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# Alteration in the GABAergic network of the prefrontal cortex in a potential animal model of psychosis

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**Summary** The GABAergic input on cortical pyramidal cells has an important influence on the firing activity of the cortex and thus in regulating the behavioural outcome. The aim of the current study was to investigate the long-term neuroplastic adaptation of the GABAergic innervation pattern after an early severe systemic impact. Therefore 40 Mongolian gerbils (*Meriones unguiculatus*) were either reared under impoverished (IR) or enriched rearing conditions (ER) and received a single early (+)-methamphetamine (MA) challenge (50 mg/kg i.p.) or saline on postnatal day 14. The density of perisomatic immunoreactive GABAergic terminals surrounding layers III and V pyramidal neurons was quantified as well as the overall GABAergic fibre density in layers I/II and V of the medial prefrontal cortex (mPFC) of young adult animals (90 days). We found that IR in combination with an early MA administration led to a significant decrease in GABAergic bouton densities while the overall GABAergic fibre density increased in all investigated layers. The results indicate a shift in inhibition from somatic to dendritic innervation of pyramidal neurons in this potential animal model of psychosis. We conclude that IR combined with early MA trigger changes in the postnatal maturation of the prefrontal cortical GABAergic triggers innervation, which may interfere with proper signal processing within the prefrontal neural network.

**Keywords:** GABA, immunohistochemistry, schizophrenia, gerbil

## Introduction

The interaction of the different transmitter systems plays a decisive role for the functioning of neural circuits throughout the brain. Several transmitters, such as gamma-aminobutyric acid (GABA), serotonin and dopamine, contribute to the modulation of activity of the cortical pyramidal neurons, and thus have an important influence on the behavioural outcome. Every segment of the pyramidal neuron, from the initial axonal segment and the cell body up to dendritic spines, receives dense GABAergic innervation (Hendry et al., 1983; Houser et al., 1983; Beaulieu et al., 1992). Intriguingly, each of these segments receives its innervation from a distinct subpopulation of GABAergic neurons (Kisvarday et al., 1990).

Somatic GABAergic boutons are mainly build by the basket cell subpopulation, which owe their name to the basket-like arrangement of synapses surrounding pyramidal cell bodies (DeFelipe and Fairen, 1982; Hendry et al., 1983). The majority of cortical basket cells express the calcium-binding protein parvalbumin [PV (Hendry et al., 1989; Kawaguchi and Kubota, 1996)] and they mostly have a fast-spiking firing pattern (Kawaguchi and Kondo, 2002). A second type of cortical GABA cells, the chandelier neurons, are also associated with PV and are known to produce mainly axo-axonic contacts, which form axonal 'cartridges' along the initial axonal segment of the pyramidal neurons (Somogyi et al., 1982; Conde et al., 1994; Gabbott and Bacon, 1996). Beside these two populations of powerful interneurons, there are additional groups of GABAergic cells, which usually contain the calcium-binding proteins calbindin (CB) or calretinin (CR) and which are known to innervate primarily the dendritic spines and shafts of the pyramidal neuron (Conde et al., 1994; Gabbott and Bacon, 1996; Radnikow et al., 2002) and are thus less powerful in regulating the firing pattern of pyramidal cells. In summary, the subpopulations of interneurons each participate differently in establishing and maintaining the activity of cortical networks. Disturbances in this inhibitory regulation may result in extensive impairments in cognitive and behav-

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ioural function, like those seen in schizophrenia (Benes and Berretta, 2001).

Our lab has developed a potential animal model of schizophrenia using a combination of a single early methamphetamine (MA) intoxication on postnatal day 14, which damages monoaminergic fibers (Ricaurte et al., 1980, 1982), and chronically impoverished rearing conditions (IR) of gerbils. Among effects in several areas of the limbic-cortical system, the model impairs the maturation of the prefrontal cortex (PFC) by inducing diminished dopamine innervation (Dawirs et al., 1994; Neddens et al., 2001), increased GABA innervation (Nossoll et al., 1997), altered shape of pyramidal cells (Blaesing et al., 2001), and 'miswiring' of prefrontal efferents (Witte et al., 2006; Bagorda et al., 2006). In effect, the model successfully mimics several characteristics of the schizophrenic human brain (Feinberg, 1982; Weinberger and Lipska, 1995; Akil et al., 1999).

Since numerous alterations concerning the prefrontal GABAergic network have been reported for schizophrenia, as e.g. a particular defect in the parvalbumin-class of interneurons [reviewed in Blum and Mann (2002)], the current study was designed to investigate whether or how the GABAergic system may be affected in our animal model. Therefore, we analyzed different GABAergic structures, namely fibers and somatic terminals in the medial PFC of the developmentally disturbed gerbils.

## Material and methods

### *Animals and rearing conditions*

All experimental procedures were approved by the appropriate committee for animal care in accordance with the guidelines of the European Communities Council Directive. Breeding gerbils (*Meriones unguiculatus*) were obtained from Harlan Winkelmann (Borchen, Germany). Gerbils were chosen due to their very small genetic variability (Thiessen and Yahr, 1977), their rich wild-type like behavioural repertoire, and complex social interaction (Rosenzweig and Bennett, 1969).

A total of 40 males (weight 66–90 g) were used in this study. Half of them were bred in standard makrolon cages (type IV) whereas the other half were bred in semi-naturally structured compounds containing branches and hiding opportunities ($1 \times 1$ m; enriched condition). At weaning (30 days), the gerbils that were born in cages were assigned to impoverished conditions (IR, animals kept alone in standard makrolon cages type III without any content except of sawdust), while the other group grew up as a group of siblings under enriched rearing conditions (ER, kept in compounds similar to those they were born in), both for further 60 days. On postnatal day 14 a total of 20 animals received a single injection of (+)-methamphetamine hydrochloride [Sigma (50 mg/kg; i.p.)], whereas the remaining 20 gerbils were sham-treated with saline, resulting in four experimental groups: ER-Sal, ER-MA, IR-Sal, IR-MA; $n = 10$ for each group. All animals had free access to food and water and were kept on natural day/night cycles during summer season.

### *Immunohistochemistry*

On PD 90, animals were transcardically perfused under deep chloralhydrate anesthesia (1.7 g/kg, i.p.). The perfusion was performed with 200 ml 0.05 M phosphate buffer (pH 6.2), containing 1% sodium metabisulfite, followed by 750 ml 5% glutaraldehyde with 1% sodium metabisulfite in 0.1 M phosphate buffer (pH 7.5). Immediately after perfusion, the brains were removed and postfixed for 30 min. Coronar sections of 50 µm were cut with a vibratome (Vibratome Series 1000, Technical Products International Inc.) of which every 3rd was collected in wash buffer at 4°C. For immunostaining the sections were rinsed $3 \times 10$ min in cold wash buffer, followed by a preincubation in 10% normal goat serum and 0.4% Triton X-100 (Sigma) for 30 min. Subsequent the sections were incubated with rabbit anti-GABA (ImmunoStar, Hudson, WI), diluted 1:5000 with 1% normal goat serum and 0.4% Triton X-100 for 48 h.

The following rinses, all three times for 10 min, and dilutions were done in 0.05 M tris–HCL buffered saline pH 7.5 (TBS). The sections were rinsed and incubated for 30 min in biotinylated goat anti-rabbit IgG (Sigma) diluted 1:20 with 1% normal goat serum, rinsed again and incubated with ExtraAvidin-Peroxidase (Sigma) diluted 1:20 for 30 min. After another rinse the sections were stained in 0.05% 3.3-diaminobenzidine (Sigma) with 0.01% $H_2O_2$ for 4 min. Then the sections were washed, mounted on glass slides, dried overnight, dehydrated with ethanol, cleared with xylene and cover slipped with DePeX (Serva, Heidelberg, Germany). To avoid deviations due to possibly lateralised innervation densities of GABA only right hemispheres were used for quantification.

### *Quantification of GABAergic profiles*

For quantification of bouton and fibre densities, brain sections were chosen in areas of interest (Fig. 1A–E) by means of anatomical characteristics according to brain atlases of the rat (Paxinos and Watson, 1986) and the mouse (Valverde, 1998); identification of the brain regions follows the nomenclature of the atlas of the rat. For the quantification of GABAergic boutons a total number of 3200 cells was analysed, with an average number of 4 analysed sections per animal and an average of 10 clearly identified pyramidal cell somata in standard test fields (0.22 $mm^2$) per section and layer (layers III and V). A cell was chosen if the unstained soma was clearly lying within the range of layer III or V of the cingular cortex area 3 (Cg3) of the mPFC and had a round to slightly oval shape which was clearly surrounded by darkly stained GABAergic boutons (see Fig. 1G). An experimenter blind to the experimental conditions marked the pyramidal cell soma manually. All boutons in a range of 1.66 µm from this soma were automatically assigned and the density was computed as a percentage of the evaluated test area. The fibre densities were quantified in standard test fields (900 $\mu m^2$) in layers V and I/II with an average of 10 test fields per section and layer (see Fig. 1F and H). Layer I/II was chosen due to their high innervation with GABAergic fibres inhibiting distal apical dendrites of pyramidal neurons. All detectable GABAergic boutons and fibres were visualised using a bright field microscope (Olympus BX61, Hamburg, Germany) and a digital camera for microscopy (SIS ColorViewII, Münster, Germany) at 600-fold magnification. Boutons and fibres were quantified by software for image analysis (KS300, Jenoptik, Jena, Germany), which uses a combination of Gauss filter and Gerig operator that depicts differences of grey values of adjacent pixels and transforms the result into binary images. In effect, fibres were depicted as lines of one pixel width, such that different diameters of fibres would not influence the measurement.

### *Data analysis*

The data were computed as arithmetic means by-case and by-group ± S.E.M. of the respective layers and were analysed for the effects of both rearing conditions and pharmacological treatment. To account for possible interactions between the somatic size of the investigated cells and the area being covered by perisomatic GABAergic boutons, the size of the pyramidal cell bodies was used as a covariate in a 2-way analysis of covariance (ANCOVA) of perisomatic terminals.

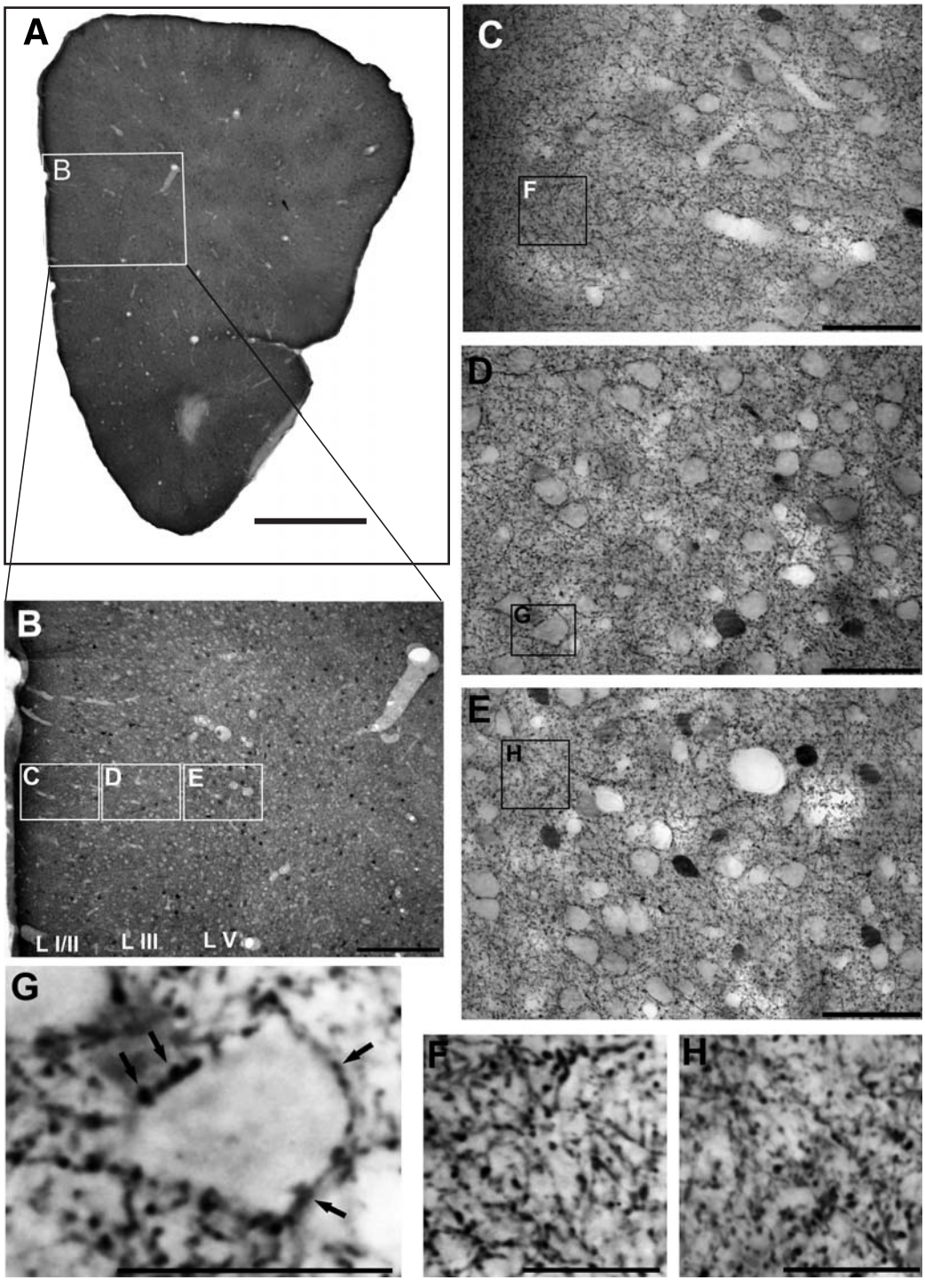


Fig. 1. Brightfield photomicrograph of a representative coronar section of the medial prefrontal cortex (**A**). The rectangle (**B**) shows the analysed section of the Cg3 region with subsequent rectangles for the analysed layers, which are magnified in (**C**, **D** and **E**). The GABAergic fibre density is generally similar in layers I/II and V (**F** and **H**). **G** shows GABAergic boutons (arrows) around an unstained pyramidal soma. Scale bars: 1 mm (**A**), 200 µm (**B**), 50 µm (**C**–**E**) and 20 µm (**G**–**H**)

Statistical analysis of the overall GABAergic fibre densities was done using a factorial ANOVA. Due to technical problems, sections from 6 animals (two from each group except IR-MA) had to be excluded from the study. All statistical analysis was computed with Statistica 6 (StatSoft, Tulsa, USA). The levels of significance were set at $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

## Results

### *Qualitative results*

The GABAergic innervation pattern is relatively homogenous throughout the cortex of gerbils and is similar to rats (Seto-Ohshima et al., 1990). It is characterised by a dense fibre innervation in all cortical layers with the highest density in the molecular layer. We identified immunonegative pyramidal neurons in layers III and V by their round or oval shape, their size and orientation, and the presence of basket-like GABAergic innervation (Fig. 1G).

## Quantitative results

### *GABAergic bouton densities*

The 2-way ANCOVA revealed a highly significant effect of rearing conditions on boutons in layer III [$F(1,29) = 28.59$, $p < 0.001$] and layer V [$F(1,29) = 25.58$, $p < 0.001$], and also a significant interaction between rearing and treatment in both layers [L III: $F(1,29) = 6.35$, $p = 0.0175$; L V: $F(1,29) = 5.0806$, $p = 0.0319$]. *Post-hoc* analysis with Newman-Keuls test showed the following results: Isolation rearing (IR) led to a significant decrease in GABAergic bouton density in layer III (−19%, $p = 0.032$), but not in layer V ($p = 0.093$). An early MA intoxication led to a further decrease in the bouton densities of both layers in IR-MA compared to IR-Sal animals (L III: −24%, $p = 0.031$; L V: −22%, $p = 0.032$). However, such an effect was not seen in animals from enriched rearing conditions (ER-MA vs. ER-Sal). Thus, bouton densities were reduced in the IR-MA group (L III: −38%, $p < 0.001$; L V: −33%, $p = 0.001$) compared to ER-Sal animals (cf. Fig. 2A).

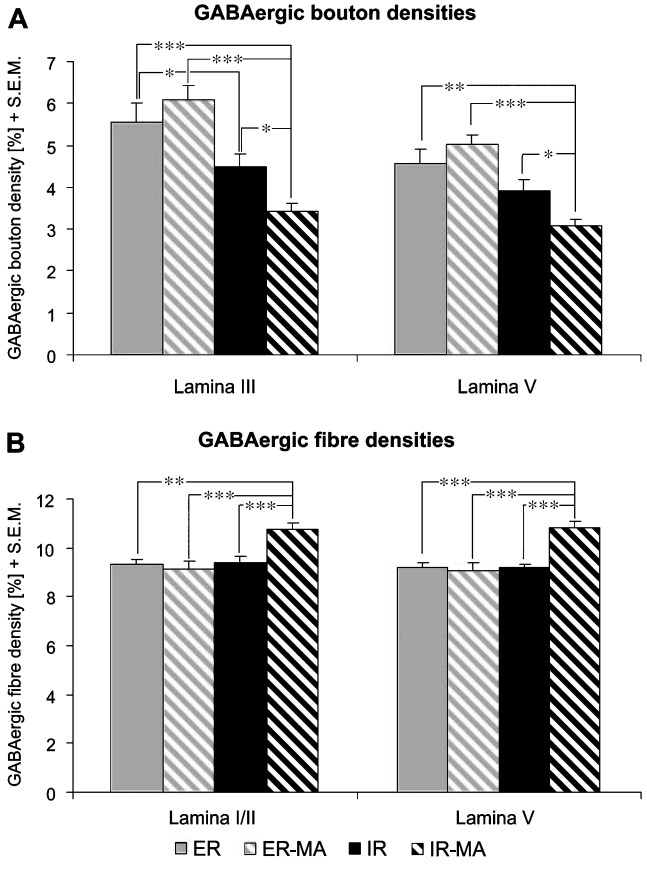


Fig. 2. GABAergic bouton (**A**) and fibre densities (**B**) in the analysed layers of the PFC of gerbils from enriched (*ER*) and impoverished rearing (*IR*) conditions treated with either methamphetamine (*MA*) or saline given by means + standard error (*S.E.M.*). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

### *GABAergic fibre densities*

A factorial ANOVA identified a significant interaction of treatment and rearing conditions in both layer V [$F(1,30) = 13.07$, $p = 0.001$] and layers I/II [$F(1,30) = 9.8844$, $p = 0.004$]. *Post-hoc* Newman-Keuls tests revealed a significant increase in layer I/II fibre density of IR-MA animals (+15, +16, +18%; all $p < 0.001$) compared to IR-Sal, ER-Sal, and ER-MA animals, respectively. A similar increase in GABAergic fibre density was found in layer V (+17 to +19%) of the IR-MA group, compared to IR-Sal, ER-Sal, and ER-MA animals [all $p < 0.001$, except ER-Sal: $p = 0.0012$ (cf. Fig. 2B)].

## Discussion

We have demonstrated that a single early MA intoxication combined with impoverished rearing (IR) significantly reduces the densitiy of GABAergic boutons that surround layers III and V pyramidal neurons in the prefrontal cortex of the Mongolian gerbil, whereas the overall GABAergic fibre density in layers I/II and V is increased compared to control animals.

### *Early MA intoxication and impoverished rearing as a model for schizophrenia*

The single early high dose of MA on PD 14 in combination with IR used in the current study is effective to disturb normal postnatal development of the dopaminergic system, by triggering a restraint of the maturation of dopamine fibres in the prefrontal cortex and the nucleus accumbens (Dawirs et al., 1994; Neddens et al., 2001, 2002) as well as a concomitant excessive maturation in several amygdaloid

nuclei and the entorhinal cortex (Busche et al., 2004). A similar pattern of cortical-subcortical dopaminergic imbalance has also been observed in the schizophrenic brain (Laruelle et al., 2003; Abi-Dargham, 2004). Early MA treatment additionally impairs PFC-related abilities and behaviours, such as working memory and spatial learning (Dawirs et al., 1996; Williams et al., 2002). Again, deficits in working memory are well known characteristics of schizophrenic patients (Goldman-Rakic, 1995; Lewis and Anderson, 1995). Furthermore, the early drug challenge in combination with IR leads to a miswiring of prefrontal efferents (Bagorda et al., 2006), in accordance with the dysconnection hypothesis of schizophrenia (Weinberger and Lipska, 1995).

Taken together, our approach using combined early MA intoxication and IR leads to several morphological changes in neuroanatomical brain networks and impairs cognitive functions, resembling some of the changes and deficits seen in schizophrenic individuals, and thus provides a potential animal model of the disease. The present study reveals that an early MA intoxication additionally decreases GABAergic boutons that surround pyramidal cell somata, indicating a loss of somatic synapses (Karube et al., 2004) and a concomitant increase in overall GABAergic fibre density in the medial prefrontal cortex. These findings raise the possibility that the local prefrontal cortical inhibitory network may be functionally disorganised.

### *The role of somatic inhibition*

The distinct classes of GABAergic synapses play differential roles in regulating the activity of pyramidal neurons. The majority of GABAergic synapses terminate on dendrites or spines of the postsynaptic cells (Beaulieu and Somogyi, 1990; Beaulieu et al., 1992; Nitsch and Riesenberg, 1995), thus they are likely to control the efficacy and plasticity of excitatory inputs onto the postsynaptic target (Miles et al., 1996; Tamas et al., 1997, 2003). However, somatic inhibition is thought to be particularly effective in controlling the output of pyramidal neurons and, importantly, has been implicated to synchronize activity patterns of whole pyramidal populations (Miles et al., 1996; Tamas et al., 1997, 2000; Gibson et al., 1999; Freund, 2003; Klausberger et al., 2003). Such oscillatory synchronization is further believed to create the necessary temporal and spatial frame for prefrontal functions such as working memory (Constantinidis et al., 2002; Lewis et al., 2005). In addition, cortical interneurons, in particular 'fast-spiking' neurons, have been shown to play an important role in shaping receptive fields as well as spatial memory fields (Jones, 1993; Rao et al., 1999, 2000). GABAergic somatic inhibition is thus exceptionally essential for the maintenance of cortical and cognitive functions and one is tempted to suggest that a decrease in this type of GABAergic inhibition and the potential subsequent deficit in synchronization might contribute to reported working memory dysfunction in schizophrenia (Lewis et al., 2005) and our animal model (Dawirs et al., 1996). In fact, post-mortem studies of schizophrenic patients reveal fewer GABAergic synapses on cortical pyramidal cells (Blum and Mann, 2002) and in addition, recent neurophysiological studies have shown, that some cognitive dysfunctions in schizophrenia are associated with an abnormal neural synchronization (Spencer et al., 2003, 2004; Lee et al., 2003; Uhlhaas et al., 2006).

### *The maturation and shift of GABAergic inhibition*

It is well documented that GABA exhibits depolarizing effects at early postnatal stages (Cherubini et al., 1991; Ganguly et al., 2001; Ben-Ari, 2002), due to an inverted electrochemical gradient for $Cl^-$ in neonatal neurons (Ben-Ari, 2002). The shift from an excitatory to an inhibitory transmitter is assumed to coincide with the first expression of PV in cortical interneurons (Berger et al., 1999) and the calcium-binding protein is therefore considered a marker of functional maturity of the neuron (Seto-Ohshima et al., 1990; Solbach and Celio, 1991). In the gerbil mPFC, the first PV-immunoreactive cells appear around PD 14 (unpublished data), that is, at the time of the MA challenge. Interestingly, the maturation of GABAergic synapses in general proceeds until early adulthood (Huang et al., 1999; Morales et al., 2002; Chattopadhyaya et al., 2004; Lewis et al., 2005), and in that, every subpopulation of presynaptic terminals exhibits a particular developmental pattern (Lewis et al., 2005). Therefore, the ability to synchronize pyramidal cell activity is assumed to be in substantial flux until adulthood (Lewis et al., 2005). Although the proliferation and formation of the typical perisomatic basket terminal seems to be a largely stereotypical process, it is additionally also dependent on neuronal activity within cortical circuits (Marty et al., 2000; Chattopadhyaya et al., 2004).

GABAergic interneurons receive direct dopaminergic input (Goldman-Rakic et al., 1989; Verney et al., 1990; Benes et al., 1993), with D1 and D2 receptor types being most abundantly expressed by PV-neurons (Le Moine and Gaspar, 1998). Dopamine modulates cortical GABA cells; both inhibitory (Retaux et al., 1991) and excitatory (Gorelova et al., 2002) effects on fast-spiking interneurons have been reported. The omission of prefrontal dopaminergic afferent fibres by an early MA challenge (Dawirs et al., 1994;

Neddens et al., 2001) might therefore induce significant alterations in the local GABAergic networks.

The dopaminergic afferents to the prefrontal cortex show a prolonged maturation (Kalsbeek et al., 1988; Dawirs et al., 1993; Rosenberg and Lewis, 1995) and continue to form synapses on GABAergic interneurons until early adulthood (Benes et al., 1996b). Pyramidal neurons are also directly innervated by dopaminergic terminals (Jay et al., 1995; Davidoff and Benes, 1998) which demonstrates the rather complex capacity of dopamine to directly and indirectly regulate the firing pattern of pyramidal neurons. By early MA intoxication we induce a restraint of the maturation of prefrontal dopaminergic afferents, which triggers reactive neuroplastic adaptation of the local network. Anatomical data suggest that pyramidal cells may adapt by increasing their dendritic range and their spine density (Blaesing et al., 2001). Our current findings indicate an increase of GABAergic fibre density, which is in line with an earlier study using electron-microscopy that already revealed an increase in non-somatic GABAergic terminals (Nossoll et al., 1997). Therefore, we find it tempting to suggest that an early MA challenge, by acutely reducing the density of monoaminergic innervation of the PFC, might trigger a reactive shift within the GABAergic networks from somatic to dendritic pyramidal inhibition.

### *GABAergic dysfunction in schizophrenia*

GABAergic dysfunction in schizophrenia has first been proposed by Roberts (1972). Since then, several studies have revealed disturbances of GABAergic networks in schizophrenic patients (for review see Benes and Berretta, 2001) or in animal models of schizophrenia (Cochran et al., 2002, 2003; Keilhoff et al., 2004; Reynolds et al., 2004; Penschuck et al., 2006). A decline in PV-immunoreactive structures, particularly in axon cartridges from chandelier neurons, seems to be one of the most prevalent observations in *post-mortem* brains from schizophrenic individuals (Woo et al., 1998; Pierri et al., 1999; Lewis et al., 1999). Furthermore, the $GABA_A$ receptor density was found to be upregulated at the axon initial segment (Volk et al., 2002) as well as at the cell body of pyramidal neurons (Benes et al., 1996a), possibly compensating for a reduction of inhibitory terminals from chandelier and basket cells (Lewis et al., 2005). In contrast to the alterations in PV-containing neurons, only few studies reported on changes in the subpopulation of CB- or CR-immunopositive cells. Iritani and colleagues (1999) found a fibre disarray from CB-containing cells in the PFC, while Daviss and Lewis (1995) described an increase in the density of CB cells but no change in the CR population in a *post-mortem* study on schizophrenic brains. This would also be in line with our findings, since an increased number of CB cells and an altered fibre pattern are likely to present an elevated GABAergic inhibition of afferent pyramidal parts.

## Conclusion

Here we present evidence for a probable dysfunctional reorganization of GABAergic networks in our potential animal model of schizophrenia. GABAergic interneurons critically contribute to the establishment of complex behaviours by controlling and synchronizing the firing patterns of pyramidal neurons. A weakened or altered inhibition may give rise to a broad array of disturbances in cognitive function, like those seen in schizophrenia (Benes and Berretta, 2001). The current study indicates a potential shift from a strong and powerful somatic inhibition to dendritic inhibition, which might attenuate the GABAergic influence on pyramidal activity and thus lead to an uncontrolled firing or abnormal synchronization. Our data coincide with findings of a reduced GABAergic somatic innervation in individuals with schizophrenia. We suggest that, in our animal model, this change in the GABAergic network is secondary, being triggered by the primary impairment of monoaminergic and namely dopaminergic afferents. Further investigations of the separate subpopulations of GABAergic interneurons in the PFC of gerbils are in process to identify the responsible cell classes for the observed alteration in the GABAergic network.

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