.e., sensorimotor gating (Swerdlow et al., 2008) and recognition memory (Millan et al., 2012), and negative symptoms, i.e., social interaction impairment (Wilson and Koenig, 2014).

The specific developmental stage of young rats that were exposed to EE was the same as in our previous studies which showed that MAM induced behavioural and neurochemical deficits in adult animals via epigenetic dysregulation during early adolescence (Bator et al., 2015; Mackowiak et al., 2014), a period corresponding to early adolescence in humans (10-13 years) (Burke et al., 2017).

Several findings indicate that the emergence of schizophrenia might be connected to impaired epigenetic regulation of gene expression (Millan, 2013). Epigenetic mechanisms control gene expression through the chemical modification of DNA and histone proteins or through the regulatory actions of small nuclear RNAs and microRNAs (Grayson and Guidotti, 2013; Millan, 2013). The protein and mRNA expression of GAD67, the enzyme responsible for the synthesis of GABA, is commonly altered in schizophrenic patients (Mitchell et al., 2015; Schmidt and Mirnics, 2015). In schizophrenia, defective GAD1 expression, a gene encoding the GAD67 protein, is linked to epigenetic abnormalities in chromatin surrounding the GAD1 promoter and transcription start site (Mitchell et al., 2015), that include changes in DNA methylation (Huang and Akbarian, 2007; Veldic et al., 2005) and histone modification, i.e., the trimethylation of histone H3 at lysine 4 (H3K4me3) (Huang et al., 2007). The involvement of H3K4me3 in the regulation of GAD1 is of special interest because reduced levels of H3K4me3 have been found in regulatory sequences of this gene in schizophrenic patients (Huang et al., 2007). Alterations in GAD67 mRNA expression and the protein level of H3K4me3 in the adult medial prefrontal cortex (mPFC) have also been observed in the MAM neurodevelopmental model of schizophrenia (Mackowiak et al., 2014). Thus, it was of interest to investigate the impact of EE not only on the development of behavioural symptoms of schizophrenia but also on the
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