European Neuropsychopharmacology (2014) **24**, 879–889

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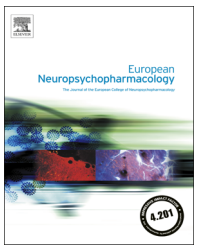

Evidence that aetiological risk factors for psychiatric disorders cause distinct patterns of cognitive deficits

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Received 20 May 2013; received in revised form 7 November 2013; accepted 2 December 2013

KEYWORDS
Psychiatric aetiology;
Phencyclidine;
Glucocorticoids;
Maternal immune activation;
Executive dysfunction

Abstract
Schizophrenia and bipolar disorder are associated with neurocognitive symptoms including deficits in attentional set shifting (changing attentional focus from one perceptual dimension to another) and reversal learning (learning a reversed stimulus/outcome contingency). Maternal infection during gestation and chronically flattened glucocorticoid rhythm are aetiological risk factors for schizophrenia and bipolar disorder. We hypothesised that these factors are causative in the neurocognitive deficits observed in schizophrenia and bipolar disorder. Here we used maternal immune activation (MIA) as a rat model of maternal infection, and sub-chronic low dose corticosterone treatment as a rat model of flattened glucocorticoid rhythm. For comparison we examined the effects of sub-chronic phencyclidine – a widely used rodent model of schizophrenia pathology. The effects of these three treatments on neurocognition were explored using the attentional set shifting task – a multistage test of executive functions. As expected, phencyclidine treatment selectively impaired set shifting ability. In contrast, MIA caused a marked and selective impairment of reversal learning. Corticosterone treatment impaired reversal learning but in addition also impaired rule abstraction and prevented the animals from forming an attentional set. The reversal learning deficits induced by MIA and corticosterone treatment were due to increases in non-perseverative rather than perseverative errors. Our data indicate that the cognitive deficits of schizophrenia and bipolar disorder may be explained by aetiological factors including maternal infection and glucocorticoid abnormalities and moreover suggest that the particular spectrum of cognitive deficits in individual patients may depend on the specific underlying aetiology of the disorder.

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http://dx.doi.org/10.1016/j.euroneuro.2013.12.005

1. Introduction

Whilst schizophrenia and bipolar disorder are distinct diagnostic classifications, they share a common burden of neurocognitive impairments (Millan et al., 2012). These impairments affect patients' ability to function and have an adverse impact on quality of life. Deficits in central executive function such as concept formation and cognitive flexibility as exemplified by impairments in the ability to form an 'attentional set' and reversal learning respectively have been observed in both schizophrenia and bipolar disorder patients (Altshuler et al., 2004; Joyce et al., 2002; Martinez-Aran et al., 2002; McKirdy et al., 2009; Pantelis et al., 1999; Zubieta et al., 2001). The causal factors underlying the shared cognitive impairments in bipolar disorder and schizophrenia remain unknown.

Bipolar disorder and schizophrenia appear to be multifactorial in their aetiology. Gestational factors including maternal infection during pregnancy greatly increase the risk of schizophrenia in offspring (Adams et al., 1993; Brown et al., 2004; Buka et al., 2008; Suvisaari et al., 1999) and may be causative in the development of the disorder. There is also evidence, albeit limited, that the risk of bipolar disorder in offspring is increased by prenatal influenza infection (Machon et al., 1997). One of the most robust biological findings in bipolar disorder is hypothalamo-pituitary adrenal (HPA) axis dysfunction characterised by a raised diurnal trough (but normal peak) levels of the glucocorticoid, cortisol (Cervantes et al., 2001). This has been suggested to be causative in some of the symptomatology of the disorder. Although the data are less consistent, there is also evidence for HPA dysfunction in schizophrenia with dexamethasone non-suppression (Dewan et al., 1982) and an increase in total diurnal cortisol reported (Ryan et al., 2004).

Animal models of aetiological factors may help us to better understand the underpinnings of neurocognitive dysfunction in psychiatric disorders. In rodents maternal infection can be modelled by administration of a cytokine activator-maternal immune activation (MIA) (Meyer et al., 2006a; Zuckerman et al., 2003; Zuckerman and Weiner, 2005a). Flattened glucocorticoid rhythm can be modelled by sub-chronic administration of low dose corticosterone to adrenally intact animals (Minton et al., 2009). These aetiological models contrast with the widely studied phencyclidine (PCP) rodent model of schizophrenia which is based on the finding that sub-chronic PCP induces loss of parvalbumin positive GABA interneurons in the cortex (Abdul-Monim et al., 2007; McKibben et al., 2010) and abnormalities in sensorimotor gating (Egerton et al., 2008). Thus, administration of PCP mimics some behavioural and pathological features of schizophrenia.

Recently there have been developments in tests of executive function including the human/primate computer test batteries such as CANTAB™ (Cambridge Cognition, UK) (Dias et al., 1996), and analogous rodent protocols, such as the attentional set shifting task (ASST) developed by Brown and colleagues (Birrell and Brown, 2000). These tasks allow for several cognitive capabilities – simple rule learning, complex discrimination, reversal, rule abstraction (intradimensional shift) and attentional set shifting (extra-dimensional shift) – to be tested in one task and moreover offer excellent opportunities for translational research.

The aim of this study was to determine whether maternal infection and flattened gluococorticoid rhythm impact on executive function. We determined the effects of MIA and flattened corticosterone rhythm on performance of rats in the ASST. For comparison we also examined the effects of sub-chronic PCP which has previously been shown to induce specific deficits in the extradimensional shift of the ASST (Goetghebeur and Dias, 2009; Rodefer et al., 2005, 2008).

2. Experimental procedures

2.1. Animals

All studies were conducted in accordance with the UK Animals (Scientific Procedures) Act. All efforts were made to minimise animal suffering. Male and female Lister hooded rats (Charles River, Kent, UK) were housed in controlled conditions (20–25 °C, lights on 7 am: lights off 7 pm) and were allowed to acclimatize for at least 5 days before any interventions.

2.2. Sub-chronic phencyclidine

Eighteen male rats (190–210 g), pair housed by treatment, received vehicle (saline, 1 ml/kg i.p. (n=10)) or PCP (5 mg/kg i.p., (n=8)) twice daily at 8 am and 8 pm from day 1 to day 7. The ASST was conducted on days 9 and 10. The dosing regimen is that previously used by Rodefer et al. (2005, 2008) however, given that PCP has a half-life of less than 4 h in male rats (Shelnutt et al., 1999) we shortened the washout time to 72 h.

2.3. Maternal immune activation

Dams were group housed adjacent to singly housed stud males. For mating, a single female was placed in the cage of a stud male for 24 h. If, after 5-7 days, pregnancy could not be confirmed (by weight gain) the female was re-mated. On gestational day (GD) 15 at around 12:00, dams were briefly anaesthetized with isoflurane (2%) and received polyinosinic–polycytidylic acid potassium salt (Poly I:C, Sigma, UK) (4 mg/kg in water) or vehicle (1 ml/kg) intravenously. Up to parturition and throughout the pre-weaning period, disturbance was kept to a minimum except for weighing (twice weekly) and cage cleaning (weekly). Male pups were weaned (postnatal day 21 or 22) and group housed (2–5) by litter up to the age of 3 months and thereafter divided into pairs (or threes if litter numbers were odd). Both MIA and control groups consisted of male offspring from 3 different litters with no common parent. One male sired two further litters (with different dams) one of which was included in each group. The MIA treatment protocol used is that used by other groups investigating the potential role of maternal infection in abnormal brain development and function in the offspring (Dickerson et al., 2010; Piontkewitz et al., 2009).

2.4. Sub-chronic corticosterone treatment

Twenty male rats were pair housed. For 15 days (days −5 to 10), animals had ad libitum access to drinking water containing either corticosterone (50 μg/ml in 0.5% ethanol (n=10)) or vehicle (0.5% ethanol (n=10)). Rats given corticosterone received around 5 mg/kg/day. The ASST was conducted on days 9 and 10. On day 11, animals were killed and their adrenal glands removed and weighed. The corticosterone protocol used is that which we have previously shown to result in a flattening of the corticosterone rhythm (Minton et al., 2009).

2.4.1. Test of executive function: attentional set shfitng task (ASST)

Executive function was assessed using the ASST (Birrell and Brown, 2000). For 10 days (days 1–10) animals were food restricted. Animals