

***BDNF* expression in cat striate cortex is regulated by binocular pattern deprivation**

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Deprivation of patterned visual information, as in early onset congenital cataract patients, results in a severe impairment in global motion perception. Previously we reported a delayed maturation of the peripheral visual field representation in primary visual area 17, based on a 2-D DIGE screen for protein expression changes and *in situ* hybridization for the activity reporter gene *ZIF268*. To corroborate these findings we here explore the binocular pattern deprivation (BD)-regulated expression of brain-derived neurotrophic factor (BDNF), a well-described neurotrophin precipitously regulated by early visual experience. To assess the timing of maturation-related *BDNF* expression we compared the central and the peripheral visual field representations of area 17 of 1, 2, 4 and 6-month-old and adult cats reared under normal visual conditions. To scrutinize the outcome of BD, four different deprivation strategies were compared, including early onset BD from birth and lasting for 2, 4 or 6 months (2BD, 4BD, 6BD), and late onset BD for 2 months upon 2 months of normal vision (2N2BD), as animal models of congenital and delayed onset cataract. During normal cortical development the *BDNF* transcript levels, measured by quantitative RT-PCR, remained stable. Higher *BDNF* mRNA levels were found in central area 17 of 2BD and 6BD animals compared to age-matched controls. In central area 17, the high *BDNF* mRNA levels at the end of the BD period may activate a mechanism by which plastic processes, halted by deprivation, may begin. We here confirm that the peripheral visual field representation of area 17 matures slower than its central counterpart. Only in central area 17 normal visual input upon BD could upregulate *BDNF* mRNA which may lead to a fast activation of local plastic adaptations.

Key words: area 17, binocular deprivation, central visual field representation, refractory period

INTRODUCTION

In the mammalian brain, the widely distributed and extensively studied neurotrophin BDNF (brain-derived neurotrophic factor) is involved in many developmental events, such as survival and differentiation of neurons, synaptogenesis and modifications of synaptic transmission (Cunha et al. 2010). BDNF is involved in several forms of synaptic plasticity (Yoshii and Constantine-Paton 2010). In primary visual cortex (area 17) in particular, BDNF signaling via TrkB (Tropomyosin kinase B) receptors is important for the development of ocular dominance columns (Cabelli et al. 1995 and 1997, Bartkowska et al. 2014), which undergo structural reorganization during the postnatal outgrowth of visual cortex (Keil et al. 2010). BDNF overexpression accelerates inhibitory circuit maturation and results in a premature opening and closure of the critical period of ocular dominance plasticity, which is also shortened in duration (Hanover et al. 1999, Huang et al. 1999). Overexpression of BDNF protein accelerates multiple forms of plasticity in de-

veloping visual cortex (Huang et al. 1999). Blocking normal vision by dark rearing or intraocular injection of tetrodotoxin induces an instant downregulation of *BDNF* mRNA (Castren et al. 1992).

Recently we were able to show that specific *ZIF268* mRNA levels typify the central and peripheral regions of area 17 during normal visual cortex development and also correlate to abnormal development due to binocular visual deprivation (BD) (Laskowska-Macios et al. 2015a). We here hypothesized that the *BDNF* gene expression profiles in BD kittens also mirror the degree of plasticity in these two cortical regions of primary visual cortex during development. In contrast to *ZIF268*, BDNF reacts fast, with downregulation after TTX injections (Lein et al. 2000) permitting to examine its levels at the current situation, in our case the direct effects of a first normal visual experience upon binocular pattern deprivation.

As we previously showed in our *ZIF268* study that the representation of the peripheral visual field develops at a slower rate compared to the central visual field, we hy-

pothesized that *BDNF* expression levels would be differential between the central and peripheral region of area 17, depending on the developmental stage and visual input, and as such indirectly capable of indicating the cortical region with the highest plasticity potential at the end of a BD period. We therefore applied quantitative real time PCR to measure and compare the *BDNF* mRNA levels in the central and peripheral visual field representations of primary visual area 17 in the context of normal and BD-regulated cortical development. Since *BDNF* mRNA expression is regulated by visual experience within 1 hour of light stimulation (Castren et al. 1992), similarly to *ZIF268* mRNA expression, we could use the same tissue as in the previous paper describing the *ZIF268* mRNA developmental expression patterns.

MATERIALS AND METHODS

Animals

All experiments were carried out in accordance with the European Parliament and the Council Directive of September 22th 2010 (2010/63/EU) and were approved by the First Ethical Commission in Warsaw (Poland). The cats were raised under a daily photoperiod of 12 h light and 12 h darkness with water and food *ad libitum* (Nencki Institute, Warsaw, Poland). All efforts were made to minimize animal discomfort. The cat brain material for this investigation has

already been used in parallel in another studies (Laskowska-Macios et al. 2015a, b, the contralateral hemisphere).

To investigate development-related *BDNF* mRNA expression, cats with normal visual experience were analyzed (n=15): kittens of 1 (1N, n=3), 2 (2N, n=3), 4 (4N, n=3), or 6 months (6N, n=3), and adult cats of 1-2 years (n=3). Binocular deprivation from pattern vision (n=11) was achieved by having the cats wearing double thickness linen masks covering their eyes (Burnat and Zernicki, 1997). This procedure reduces retinal illumination to a similar level as lid suturing, but is less traumatic (Kossut et al. 1978). For deprivation from birth, in the early onset groups, the masks were put on from eyelid opening (P8) and removed at the age of 2 (2BD, n=2), 4 (4BD, n=3) or 6 months (6BD, n=3). Animals from the delayed onset group were deprived for the third and fourth month of life after two initial months of normal visual input (2N2BD, n=3). The masks were replaced daily in a normally lit animal facility room where the kittens lived. The changing procedure lasted no longer than 1 minute per day for each cat, which is not sufficient to maintain normal vision (Schwarzkopf et al. 2007, Mitchell et al. 2011) and allowed constant adjustment of the size of the masks to the growing head. The kittens remained with their mothers until the age of seven weeks, and then they were moved to large cages (3×2.6×2.35 m) where they played and interacted freely (Zapasnik and Burnat, 2013).

On the day of euthanasia, all animals were maintained overnight in total darkness followed by 1-hour light stimulation upon removal of the hoods, during this 1-hour light stimulation cats were placed in a well-lit room. After an overdose of sodium pentobarbital (Nembutal, 60 mg/kg) brains were dissected, instantly frozen by immersion in dry cooled isopentane (Merck Eurolab) and stored at -70°C. For each experimental condition we collected tissue from two regions of interest, the central and the peripheral region of area 17, from one 200 µm-thick coronal section at Horsley-Clarke level posterior 6.0, which both are placed within binocular zone (Tusa et al. 1978, 5–10 deg and 15–20 deg lateral from *area centralis*, respectively, Laskowska-Macios et al. 2015a, Fig. 1).

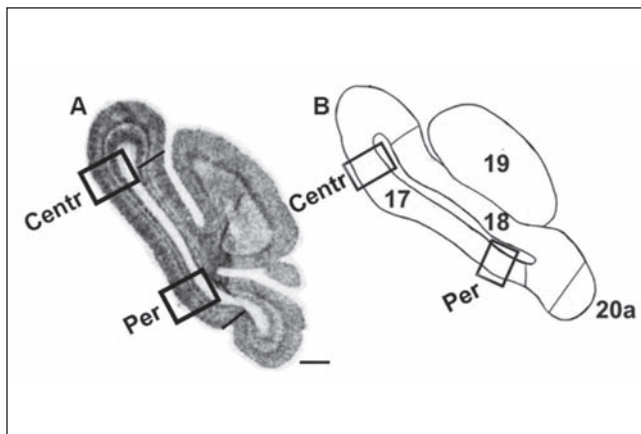


Fig. 1. Illustration of the regions of interest related to tissue sampling in primary area 17. A. Photograph of *in situ* hybridization detection of *ZIF268* mRNA in area 17 of a 2-month old normal kitten in a coronal section (P6.0) adjacent to the one used for tissue sampling for RT-PCR measurements of *BDNF* mRNA levels. B. Relevant level of the Rosenquist retinotopic map (1985) at Horsley-Clarke coordinate posterior 6 (P6.0), confirming the anatomical position of areas 17–20a. Black lines demarcate the areal borders of area 17. Brain tissue was collected from the central and peripheral visual field representation (black boxes), which are placed within the binocular zone (5–10 deg and 15–20 deg laterally from the area centralis, respectively, Laskowska-Macios et al. 2015a). Scale bar: 1 mm.

Quantitative real-time polymerase chain reaction (RT-PCR)

All quantitative RT-PCR experiments have been done as described by Cnops et al. (2007). The RNA extraction was performed with the RNeasy Plus Universal Mini Kit (Qiagen) according to the manufacturer's instructions. After spectrophotometric measurements of RNA content and purity (NanoDrop instrument), RNA samples of identical quantity were reverse transcribed with QuantiTec Reverse Transcription Kit for RT-qPCR (Qiagen) according to the

manufacturer's instructions. For the real-time PCR experiments, we used primers and TaqMan probes (Applied Biosystems), which were designed with the Primer Express program (Applied Biosystems), based on the cat *BDNF* sequence (*Felis catus* brain-derived neurotrophic factor (*BDNF*), mRNA transcript, ref number: NM_001009828.1, NCBI pubmed; Forward primer: 5'-cggtcaccgtccttgaaaa-3'; Reverse primer: 5'-ggattgcacttggtctcgtagaa-3'; and TaqMan probe: 5'-tcctgtatcgaaaggccaactgaagc-3') or cat *GAPDH* sequence (Access. no. AB038241; Forward primer: 5'-tggaaagcccatcaccatct3-'; Reverse primer: 5'-caacatactcagcaccagcatca-3'; and TaqMan probe: 5'-ccaggagcgagatcccgcca-3'). The cDNAs were analyzed by PCR apparatus with the 7500 Real-Time PCR System (Applied Biosystems) in a 25- μ l reaction of 1x Absolute QPCR Mix (Westburg, Leusden, The Netherlands) with primers at final concentration of 300 nM and probes of 200 nM. Serial dilutions of control cDNA for generating standard curves were run in duplicate for each gene, whereas target samples were run in triplicate on the same well plate under the standard amplification settings: 2 \times 50°C for 2 min, 1 \times 95°C for 15 min, 40 \times 95°C for 15 s, and 60°C for 1 min.

To compare samples between different runs, we included a reference control in every well-plate (mix of all samples 1:1 μ g cDNA). Data were expressed relative to this reference control (Wong and Medrano 2005). Analysis was carried out using ABI Prism 7500 SDS software. *BDNF* quantities were normalized to the endogenous control *GAPDH* to account for variability in initial mRNA concentrations and differences in reverse transcription efficiency. The relative amount of transcript was quantified by the comparative cycle threshold (Ct) method: Ct values ranged for *BDNF* between (22–30) and for the reference gene between (21–30), the number of cycles carried out was 40.

To investigate the effect of group of animals and region of area 17 on *BDNF* expression the statistical analysis was performed using a nested-design ANOVA model to investigate the effects of group and region nested in cat by means of data analysis software system STATISTICA version 10 (Pavlidis 2003, as before in Laskowska-Macios et al. 2015a). There was a significant effect of interaction between both factors (group and region, $F=2.87$, $df=55$, $P=0.027$). *Post hoc* test was carried using the Tukey HSD method, $P=0.05$.

RESULTS

During normal development the visual cortex showed stable *BDNF* mRNA expression, with hardly any significant differences between central and peripheral visual field representations for any of the ages tested (Fig. 2a and b, white bars). Only 1N animals showed significantly higher levels as compared with the 4N group, and only within the peripheral visual field representation ($p=0.02$).

In BD kittens, higher *BDNF* mRNA expression as compared to age-matched controls was observed in the central visual field representation of 2BD and 6BD animals (Fig. 2a, indicated by #, $p=0.0002$ and $p=0.001$, respectively). In the peripheral visual field representation none of the BD groups differed from age-matched controls (Fig. 2b). However some differences in *BDNF* expression between BD groups were observed depending on age and timing of the BD period. In the central visual field representation *BDNF* expression was higher in 2BD animals as compared to 4BD and 2N2BD animals ($p=0.007$ and $p=0.0006$, respectively). Similarly, it was also higher in 6BD animals as compared to 2N2BD (Fig. 2a, $p=0.003$). In the peripheral visual field representation the *BDNF* signal in the 2N2BD group did not differ from age-matched 4BD animals and was lower compared to 2BD and 6BD (Fig. 2b, $p=0.008$ and $p=0.003$ respectively).

DISCUSSION

Normal development

We observed rather stable *BDNF* mRNA expression levels in animals with normal visual experience. Importantly, *BDNF* protein is rapidly regulated in visual cortex by visual input during development as well as in adulthood (Bozzi et al. 1995, Rossi et al. 1999) making its protein and

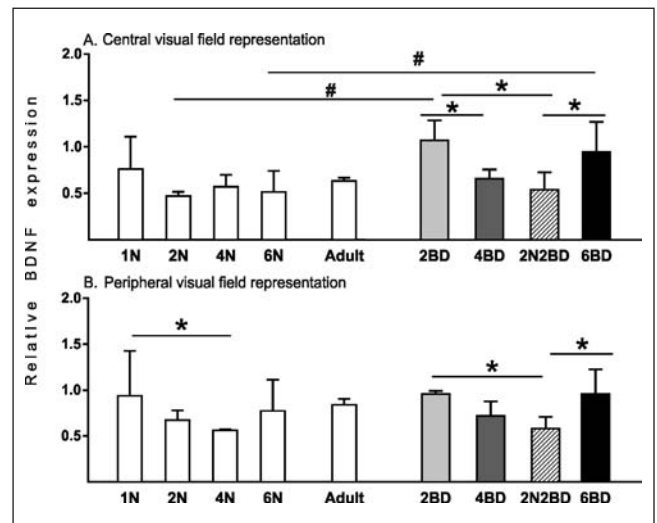


Fig. 2. The effect of age on the *BDNF* mRNA expression levels in area 17 of normal and deprived cats. A. Central visual field representation. B. Peripheral visual field representation. *BDNF* mRNA expression in normal cats (white bars) and BD cats (grey/black bars). Asterisks above bars denote significant differences ($p<0.05$) for a given region between age groups. Differences between BD groups and age-matched controls are indicated by # $p<0.05$. Note the higher *BDNF* mRNA levels in the central region of 2BD and 6BD animals, as compared to age-matched controls. Results are means with \pm SD.

messenger RNA perfect tools for mapping visually-driven activity. In contrast to the previously described early developmental upregulation of *ZIF268* mRNA expression (Laskowska-Macios et al. 2015a), here we did not observe any marked changes in the *BDNF* mRNA levels that could relate to specific stages of normal cortical development. The developmental increase in *BDNF* expression in area 17 in kittens younger than 1 month was previously described by Lein and Shatz (2000) using *in situ* hybridization to probe visual cortex. Also in mice reared in an enriched environment *BDNF* protein levels are enhanced very precociously, at a very early age, namely at P7 in the visual cortex (Cancedda et al. 2004). In rat, the developmental increase in the percentage of cells containing *BDNF* protein was shown to include both pyramidal and parvalbumin-positive neurons (Tropea et al. 2001). This is not surprising since *BDNF* signaling is involved both in the maturation of excitatory synapses as well as cortical inhibition (for review see Yoshii and Constantine-Paton, 2010). Our recent proteomic study, performed on the same brain tissue of the same age conditions, revealed distinct expression profiles in 1 month kittens for protein markers of inhibitory neurons including *GAD67*, *GAD65* and the parvalbumin interneuron marker *CRMP4* (Laskowska-Macios et al. 2015b, Cnops et al. 2008), again indicating that the balance between cortical inhibition and excitation is established during the critical period for ocular dominance formation, in cat at its peak at 1 month of postnatal life (reviewed by Morishita and Hensch, 2008). Several levels of regulation of *BDNF*, including proteolytic processing and the use of distinct receptors and signaling cascades may explain how this neurotrophin exerts so many different functions. Next to alternative splicing, also the production of multiple transcripts, based on alternative promoter use and transcriptional terminations, even in a cell specific way, is yet another level of *BDNF* regulation (Liu et al. 2005 and 2006, Rousseaud et al. 2015).

The effect of binocular deprivation

To our knowledge *BDNF* expression has never been investigated neither under BD nor after 1-hour light stimulation following a BD period. Although we are aware of limitations of the statistical analysis of small samples, like in the small 2BD group ($n=2$), the analysis with nested-design ANOVA model that we performed allowed us to show for central area 17, after one-hour of light stimulation, an upregulation of *BDNF* expression in the 2BD and 6BD groups as compared to age-matched controls. These results are surprising in the context of the previous analysis of *ZIF268* expression levels that showed a clear age-dependent decrease from 2BD to 6BD, together with an upregulation in all BD groups as compared to age-matched controls (Las-

kowska-Macios et al. 2015a). Thus based on our *ZIF268* findings, we assumed the 2BD and 4BD conditions to have more capacity for plastic changes to compensate for the deprivation period than 6BD and 2N2BD groups. This notion was supported by the behavioral studies showing that adult 6BD cats and 2N2BD, in contrast to the 2BD condition, showed impairments for motion perception typifying peripheral processing, but not for form perception characterizing central visual processing (Zapasnik and Burnat 2013, Burnat et al. 2002, 2005).

The effect of visual experience on the *BDNF* expression levels was previously only examined in dark reared animals, without light stimulation following the dark rearing period. Most likely, dark rearing decreases *Bdnf* mRNA in rat visual cortex during early development and in adulthood (Castren et al. 1992, Pollock et al. 2001, Pollock and Frost 2003). Also the cellular *BDNF* immunolabeling is decreased in visual cortex of dark reared rats (Tropea et al. 2001). *BDNF* protein disappears from dendrites and remains only in cell somata of dark reared animals. Essential to understanding our findings, 2 hours of light exposure restores dendritic *Bdnf* labeling in dark reared animals (Tropea et al. 2001), supporting the role of *BDNF* signaling in regulating dendritic arborization in fast response to visual experience. In adult rats exposure to light after darkness also restored high *Bdnf* expression (Castren et al. 1992).

Possibly, the way in which *BDNF* is regulated in BD animals may be explained by the refractory period hypothesis, which postulates an existence of a period between early postnatal life and adulthood, near the critical period offset, when the inhibitory synaptic transmission and ocular dominance plasticity cannot be rejuvenated by dark rearing (Huang et al. 2010). Therefore, the lack of an elevated *BDNF* signal in the 2N2BD and 4BD conditions may indicate an existence of such a refractory period at the age of 4 months in kittens. The visual cortex of 2BD animals may still be at the early stage of development when ocular dominance plasticity is highest, as in 1-month-old kittens (Hubel and Wiesel 1970, Cynader and Mitchell 1980, Daw et al. 1999), which may account for the higher *BDNF* expression in this group. The higher *BDNF* mRNA expression level in the central region of 6BD animals as compared to age-matched controls supports this refractory period hypothesis, since the high *BDNF* levels may activate a mechanism by which normal development is restored faster in central than in peripheral regions. This is in line with role of *BDNF* in mediating plasticity and maturation of cortical inhibitory circuitry described by Huang and colleagues (1999). In fact, our previous *ZIF268* expression analysis showed that the development of the peripheral region of area 17 may be more delayed than the central region due to BD and perhaps this is the reason why we did not observe changes in *BDNF* expression in BD-related peripheral area 17 samples at the analyzed ages as compared to age-matched controls

(Laskowska-Macios et al. 2015a). In line with a recent review by Burnat (2015) justifying the possibility to halt the maturation of visual peripheries relatively long and easy, we speculate that the peripheral region of the BD animals is not mature enough to show the typical upregulation of *BDNF*, or else remains immature for life due to BD induced adaptations.

BDNF overexpression results in a premature opening and closure of the critical period for ocular dominance plasticity (Hanover et al. 1999, Huang et al. 1999) and was shown to rescue the visual cortex from the maturational delay effect of dark rearing (Gianfranceschi et al. 2003). Also, overexpression of the *BDNF* downstream effector H-Ras was shown to accelerate different forms of plasticity in developing visual cortex (Kaneko et al. 2010). Thus, in central area 17, the high *BDNF* levels in the 2BD and 6BD groups induced by the 1-hour light stimulation at the end of the BD period may activate a mechanism by which normal development is restored faster than in peripheral area 17, due to the important role of *BDNF* signaling in mediating plasticity and maturation of inhibitory innervations (Huang et al. 1999).

In conclusion we propose that due to the upregulation of *BDNF* mRNA in the central visual field representations of 2BD and 6BD kittens, *BDNF* signaling mediates fast plasticity processes after restoration of normal visual input. A further analysis of *BDNF* signaling effectors in 2BD and 6BD kittens after several hours or days of normal visual input will be needed to verify this hypothesis. Also a more detailed investigation is needed to shed light on the role of potentially different biologically active isoforms of *BDNF* that interact via different receptors expressed by neurons and glia (Saiepour et al. 2015, Kowiański et al. 2017) to decipher the exact contribution of *BDNF* signaling to visual cortex maturation upon restoration of vision.

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