



Journal of Psychopharmacology
1–4

© The Author(s) 2016
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0269881116667668
jop.sagepub.com



Modelling the cognitive and neuropathological features of schizophrenia with phencyclidine

Gavin P Reynolds¹ and Joanna C Neill²

Abdul-Monim Z, Neill JC and Reynolds GP (2007) Sub-chronic psychotomimetic phencyclidine induces deficits in reversal learning and alterations in parvalbumin-immunoreactive expression in the rat. *J Psychopharmacol* 21:198–205.

Abstract

Here, Reynolds and Neill describe the studies that preceded and followed publication of this paper, which reported a deficit in parvalbumin (PV), a calcium-binding protein found in GABA interneurons known to be reduced in schizophrenia patients, in conjunction with a deficit in reversal learning in an animal model for schizophrenia. This publication resulted from common research interests: Reynolds in the neurotransmitter pathology of schizophrenia, and Neill in developing animal models for schizophrenia symptomatology. The animal model, using a sub-chronic dosing regimen (sc) with the non-competitive NMDA receptor antagonist PCP (phencyclidine), evolved from previous work in rats (for PCP) and primates (for cognition). The hypothesis of a PV deficit came from emerging evidence for a GABAergic dysfunction in schizophrenia, in particular a deficit in PV-containing GABA interneurons. Since this original publication, a PV deficit has been identified in other animal models for schizophrenia, and the PV field has expanded considerably. This includes mechanistic work attempting to identify the link between oxidative stress and GABAergic dysfunction using this scPCP model, and assessment of the potential of the PV neuron as a target for new antipsychotic drugs. The latter has included development of a molecule targeting KV3.1 channels located on PV-containing GABA interneurons which can restore both PV expression and cognitive deficits in the scPCP model.

Keywords

Schizophrenia, parvalbumin, GABA, PCP, cognition, rat

This paper demonstrated an association in an animal model between two abnormalities seen in schizophrenia: a pathology of a subtype of GABAergic neurons, and cognitive dysfunction shown by a deficit in operant reversal learning, an animal correlate of human problem solving and reasoning. It emerged from a collaboration between two groups: one interested in the neuronal and neurotransmitter pathology of schizophrenia (Reynolds), the other developing animal models to study cognitive deficits in schizophrenia and other disorders (Neill), with both having interests in the mechanisms and effects of drugs for the treatment of psychosis. The work had been done some three years previously and published in part at that time (Reynolds et al., 2004) and alluded to in the preceding Abdul-Monim publication (Abdul-Monim et al., 2006) – preparing a PhD thesis had delayed full publication of the study.

The work represented, for us, an obvious continuation of the search to understand better the parvalbumin (PV) deficit in schizophrenia. It can be traced back over 30 years to the observation from post-mortem studies of a (lateralised) elevation in dopamine in the amygdala in schizophrenia (Reynolds, 1983). At the time there was increasing evidence from both imaging and post-mortem studies of a genuine, if subtle, neuropathology of this disease (e.g. Roberts and Crow, 1987), and it seemed likely that changes in dopamine reflect effects of abnormalities in other neurotransmitter systems rather than a primary hyper-innervation of dopaminergic neurons, for which there was no evidence.

A simple, perhaps naive, approach to understanding this finding is to speculate that a loss of inhibitory GABAergic interneurons might be the cause of the dopaminergic hyper-function. Some early post-mortem studies of co-localised neuropeptides certainly suggested limbic GABAergic deficits in schizophrenia (Roberts et al., 1983), and a study of GABA uptake sites indicated that there was a deficit of GABAergic synapses in the hippocampus (Reynolds et al., 1990). Interestingly, this deficit correlated with the elevation of dopamine in the left amygdala, providing some support for the suggestion that the elevation in dopamine might be secondary to inhibitory neuronal deficits. Over the next few years, further work, particularly that emerging from Francine Benes' lab in Boston, established clearly that there were cortical and limbic deficits in GABAergic interneurons in schizophrenia (e.g. Benes and Berretta, 2001; Benes et al., 1991, 1998).

¹Sheffield Hallam University, Biomolecular Sciences Research Centre, Sheffield, UK

²Manchester Pharmacy School, University of Manchester, Manchester, UK

Corresponding author:

Joanna C. Neill, Manchester Pharmacy School, University of Manchester, Manchester M13 9PT, UK.
Email: joanna.neill@manchester.ac.uk

In considering the possible aetiological influence on this GABAergic neuropathology, it was interesting to note that cortical GABAergic cells could be divided into three groups based on their component calcium-binding protein (CBP), of which those containing calbindin and calretinin were expressed early in development, but in those with PV, the CBP was expressed later (Solbach and Celio, 1991), in fact after birth in humans. This indicated a possible period during development, prior to PV expression, when this subgroup of GABAergic neurons was vulnerable to damage associated with some of the developmental risk factors for the emergence of schizophrenia.

Testing the hypothesis of a specific reduction in PV-immunoreactive neurons in schizophrenia, we identified this in the cortex almost 20 years ago (Beasley and Reynolds, 1997). This finding was replicated in a further series (Beasley et al., 2002), and we also found that in the hippocampus, deficits in PV-immunoreactive neurons were >50% (Zhang and Reynolds, 2002). This reduction in PV-positive neurons is one of the most robust findings in the disease; analysis of 100 neurochemical studies in a series of post-mortem brain tissues demonstrated that the strongest findings in schizophrenia were frontal cortical or hippocampal deficits in PV, reelin and glutamic acid decarboxylase, all of which are associated with subtypes of GABAergic neurons (Torrey et al., 2005).

One important question that emerged was whether this finding could be replicated in emerging animal models for various aspects of schizophrenia. A robust animal model would enable enhanced understanding of these pathological mechanisms and provide a means to test the efficacy of new improved drug targets.

The Neill group was searching for an animal model that could replicate the psycho- and neuropathology of schizophrenia, particularly the cognitive deficits. It was becoming clear that cognition and negative symptoms of schizophrenia were critical for outcome and represented an unmet clinical need (Green, 1996). This led to establishment of the MATRICS initiative whereby seven domains of cognition were shown to be impaired in the illness. These were working memory, attention, social cognition, executive function, problem solving and reasoning, and visual and verbal memory (Green et al., 2004; Marder and Fenton, 2004). It is still the case today that no treatment has yet received a licence for the treatment of cognitive deficits or negative symptoms in schizophrenia, in spite of several large Phase III clinical trials in this area (Citrome, 2014).

The work of the Neill group at the University of Bradford, investigating the efficacy of novel compounds to improve cognition in rodents in the area of cognition and schizophrenia, evolved from the initial work of Domeney, Costall and Naylor in non-human primates, the common marmoset, *Callithrix jacchus*. In marmosets, this group were well known for studying task-dependent reversal learning deficits using a miniature version of the Wisconsin Card Sorting Test (see, e.g., Barnes et al., 1990; Smith et al., 1999). Around the same time, Jentsch and colleagues were conducting elegant studies treating rats and primates with a sub-chronic dosing regimen of the uncompetitive NMDA receptor antagonist phencyclidine (scPCP) to induce cognitive disturbances of putative relevance to schizophrenia, accompanied by dopamine dysregulation in the prefrontal cortex (Jentsch et al., 1997; reviewed in Jentsch and Roth, 1999). Their work originated from the initial observation that administration of PCP to healthy humans could induce psychotic symptoms and exacerbate positive symptoms in schizophrenia patients (Luby,

1959). The use of scPCP was considered to fulfil both the hypoglutamatergic (Olney et al., 1999) and hyperdopaminergic (Jentsch and Roth, 1999) hypotheses of schizophrenia.

Employing the scPCP treatment regimen of Jentsch and Roth (1999), we identified a significant and selective reversal learning deficit induced by scPCP given at a dose of 2 mg/kg intraperitoneally (i.p.) twice a day for seven days followed by seven days drug free in female Lister Hooded rats (Abdul-Monim et al., 2006). This effect was reversed by an acute low dose of the dopamine/serotonin antagonist schizophrenia drugs clozapine, olanzapine and ziprasidone but not by the dopamine antagonist drug haloperidol, confirming some level of predictive validity of the drug effects in our model. The issue of predictive validity of the animal model is discussed in more detail in Neill et al. (2014). Face validity of our model was confirmed by the selective reversal learning deficit induced by scPCP, similar to deficits seen in patients in the Wisconsin Card Sorting Test (Braff et al., 1991). The operant serial reversal learning test we used was based on the test developed by Jones et al. (1991) who showed deficits in isolation-reared rats. We did not replicate their finding in isolates (Abdul-Monim et al., 2003). However, we did find that both acute and scPCP treatment produce a reliable selective impairment when the rule changes (i.e. in the reversal phase only), which seems of some relevance to the disorder. While there was evidence that PV gene expression might be compromised in another scPCP model involving 28 days of intermittent dosing in male rats (Cochran et al., 2003), determination of PV neurons had not previously been made in animals with scPCP-induced deficits. Therefore, the work in our 2007 paper was the first to link a deficit in cognition with a pathological deficit directly, both of considerable relevance to schizophrenia.

The reversal learning test assesses only one of the seven domains of cognition impaired in the illness. Work in the Neill laboratory since this time has aimed to establish other tests for these domains of cognition and also tests of relevance to negative symptoms in the illness. To this end, we have produced robust and selective deficits using scPCP in female Lister Hooded rats in novel object recognition (visual short-term recognition memory; Grayson et al., 2007), attentional set shifting (executive function; McLean et al., 2008) and the 5-choice continuous performance task (5C-CPT, attention and vigilance; Barnes et al., 2012) for cognition (reviewed in Neill et al., 2010). In addition, we have shown robust social behaviour deficits building from the earlier work of Frank Sams-Dodd (1995) and reviewed in Neill et al. (2014), and also in affective bias for negative symptoms of schizophrenia (Sahin et al., 2016).

Several neuropathological deficits of relevance to schizophrenia have also been uncovered in this animal model. Since 2007, we have repeatedly demonstrated reduced PV in the prefrontal cortex in post-mortem brain tissue by immunohistochemistry (reviewed in Neill et al., 2010) and reduced N-acetyl aspartate, a measure of neuronal integrity, in the prefrontal cortex in vivo using magnetic resonance spectroscopy as well as via high performance liquid chromatography post-mortem (Marsh, 2015; Reynolds et al., 2005, when rats were given scPCP intermittently over 28 days). We have also shown reductions in brain-derived neurotrophic factor (Snigdha et al., 2011) and monoamine receptors (Choi et al., 2009). In rats performing the novel object recognition test, we have demonstrated that scPCP impairs recognition memory in retention and dopamine release in the prefrontal cortex as measured by in vivo microdialysis (Snigdha et al., 2008). We

have therefore demonstrated behavioural and neuropathological deficits of relevance to schizophrenia induced by scPCP. However, the PV deficit is our most robust finding and perhaps of most relevance to the disorder, as explained above.

We have used our model to assess efficacy of several novel drug targets for cognition and negative symptoms in schizophrenia, and a small but successful university-based contract research organisation with industry collaborations has been established (www.b-neuro.com). One collaboration of particular relevance for PV and GABA interneuron pathology in schizophrenia is with Autifony, a company developing novel Kv3.1 channel modulators for the treatment of age-related hearing loss and schizophrenia. The voltage-gated potassium channel Kv3.1 regulates high-frequency neuronal firing, and these channels are mainly located on PV-containing GABAergic interneurons. Autifony's lead compound for schizophrenia AUT000206 reliably reverses scPCP-induced deficits in cognition and social behaviour (Leger et al., 2014). Most importantly, when given over 21 days, AUT00206 restores cognition *and* the PV deficit in the scPCP model at the same time, in the same animals (Leger et al., 2015). Both effects are lost when the drug is discontinued. These findings suggest that this molecule will not only restore function and improve symptoms, but that it could rescue neuropathological deficits in the illness, mediating symptomatology. Demonstrating the success and reproducibility of the scPCP model, it has since been adopted by several other laboratories in academia and the pharmaceutical industry (for a recent review, see Meltzer et al., 2013; Neill et al., 2014).

Of course, this model lacks some construct validity in that it does not incorporate genetic, environmental or neurodevelopmental risk factors for schizophrenia. Nevertheless, in support of the key role of PV deficits in modelling schizophrenia, we and others have demonstrated this pathology in a range of other rodent models, developmental and pharmacological, that can produce behavioural deficits modelling certain aspects of schizophrenia. These include isolation rearing (Harte et al., 2007), prenatal or neonatal inflammatory challenge with lipopolysaccharide (Jenkins et al., 2009; Wischhof et al., 2015) and chronic or acute high-dose methamphetamine (Veeraskul et al., 2016). Others have observed PV neuronal losses following prenatal methylazoxymethanol (Penschuck et al., 2006) or repeated ketamine administration (Sabbagh et al., 2013).

Despite the progression of this work, we still cannot say for certain whether a hyper-function of dopamine is a direct consequence of the PV/GABA deficit, although a recent study did indicate that this might be the case (Boley et al., 2014). This showed that a specific reduction of PV expression in the rat hippocampus does result in increased dopamine activity consistent with the originally identified inverse correlation between a hippocampal GABA marker and amygdala dopamine in schizophrenia (Reynolds et al., 1990).

Most recently, in a further collaborative study, we have obtained preliminary evidence that the scPCP-induced reduction in PV might reflect an epigenetic effect. Increased DNA methylation of the *Pvalb* promoter, in the absence of any effect on global methylation, was observed in rats previously receiving scPCP. Conceivably, this could result in diminished transcription and consequent expression of PV (Fachim et al., 2016). Of particular interest is that in some unpublished work currently underway, promoter sequence hypermethylation of the PV gene may also be present in schizophrenia. Given that the rat promoter sequence studied is rich in recognition

sites for the nuclear factor erythroid 2 (NF-E2)-related factor 2 transcription factor important in antioxidant effects, these findings may provide a mechanistic link to understand better the relationship between oxidative stress and NMDA receptor hypofunction in GABAergic neurons (Hardingham and Do, 2016).

Clearly PV and GABAergic interneuron dysfunction is central to the pathology of schizophrenia, at least in some patients. Over the past 30 years, research in this area has been steadily increasing. This has led to new animal model development, and has greatly enhanced understanding of the mechanisms by which this system is disturbed in schizophrenia, as described above. There have been several positive results with new non-dopaminergic drug targets in preclinical studies and in clinical trials up to Phase II. Unfortunately, however, this has not yet extended into Phase III trials. This is probably more related to limitations in the design of the trials and complexity of the illness than to the drug target itself. With novel molecules such as AUT00206 in the pipeline, lessons learned from recent Phase III failures and increased emphasis on a holistic approach to treatment, incorporating pharmacological, physical and psychological therapies, this is an exciting time for drug discovery in this area.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

- Abdul-Monim Z, Reynolds GP and Neill JC (2003) The atypical antipsychotic ziprasidone, but not haloperidol, improves PCP-induced cognitive deficits in a reversal learning task. *J Psychopharmacology* 17: 57–66.
- Abdul-Monim Z, Reynolds GP and Neill JC (2006) The effect of atypical and classical antipsychotics on sub-chronic PCP induced cognitive deficits in a reversal-learning paradigm. *Behav Brain Res* 169: 263–273.
- Barnes JM, Costall B, Coughlan J, et al. (1990) The effects of ondansetron, a 5-HT₃ receptor antagonist, on cognition in rodents and primates. *Pharmacol Biochem Behav* 35: 955–962.
- Barnes S, Young J and Neill JC (2012) Rats tested after a washout period from sub-chronic PCP administration exhibited impaired performance in the 5-choice continuous performance test (5C-CPT) when the attentional load was increased. *Neuropharmacology* 62: 1432–1441.
- Beasley CL and Reynolds GP (1997) Parvalbumin-immunoreactive neurons are reduced in the frontal cortex of schizophrenics. *Schiz Res* 24: 349–355.
- Beasley CL, Zhang ZJ, Patten I, et al. (2002) Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium binding proteins. *Biol Psychiatry* 52: 708–715.
- Benes FM and Berretta S (2001) GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* 25: 1–27.
- Benes FM, Kwok EW, Vincent SL, et al. (1998) A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. *Biol Psychiatry* 44: 88–97.
- Benes FM, McSparran J, Bird ED, et al. (1991) Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. *Arch Gen Psychiatry* 48: 996–1001.
- Boley AM, Perez SM and Lodge DJ (2014) A fundamental role for hippocampal parvalbumin in the dopamine hyperfunction associated with schizophrenia. *Schiz Res* 157: 238–243.

- Braff DL, Heaton R and Kuck J (1991) The generalised pattern of neuropsychological deficit in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. *Arch J Psychiatry* 47: 181–188.
- Choi YK, Snigdha S, Shahid M, et al. (2009) Sub-chronic effects of phencyclidine on dopamine and serotonin receptors: implications for schizophrenia. *J Mol Neurosci* 38: 227–235.
- Citrome L (2014) Unmet needs in the treatment of schizophrenia: new targets to help different symptom domains. *J Clin Psychiatry* 75: S21–S26.
- Cochran SM, Kennedy M, McKerchar CE, et al. (2003) Induction of metabolic hypofunction and neurochemical deficits after chronic intermittent exposure to phencyclidine: differential modulation by antipsychotic drugs. *Neuropsychopharmacology* 28: 265–275.
- Fachim HA, Srisawat U, Dalton CF, et al. (2016) Sub-chronic administration of phencyclidine produces hypermethylation in the parvalbumin gene promoter in rat brain. *Epigenomics*. Epub ahead of print 16 August. DOI: 10.2217/epi-2016-0050.
- Grayson B, Idris NF and Neill JC (2007) Atypical but not classical antipsychotics attenuate a sub-chronic PCP-induced cognitive deficit in the novel object recognition task in the rat. *Behav Brain Res* 184: 31–38.
- Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 153: 321–330.
- Green MF, Kern RS and Heaton RK (2004) Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schiz Res* 72: 41–51.
- Hardingham GE and Do KQ (2016) Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. *Nat Rev Neurosci* 17: 125–134.
- Harte MK, Powell SB, Swerdlow NR, et al. (2007) Deficits in parvalbumin and calbindin immunoreactive cells in the hippocampus of isolation reared rats. *J Neural Transm* 114: 893–898.
- Jenkins TA, Harte MK, Stenson G, et al. (2009) Neonatal lipopolysaccharide induces pathological changes in parvalbumin immunoreactivity in the hippocampus of the rat. *Behav Brain Res* 205: 355–359.
- Jentsch JD and Roth RH (1999) The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 20: 201–225.
- Jentsch JD, Tran A, Le D, et al. (1997) Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilization and impairs prefrontal cortical dependent cognition in the rat. *Neuropsychopharmacology* 17: 92–99.
- Jones GH, Marsden CA and Robbins TW (1991) Behavioural rigidity and rule learning deficits following isolation-rearing in the rat: neurochemical correlates. *Behav Brain Res* 43: 35–50.
- Leger M, Alvaro G, Large CH, et al. (2015) Efficacy of AUT6, a novel and selective Kv3 channel modulator, to alleviate cognitive and neurobiological dysfunction in the sub-chronic PCP rat model of schizophrenia symptomatology. *J Psychopharmacol* 29: A66.
- Leger M, Grayson B, Marsh S, et al. (2014) KV3 channel modulation alleviates cognitive dysfunction and negative symptoms in an animal model of schizophrenia: first identification of a potentially disease modifying target for schizophrenia. *J Psychopharmacol* 28: A111.
- Luby ED, Cohen BD, Rosenbaum G, et al. (1959) Study of a new schizophrenomimetic drug; sernyl. *AMA Arch Neurol Psychiatry* 81: 363–369.
- Marder SR and Fenton W (2004) Measurement and treatment research to improve cognition in schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. *Schiz Res* 72: 5–9.
- Marsh S (2015) *Investigation of the neuronal marker N-acetylaspartate as a potential biomarker for neurological diseases*. PhD Thesis, University of Manchester, UK.
- McLean SL, Beck JP, Woolley ML, et al. (2008) A preliminary investigation into the effects of antipsychotics on sub-chronic phencyclidine-induced deficits in attentional set-shifting in female rats. *Behav Brain Res* 189: 152–158.
- Meltzer HY, Rajagopal L, Huang M, et al. (2013) Translating the N-methyl-D-aspartate receptor antagonist model of schizophrenia to treatments for cognitive impairment in schizophrenia. *Int J Neuropsychopharmacol* 16: 2181–2194.
- Neill JC, Barnes S, Cook S, et al. (2010) Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism. *Pharmacol Ther* 128: 419–432.
- Neill JC, Harte MK, Haddad PM, et al. (2014) Acute and chronic effects of NMDA receptor antagonists in rodents, relevance to negative symptoms of schizophrenia: a translational link to humans. *Eur Neuropsychopharmacol* 24: 822–835.
- Olney JW, Newcomer JW and Farber NB (1999) NMDA receptor hypofunction model of schizophrenia. *J Psychiatr Res* 33: 523–533.
- Penschuck S, Flagstad P, Didriksen M, et al. (2006) Decrease in parvalbumin-expressing neurons in the hippocampus and increased phencyclidine-induced locomotor activity in the rat methylazoxymethanol (MAM) model of schizophrenia. *Eur J Neurosci* 23: 279–284.
- Reynolds GP (1983) Increased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. *Nature* 305: 527–529.
- Reynolds GP, Abdul-Monim Z, Neill JC and Zhang ZJ (2004) Calcium binding protein markers of GABA deficits in schizophrenia - post mortem studies and animal models. *Neurotox Res* 6: 1–6.
- Reynolds GP, Czudek C and Andrews HB (1990) Deficit and hemispheric asymmetry of GABA uptake sites in the hippocampus in schizophrenia. *Biol Psychiatry* 27: 1038–1044.
- Reynolds LM, Cochran SM, Morris BJ, et al. (2005) Chronic phencyclidine administration induces schizophrenia-like changes in N-acetylaspartate and N-acetylaspartylglutamate in rat brain. *Schiz Res* 73: 147.
- Roberts GW and Crow TJ (1987) The neuropathology of schizophrenia—a progress report. *Br Med Bull* 43: 599–615.
- Roberts GW, Ferrier IN, Lee Y, et al. (1983) Peptides, the limbic lobe and schizophrenia. *Brain Res* 288: 199–211.
- Sabbagh JJ, Murtishaw AS, Bolton MM, et al. (2013) Chronic ketamine produces altered distribution of parvalbumin-positive cells in the hippocampus of adult rats. *Neurosci Lett* 550: 69–74.
- Sahin C, Doostdar N and Neill JC (2016) Towards the development of improved tests for negative symptoms of schizophrenia in a validated animal model. *Behav Brain Res* 312: 93–101.
- Sams-Dodd F (1995) Distinct effects of D-amphetamine and phencyclidine on the social behaviour of rats. *Behav Pharmacol* 6: 55–65.
- Smith AG, Neill JC and Costall B (1999) The dopamine D3/D2 receptor agonist 7-OH-DPAT induces cognitive impairment in the marmoset. *Pharmacol Biochem Behav* 63: 201–211.
- Snigdha S, Li Z, Dai J, et al. (2008) *Effect of PCP to attenuate DA efflux in rats performing the object recognition task: an in vivo investigation*. Program No. 791.4/TT40.2008 Neuroscience Meeting Planner Washington DC: SfN, 2008.
- Snigdha S, Neill JC, McLean SL, et al. (2011) Phencyclidine (PCP)-induced disruption in cognitive performance is gender-specific and associated with a reduction in brain-derived neurotrophic factor (BDNF) in specific regions of the female rat brain. *J Mol Neurosci* 43: 337–344.
- Solbach S and Celio MR (1991) Ontogeny of the calcium binding protein parvalbumin in the rat nervous system. *Anat Embryol* 184: 103–124.
- Torrey EF, Barci BM, Webster MJ, et al. (2005) Neurochemical markers for schizophrenia, bipolar disorder, and major depression in post-mortem brains. *Biol Psychiatry* 57: 252–260.
- Veerasakul S, Thanoi S, Reynolds GP, et al. (2016) Effect of methamphetamine exposure on expression of calcium binding proteins in rat frontal cortex and hippocampus. *Neurotox Res*. Epub ahead of print 14 May. DOI: 10.1007/s12640-016-9628-2.
- Wischhof L, Irsack E, Osorio C, et al. (2015) Prenatal LPS-exposure – a neurodevelopmental rat model of schizophrenia – differentially affects cognitive functions, myelination and parvalbumin expression in male and female offspring. *Prog Neuropsychopharmacol Biol Psychiatry* 57: 17–30.
- Zhang ZJ and Reynolds GP (2002) A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. *Schiz Res* 55: 1–10.