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Research Report

Therapeutic effects of a restraint procedure on posttraumatic place learning in fimbria-fornix transected rats

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ABSTRACT

Restraint procedures have been shown to influence the neural processes in the brain (dendritic changes or changes in the expression of neurotrophines, etc.) as well as to alter the behavioural performance. While many report deleterious effects of this procedure in normal animals, there are also indications of positive effects in the context of brain injury. In order to address the issue from the perspective of functional posttraumatic recovery, we studied 6 experimental groups of rats—3 groups undergoing a fimbria-fornix transection, and 3 groups remaining neurally intact. Within the lesioned and intact groups, respectively, one group of animals was subjected to an 8-day long restraint procedure (2 h daily) that ended immediately prior to the infliction of trauma; another group was subjected to the same procedure starting immediately after the infliction of trauma; and one group was not subjected to the restraint procedure at all. After a brief period of postoperative pause, the animals were tested on their acquisition of an 8-arm radial maze based place learning task and the effects of the restraint procedure on the task acquisition were evaluated. The results show that within the neurally intact groups, the administration of this procedure had no effect at all. However, the lesioned groups that were subjected to the restraint procedure showed significantly improved acquisition of the studied task compared to the lesioned animals that did not undergo the restraint procedure. The improved task performance suggests a therapeutic effect of this manipulation on the functional recovery after a mechanical trauma.

1. Introduction

Every type of injury to the brain initiates a multitude of neural processes that are likely to influence the posttraumatic plastic reorganization of the brain—and thereby potentially the outcome of subsequent rehabilitation training. Posttraumatic functional outcome can be influenced by, for instance, the immediate pretraumatic and/or posttraumatic activity within endocrine (Grasso et al., 2004; Stein, 2005), neurotransmitter (Barbay et al., 2006; M'Harzi et al., 1988) and neurotrophic (Radecki et al., 2005) systems—all of which may respond to various types of intense activity and/or experience (e.g. Harvey et al., 2006; Murakami et al., 2005; Shansky et al., 2006; Vaynman et al., 2004).

This study utilized the restraint procedure as experimental paradigm. During such a procedure the animal is placed in a wire mesh restrainer, plastic tube or box that effectively restrains its mobility. The level of immobilization varies from a complete

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the fibres of this bundle remained intact. Fig. 1 shows that there were only minor variations between the extents of lesion in individual animals. Likewise, the lesions of the fimbria-fornix transected groups that were subjected to the restraint procedure (either preoperatively or postoperatively) were of similar extent as the lesions of the fimbria-fornix transected group not exposed to restraint procedure.

2.2. *Changes in body weights*

The results regarding changes in body weights are illustrated in Fig. 2. The initial analysis of the changes in body weight by MANOVA revealed no significant effects of neither lesion ($F=0.716$; $p=0.401$) nor interaction between the lesion and the exposure to restraint procedure ($F=1.739$; $p=0.193$). The only significant effects were seen on the parameter restraint procedure ($F=13.665$; $p<0.001$). The comparison of mean percentage values reflecting the change in body weights within the Restraint and No Restraint subjects revealed significant differences ($p<0.001$).

2.3. *Behaviour*

The behavioural results are illustrated in Fig. 3. The overall MANOVA for all 30 sessions revealed significant effects of lesion ($F=1891.7$ and $F=840.9$ for total number of errors, and the number of distal errors, respectively, in both cases $p<0.001$), the restraint procedure ($F=43.1$ and $F=31.3$ for total number of errors, and the number of distal errors, respectively, in both cases $p<0.001$), session number ($F=87.2$; $p<0.001$ for total number of errors and $F=80.9$; $p<0.001$ for the number of distal errors), and interaction between lesion and restraint procedure on both the behavioural parameters ($F=31.3$; $p<0.001$ for total number of errors, and $F=21.8$; $p<0.001$ for the number of distal errors). *t*-test comparisons between the Sham/No Restraint group to the FF/No Restraint group, the

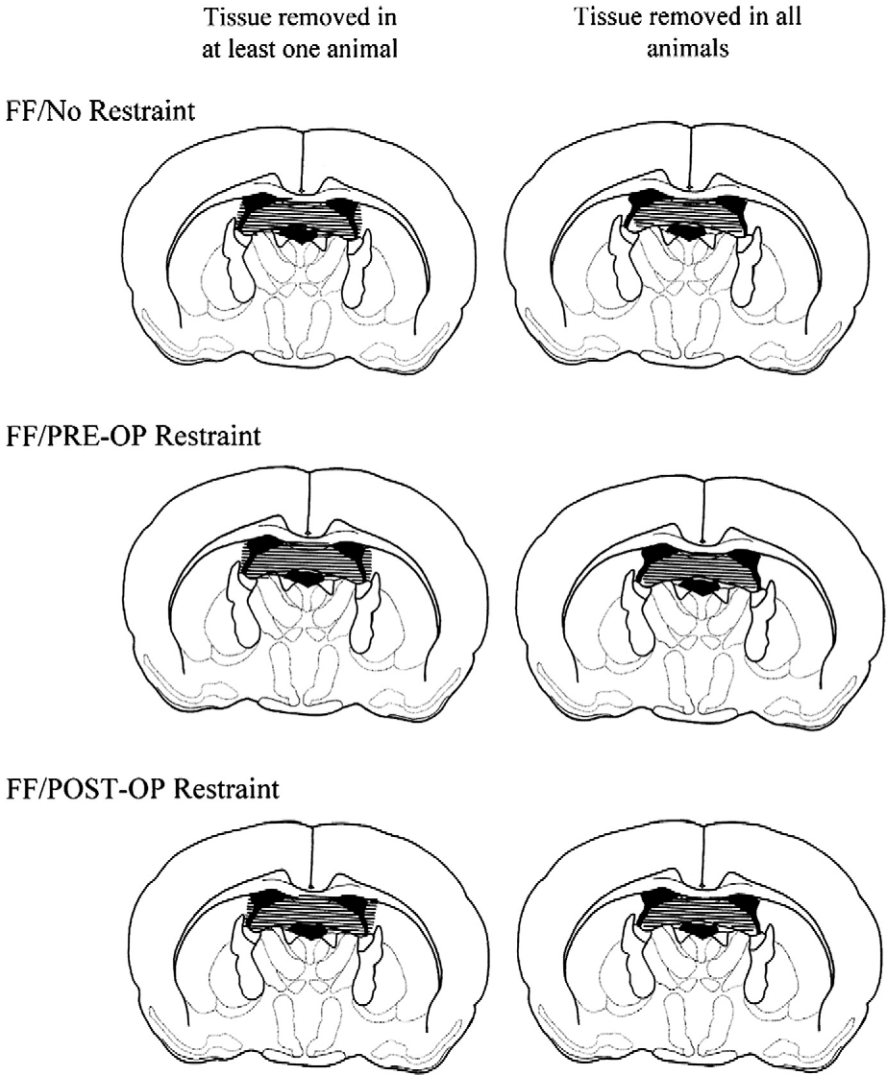

Fig. 1 – Illustrations of the lesions of the three groups that were subjected to the fimbria-fornix transection: the lesioned group not exposed to any restraint procedure (FF/No Restraint), the lesioned group restrained preoperatively (FF/PRE-OP Restraint), and the lesioned group restrained postoperatively (FF/POST-OP Restraint). The horizontal stripes indicate the lesioned area. The diagrams show level 7.70 mm in front of the interaural line (Paxinos and Watson, 1986).

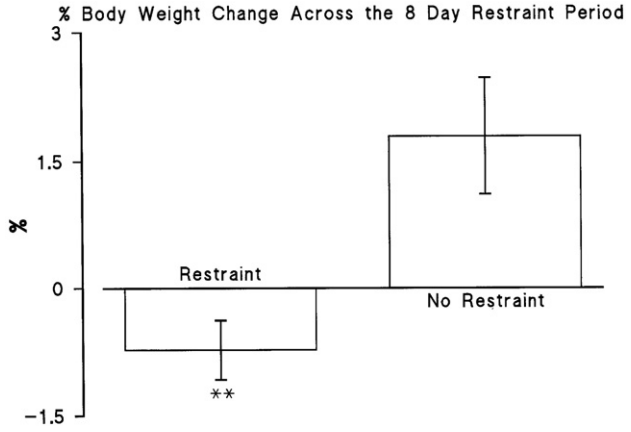

Fig. 2 – Percentage change in body weight during the administration of the restraint procedure. 'Restraint' includes all animals that were subjected to the restraint procedure, 'No Restraint' includes all animals not subjected to the restraint procedure. Values are given as means with S.E.M. **: significantly ($p<0.01$) different from the No Restraint group. The '0' level represents the body weight prior to restraint procedure. Negative values indicate weight loss, while positive values indicate weight gain.

Sham/PRE-OP Restraint group to the FF/PRE-OP Restraint group and the Sham/POST-OP Restraint group to the FF/POST-OP Restraint group all reached $p<0.001$ level of significance with respect to both examined parameters.

Separate analysis was performed for the first ten sessions (sessions 1–10) and the last ten sessions (sessions 21–30). MANOVA during the first 10 sessions showed significant effects of lesion ($F=617.2$; $p<0.001$ for total number of errors and $F=299.9$; $p<0.001$ for the number of distal errors), restraint procedure ($F=4.7$; $p<0.01$ for the number of total errors and $F=7.4$; $p<0.001$ for the number of distal errors), and session number ($F=54.5$; $p<0.001$ for the total number of errors, and $F=42.01$; $p<0.001$ for the number of distal errors). Furthermore, there was a significant interaction between the session number and lesion ($F=34.9$; $p<0.001$ regarding the total number of errors, and $F=16.9$; $p<0.001$ regarding the number of distal errors) and a significant interaction between the lesion and the restraint procedure on the parameter number of distal errors ($F=3.4$; $p<0.05$). The group comparisons uncovered expected lesion effects between the individual groups of fimbria-fornix transected animals and their respective sham operated controls — the lesioned groups demonstrated a significantly ($p<0.001$) impaired task performance reflected in higher number of both the total and the distal errors. MANOVA performed for the last ten sessions (sessions 21–30) revealed significant effects of lesion on both the behavioural parameters ($F=272.5$; $p<0.001$ for total number of errors and $F=108.0$; $p<0.001$ for the number of distal errors), restraint procedure ($F=29.4$; $p<0.001$ for the number of total errors and $F=31.1$; $p<0.001$ for the number of distal errors), and session number ($F=2.2$; $p<0.05$ for the total number of errors). Furthermore, there was a significant interaction between the session number and lesion ($F=2.3$; $p<0.05$ on the total number of errors) and a significant interaction between the lesion and the restraint procedure ($F=31.1$; $p<0.001$ regarding the parameter total number of errors and $F=32.0$; $p<0.001$ regarding the parameter number of distal errors).

Administration of the restraint procedure for 8 consecutive days either preoperatively or postoperatively had no significant effects in the sham operated control groups (regardless of whether analyzing all 30 sessions or first and last 10 sessions, respectively). *t*-test comparison examining the effect of preoperative restraint stress relative to No Restraint across 30 sessions reached levels of $p=0.693$ for total number of errors, $p=0.702$ for the number of distal errors, while the administration of the postoperative restraint led to levels of $p=0.549$ for the total number of errors and $p=0.529$ for the number of distal errors. Likewise, there was no significant effect when comparing the preoperative restraint to the postoperative restraint in

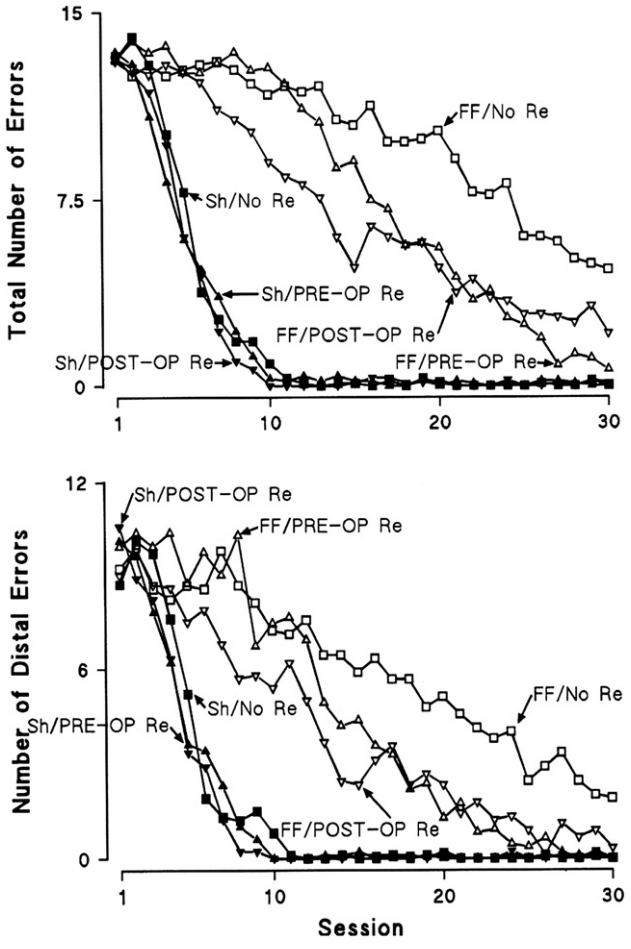

Fig. 3 – Performance of the six experimental groups during the 30 sessions of task acquisition. Black symbols: the task acquisition of the sham operated control groups; open symbols: the task acquisition of the fimbria-fornix transected groups. Black square: Sham/No Restraint; black upwards pointing triangle: Sham/PRE-OP Restraint; and the black downwards pointing triangle: Sham/POST-OP Restraint. Open square: FF/No Restraint; open upwards pointing triangle: FF/PRE-OP Restraint; and the open downwards pointing triangle: FF/POST-OP Restraint. Significant group differences are given in the Results section. Values are given as means.

restraint in the lesioned groups revealed that the postoperatively restrained animals had significantly lower number of total as well as distal errors.

Likewise, analysis of the last ten sessions (sessions 21–30) revealed significant effects of lesion, restraint procedure, and session number on both of the behavioural parameters. Not surprisingly, the lesion effects were still pronounced even during the last ten sessions. Comparing the behavioural performance of the fimbria-fornix transected groups (across the restraint groups) with the performance of the sham operated animals revealed that the lesioned groups had significantly higher number of both total and distal errors. However, there was still a significant performance-enhancing effect of the preoperative and postoperative restraint procedure, respectively, in the lesioned animals compared to the lesioned, not restrained animals. The animals exposed to the preoperative or postoperative restraint, had significantly lower number of total as well as distal errors. A direct comparison of the effects of preoperative restraint with the effects of postoperative restraint in the fimbria-fornix operated groups did not reveal a significant effect on the parameter total number of errors ($p=0.071$), however the lesioned, postoperatively restrained group had a tendency to have a slightly higher number of errors. This tendency reached significance ($p<0.05$) in the number of distal errors.

3.2.1. *The therapeutic effects of the restraint procedure*

The present study demonstrated – in contradiction to what could have been expected based on the literature – an enhanced posttraumatic performance on an allocentric place learning task. The exposure to 2 h of a restraint procedure for 8 days either prior to or after the infliction of brain injury led to an improved acquisition of the task in the lesioned groups. Hence, the administration of the restraint had a recovery-enhancing effect.

The studies examining the behavioural effects of restraint procedure have more often than not demonstrated functional impairments in the restraint-exposed individuals (Abidin et al., 2004; Conrad et al., 1996, 2004; Kitraki et al., 2004; Luine et al., 1994a; Sandi et al., 2003). However, it needs to be remembered that the absolute majority of these studies has been performed on non-lesioned animals. The presence of brain injury dramatically changes the homeostasis of the entire system, leading to activation of various endogenous pathways (including gene expression) as well as to lesion-induced remodelling of the neural network in attempt to cope with the altered situation (Carmichael, 2006; Carmichael et al., 2005; Dancause et al., 2005; Li and Carmichael, 2006). The relationship between the processes facilitating the neural degeneration and the processes promoting neural repair and recovery is intricately intertwined. The morphological changes that take place in response to brain injury (Bramlett and Dietrich, 2002, 2004; Bramlett et al., 1997; Corbett et al., 2006; Grady et al., 2003; Smith et al., 1997) as well as in response to the restraint stress (Brown et al., 2005; Jackson and Moghaddam, 2006; Liston et al., 2006; Magarinos and McEwen, 1995; Magarinos et al., 1997; Radley et al., 2006; Watanabe et al., 1992) in combination might have provided a more optimal tuning of the neural system for the posttraumatic learning, thus mediating the functional recovery.

The recovery-enhancing changes in neural remodelling of the brain injured individuals induced by the restraint procedure might have included modifications in the gene expression of the neurotrophic factors, in particular factors of the neurotrophine family: brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF). Both up- and down-regulation of BDNF in various brain regions have been demonstrated in response to stress (Franklin and Perrot-Sinal, 2006; Givalois et al., 2001; Marmigere et al., 2003; Murakami et al., 2005; Rage et al., 2002; Scaccianoce et al., 2000; Smith et al., 1995). Interestingly, Radecki et al. (2005) showed that an infusion of BDNF can protect against the immobilization-induced impairments on a water maze based place learning task. At the same time, neurotrophines have been shown to protect against neural degeneration (Canudas et al., 2005) and against apoptotic cell-death following brain injury by inhibiting caspase 3 activation (Kim and Zhao, 2005).

Behavioural stimulation has a direct impact on the neural circuitry and its timing is crucial (Biernaskie et al., 2004; Briones et al., 2006). Early start of a rehabilitative training may lead to an improved functional outcome as well as a reduction of neurodegenerative events (Lippert-Grüner et al., 2007b; Maegele et al., 2005). The latter studies utilized an experimental early rehabilitation model combining an enriched environment, multisensory stimulation and motor training after traumatic brain injury, and demonstrated that such behavioural stimulation was associated with reduced CNS lesion volume and enhanced neuromotor functioning tested up to 30 days post-injury (Lippert-Grüner et al., 2007a). Although the treatment schedule as well as the general experimental design utilized in the current study differed drastically from the one utilized in the above mentioned research, one could imagine that the exposure to the restraint procedure shared at least some of the (potentially crucial) aspects of the early stimulation, thus enhancing the posttraumatic functioning.

It has become an established fact that exposure to stressful experience in general leads to an activation of the catecholaminergic pathways (Anisman and Zacharko, 1986, 1990; Cuadra et al., 1999), and in particular to the activation of central dopaminergic systems (Blanc et al., 1980; Cuadra et al., 1999; Deutch et al., 1985; Gresch et al., 1994; Orsini et al., 2002; Puglisi-Allegra et al., 1991; Ventura et al., 2001). Stress has been shown to have differential effects on the dopaminergic activation in the mesocortical and mesolimbic areas (Abercrombie et al., 1989) with repeatedly reported increase in the medial prefrontal cortex (Abercrombie et al., 1989; Beck and Luine, 1999; Cuadra et al., 1999; Smith et al., 2006). The increased dopaminergic efflux can potentially have beneficial implications in the context of a mechanical injury to the fimbria-fornix. We have previously found that the alternative neural substrate mediating the acquisition of an allocentric place learning task posttraumatically is highly dependent on catecholaminergic, predominantly dopaminergic, contributions—mainly within the prefrontal cortex (Mogensen et al., 2002, 2004a, 2007; Wörtwein et al., 1995). Since the administration of restraint procedure has been shown to elevate the dopamine levels in the prefrontal cortex, it is tempting to speculate that the beneficial effects of restraint seen in the current study were, at least partly, due to the enhanced availability of dopamine in this part of the brain. Such an

explanation would account for the restraint-induced effects in both preoperatively and postoperatively restrained lesion groups. Additionally, it can be mentioned that there are indications that dopaminergic agonists might be used as a pharmacological treatment to supplement rehabilitative therapy following brain injury (Barbay et al., 2006; M'Harzi et al., 1988).

The current data do not offer a further clarification of the obtained results and thus, a more detailed explanation of the restraint-induced therapeutic effects will have to await further experimentation. Only few studies can be cited in support of our results. Luine et al. (1996) showed that chronic stress can lead to a significant enhancement of performance on a spatial working memory task in an 8-arm radial maze 10–13 days post-stress. However, these results were obtained in neurally intact females. Bisagno et al. (2004) showed also in female rats that chronic stress can have a therapeutic effect on object recognition impairments induced by chronic amphetamine treatment and can counteract the anxiogenic effects of amphetamine on spontaneous exploration in an open field. Future studies will hopefully shed light onto the mechanisms mediating the beneficial effects of the currently applied procedure.

4. Experimental procedures

4.1. *Subjects and experimental groups*

All experimental procedures were approved by the Danish National Review Committee for the use of Animal Subjects ("Dyreforsøgstilsynet"). All procedures were in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). Every attempt was made to minimize animal suffering and use as few animals as possible.

Fifty-eight experimentally naive, male Wistar albino rats weighing approximately 300 g at the beginning of the experiment served as subjects. The animals were housed two per cage under controlled conditions of temperature (22±2 °C) and humidity (50±5%). The animal quarters were kept on a 12 h light cycle (on at 7.00 am). Water was always available. All experimental procedures were performed during the light phase. The animals were fed commercial rat chow once daily after training and were maintained at approximately 85% of their ad libitum body weights. The rats were randomly divided into six experimental groups:

Sham surgery group not subjected to any restraint procedure (Sham/No Restraint) (n=10),
Sham surgery group subjected to an 8-day long restraint procedure (2 h daily) immediately prior to the surgery (Sham/PRE-OP Restraint) (n=10),
Sham surgery group subjected to an 8-day long restraint procedure (2 h daily) immediately after the surgery (Sham/POST-OP Restraint) (n=9),
Fimbria-fornix transected group not subjected to any restraint procedure (FF/No Restraint) (n=9).
Fimbria-fornix transected group subjected to an 8-day long restraint procedure (2 h daily) immediately prior to the surgery (FF/PRE-OP Restraint) (n=11), and
Fimbria-fornix transected group subjected to an 8-day long restraint procedure (2 h daily) immediately after the surgery (FF/POST-OP Restraint) (n=9).

4.2. *Apparatus*

4.2.1. *8-arm radial maze*

All training and testing was performed in an open, black, one-unit 8-arm radial maze with 2.7 cm high walls and 9.2 cm wide corridors. The 8 arms radiated equidistantly from a circular central area with a diameter of 50.0 cm. Each arm was 60.0 cm long, and at the end of the arm a circular food well (diameter: 4.8 cm, depth: 2.3 cm) contained the reinforcements in the form of 45 mg food pellets (Precision Food Pellets of Campden Instruments, England). The maze was placed in the middle of a well-lit room, in which no other animals were present during training and testing, and in which a multitude of two- as well as three-dimensional distal cues were available.

4.2.2. *Restraint box*

Locally manufactured restraint boxes made out of hard cardboard were used for the restraint procedure. The boxes allowed complete immobilization of the animals and had the following dimensions: length 17 cm; height 5 cm; and width 5 cm. The boxes were equipped with a closing lid and appropriate openings allowing the animal to breath and move the tail freely. The lid was adjustable which allowed adjustments according to differences in body weight. Once the animal was secured in the restraint box, it was placed in a ventilated room separate from the animal quarters. Control animals were left undisturbed in their cages during the administration of the restraint procedure. In order to monitor the overall effects of the restraint procedure, all animals were weighed immediately prior to every administration of the restraint procedure. Percentage change in body weight (net change in weight across the administration of the restraint procedure×100/body weight at the beginning of the restraint procedure) was calculated for each animal.

4.3. *Behavioural procedures*

Preoperatively, all animals were habituated to the maze and then shaped. The habituation lasted for two sessions. Each session allowed the rats 25 min of undisturbed exploration of the maze. During the first habituation session, 45 mg reinforcement pellets were scattered all over the maze, whereas in the second habituation session, the reinforcement pellets were present only in and around the food wells. On the third session, the shaping procedure was initiated. During shaping, 15 trials (runs) were given per session (daily), and the start arm of each trial was randomly selected. The reinforcement pellets were present in the food wells of all arms but the start arm, and the animal was released from the end of the start arm. After reaching the end of any of the response arms, the animal was allowed freely to eat four reinforcement pellets. Subsequently, the animal was picked up and the next trial was initiated. The shaping procedures continued until all animals promptly (within less than 10 s) entered one of the response arms when released. During shaping, animals were kept food deprived to approximately 85% of their ad libitum body weight. During administration of the restraint procedures and the

posttraumatic pause, food and water were freely available. After completion of shaping, one of the lesioned groups (FF/PRE-OP Restraint) and one of the control operated groups (Sham/PRE-OP Restraint) underwent 2 h of daily restraint procedure lasting for 8 consecutive days. The restraint procedure was administered during the interval 4 to 6 pm except the eighth restraint session in the PRE-OP Restraint groups and the first session in the POST-OP Restraint groups that were timed according to surgery. The last restraint session of the PRE-OP Restraint groups took place immediately prior to surgery. After the completion of the surgical procedures, one of the lesioned groups (FF/POST-OP Restraint) and one of the control operated groups (Sham/POST-OP Restraint) were subjected to the restraint procedure (2 h daily for 8 consecutive days). The first post-surgical restraint session took place immediately after the effects of anaesthesia ceased. Immediately following the last restraint session of the POST-OP Restraint groups, both restrained and non-restrained subjects were placed on food deprivation. Initially, a 7-day period allowed the animals to reach the 85% deprivation level. Subsequently, the 8-arm radial maze-related procedures were initiated. During the first three sessions, the animals were briefly reshaped. On the fourth session, the acquisition training and testing of the place learning task began. All animals were given one daily place learning session on 30 consecutive days. At each acquisition session, 15 trials (runs) were given and 4 reinforcement pellets were present in all arms except the start arm. One arm (defined according to its spatial location within the experimental room) was defined as the goal arm for all trials throughout the task acquisition period. The remaining seven arms served as (for each trial randomly selected) start arms. To avoid the possibility of successful task solution being based on local (intra-maze) cues, we rotated the maze between sessions (in such a way that only the spatial position but not the intra-maze identity of the goal arm remained constant between sessions). When entering the goal arm, the rat was allowed to reach the food well and consume the four reinforcement pellets. If, however, an incorrect arm was entered, the animal was picked up before reaching the food well and returned to a holding cage where it remained until the next trial. After a correct trial, the animal was likewise transferred to a holding cage until the next trial. The inter-trial periods were of approximately 1 min duration. From each trial, two parameters were recorded: the total number of errors and the number of 'distal' errors—defined as all errors but those to the two arms adjacent to the goal arm.

4.4. *Surgery*

Surgery lasting approximately 30 min per animal was performed with the aid of a surgical microscope under clean but non-sterile conditions. The animals were anaesthetized by intraperitoneal injection of Dormitor Vet (0.12 mg/kg body weight) and Ketamine (Ketaminol Vet) (18 mg/kg body weight). Additionally, every animal was administered 1% Atropin sulphate (0.9 mg/kg body weight). Bilateral transections of the fimbria-fornix were performed stereotaxically using a wire-knife. Detailed descriptions of the surgical procedures have previously been published (e.g., Mogensen et al., 2004a,b, 2005).

4.5. *Histology*

After completion of the behavioural testing, all animals were deeply anaesthetized and transcardially perfused with saline, followed by 10% formalin in saline solution. After perfusion, the brains were removed from the skull and allowed to sink at 4 °C in a 10% formalin in saline solution containing 20% sucrose. The brains were cut horizontally at 40 μm on a vibratome. The Nissl-stained sections were examined with the help of a microfiche reader, and the locus and size of lesion were verified.

4.6. *Statistical analysis*

All behavioural data were originally analyzed using a multivariate analysis of variance (MANOVA) in order to identify potential interactions among the independent variables and the association with dependent variables. The two parameters (total number of errors and the number of 'distal' errors) from all acquisition sessions were analyzed in this manner. If the analysis of variance allowed so, Student's *t*-tests for independent samples were applied to examine significant differences between individual groups. Furthermore, similar but separate analyses were performed for the first 10 acquisition sessions (sessions 1–10) and the last 10 acquisition sessions (sessions 21–30), including multivariate analysis with tests of between-subjects effects. The differences in the performance of individual groups were examined by applying Student's *t*-test for independent measures in those cases where MANOVA permitted doing so. The data regarding the body weight changes during the period of restraint were initially analyzed by using MANOVA in order to test effects and potential interactions of the lesion and restraint procedure. Since no significant effects of lesion or the interaction between lesion and the restraint procedure were found, the body weight data were pooled across experimental groups according to whether the animals underwent the restraint procedure or not. The percentage change in body weight was calculated as the net change in weight (the body weight just prior to the first administration of the restraint procedure minus the body weight on the last day of the administration of the restraint procedure × 100/body weight at the first day of the exposure to the restraint procedure). The mean percentage values were compared applying the Student's *t*-test. All significances are given two-tailed. Effects were considered statistically significant if $p<0.05$.

REFERENCES

Abercrombie, E.D., Keefe, K.A., Difrischia, D.S., Zigmond, M.J., 1989. Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J. Neurochem. 52, 1655–1658.

Abidin, I., Yargicoglu, P., Agar, A., Gumuslu, S., Aydin, S., Ozturk, O., Sahin, E., 2004. The effect of chronic restraint stress on spatial learning and memory: relation to oxidant stress. Int. J. Neurosci. 114, 683–699.

Adlard, P.A., Perreau, V.M., Cotman, C.W., 2004. Chronic immobilization stress differentially affects the expression of BDNF mRNA and protein in the mouse hippocampus. Stress and Health 20, 175–180.

Anisman, H., Zacharko, R.M., 1986. Behavioral and neurochemical consequences associated with stressors. Ann. N. Y. Acad. Sci. 467, 205–225.
Anisman, H., Zacharko, R.M., 1990. Multiple neurochemical and behavioral consequences of stressors: implications for depression. Pharmacol. Ther. 46, 119–136.
Bain, M.J., Dwyer, S.M., Rusak, B., 2004. Restraint stress affects hippocampal cell proliferation differently in rats and mice. Neurosci. Lett. 368, 7–10.
Barbay, S., Zoubina, E.V., Dancause, N., Frost, S.B., Eisner-Janowicz, I., Stowe, A.M., Plautz, E.J., Nudo, R.J., 2006. A single injection of D-amphetamine facilitates improvements in motor training following a focal cortical infarct in squirrel monkeys. Neurorehabil. Neural Repair 20, 455–458.
Beck, K.D., Luine, V.N., 1999. Food deprivation modulates chronic stress effects on object recognition in male rats: role of monoamines and amino acids. Brain Res. 830, 56–71.
Bisagno, V., Grillo, C.A., Piroli, G.G., Giraldo, P., McEwen, B., Luine, V.N., 2004. Chronic stress alters amphetamine effects on behavior and synaptophysin levels in female rats. Pharmac. Biochem. Behav. 78, 541–550.
Biernaskie, J., Chernenko, G., Corbett, D., 2004. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. J. Neurosci. 24, 1245–1254.
Blanc, G., Herve, D., Simon, H., Lisoprawski, A., Glowinski, J., Tassin, J.P., 1980. Response to stress of mesocortico-frontal dopaminergic neurones in rats after long-term isolation. Nature 284, 265–267.
Bowman, R.E., 2005. Stress-induced changes in spatial memory are sexually differentiated and vary across the lifespan. J. Neuroendocrinol. 17, 526–535.
Bowman, R.E., Zrull, M.C., Luine, V.N., 2001. Chronic restraint stress enhances radial arm maze performance in female rats. Brain Res. 904, 279–289.
Bowman, R.E., Ferguson, D., Luine, V.N., 2002. Effects of chronic restraint stress and estradiol on open field activity, spatial memory, and monoaminergic neurotransmitters in ovariectomized rats. Neuroscience 113, 401–410.
Bowman, R.E., Beck, K.D., Luine, V.N., 2003. Chronic stress effects on memory: sex differences in performance and monoaminergic activity. Horm. Behav. 43, 48–59.
Bowman, R.E., Maclusky, N.J., Diaz, S.E., Zrull, M.C., Luine, V.N., 2006. Aged rats: sex differences and responses to chronic stress. Brain Res. 1126, 156–166.
Bramlett, H.M., Dietrich, W.D., 2002. Quantitative structural changes in white and gray matter 1 year following traumatic brain injury in rats. Acta Neuropathol. (Berl) 103, 607–614.
Bramlett, H.M., Dietrich, W.D., 2004. Pathophysiology of cerebral ischemia and brain trauma: similarities and differences. J. Cereb. Blood Flow Metab. 24, 133–150.
Bramlett, H.M., Dietrich, W.D., Green, E.J., Busto, R., 1997. Chronic histopathological consequences of fluid-percussion brain injury in rats: effects of post-traumatic hypothermia. Acta Neuropathol. (Berl) 93, 190–199.
Briones, T.L., Woods, J., Wadowska, M., Rogozinska, M., 2006. Amelioration of cognitive impairment and changes in microtubule-associated protein 2 after transient global cerebral ischemia are influenced by complex environment experience. Behav. Brain Res. 168, 261–271.
Brown, S.M., Henning, S., Wellman, C.L., 2005. Mild, short-term stress alters dendritic morphology in rat medial prefrontal cortex. Cereb. Cortex 15, 1714–1722.
Canudas, A.M., Pezzi, S., Canals, J.M., Pallas, M., Alberch, J., 2005. Endogenous brain-derived neurotrophic factor protects dopaminergic nigral neurons against transneuronal degeneration induced by striatal excitotoxic injury. Brain Res. Mol. Brain Res. 134, 147–154.
Carmichael, S.T., 2006. Cellular and molecular mechanisms of neural repair after stroke: making waves. Ann. Neurol. 59, 735–742.
Carmichael, S.T., Archibeque, I., Luke, L., Nolan, T., Momiy, J., Li, S., 2005. Growth-associated gene expression after stroke: evidence for a growth-promoting region in peri-infarct cortex. Exp. Neurol. 193, 291–311.
Conrad, C.D., Galea, L.A., Kuroda, Y., McEwen, B.S., 1996. Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment. Behav. Neurosci. 110, 1321–1334.
Conrad, C.D., Ledoux, J.E., Magarinos, A.M., McEwen, B.S., 1999. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav. Neurosci. 113, 902–913.
Conrad, C.D., Jackson, J.L., Wieczorek, L., Baran, S.E., Harman, J.S., Wright, R.L., Korol, D.L., 2004. Acute stress impairs spatial memory in male but not female rats: influence of estrous cycle. Pharmacol. Biochem. Behav. 78, 569–579.
Cook, S.C., Wellman, C.L., 2004. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J. Neurobiol. 60, 236–248.
Corbett, D., Giles, T., Evans, S., McLean, J., Biernaskie, J., 2006. Dynamic changes in CA1 dendritic spines associated with ischemic tolerance. Exp. Neurol. 202, 133–138.
Cuadra, G., Zurita, A., Lacerra, C., Molina, V., 1999. Chronic stress sensitizes frontal cortex dopamine release in response to a subsequent novel stressor: reversal by naloxone. Brain Res. Bull. 48, 303–308.
Dagnino-Subiabre, A., Zepeda-Carreno, R., Az-Veliz, G., Mora, S., Aboitiz, F., 2006. Chronic stress induces upregulation of brain-derived neurotrophic factor (BDNF) mRNA and integrin alpha5 expression in the rat pineal gland. Brain Res. 1086, 27–34.
Dancause, N., Barbay, S., Frost, S.B., Plautz, E.J., Chen, D., Zoubina, E.V., Stowe, A.M., Nudo, R.J., 2005. Extensive cortical rewiring after brain injury. J. Neurosci. 25, 10167–10179.
de Bruin, J.P., Moita, M.P., de Brabander, H.M., Joosten, R.N., 2001. Place and response learning of rats in a Morris water maze: differential effects of fimbria fornix and medial prefrontal cortex lesions. Neurobiol. Learn. Mem. 75, 164–178.
Deutch, A.Y., Tam, S.Y., Roth, R.H., 1985. Footshock and conditioned stress increase 3,4-dihydroxyphenylacetic acid (DOPAC) in the ventral tegmental area but not substantia nigra. Brain Res. 333, 143–146.
Franklin, T.B., Perrot-Sinal, T.S., 2006. Sex and ovarian steroids modulate brain-derived neurotrophic factor (BDNF) protein levels in rat hippocampus under stressful and non-stressful conditions. Psychoneuroendocrinology 31, 38–48.
Ginsberg, S.D., Martin, L.J., 1998. Ultrastructural analysis of the progression of neurodegeneration in the septum following fimbria-fornix transection. Neuroscience 86, 1259–1272.
Ginsberg, S.D., Martin, L.J., 2002. Axonal transection in adult rat brain induces transsynaptic apoptosis and persistent atrophy of target neurons. J. Neurotrauma 19, 99–109.
Givalois, L., Marmigere, F., Rage, F., Ixart, G., Arancibia, S., Tapia-Arancibia, L., 2001. Immobilization stress rapidly and differentially modulates BDNF and TrkB mRNA expression in the pituitary gland of adult male rats. Neuroendocrinology 74, 148–159.
Grady, M.S., Charleston, J.S., Maris, D., Witgen, B.M., Lifshitz, J., 2003. Neuronal and glial cell number in the hippocampus after experimental traumatic brain injury: analysis by stereological estimation. J. Neurotrauma 20, 929–941.
Grasso, G., Sfacteria, A., Cerami, A., Brines, M., 2004. Erythropoietin as a tissue-protective cytokine in brain injury: what do we know and where do we go? Neuroscientist 10, 93–98.
Gresch, P.J., Sved, A.F., Zigmond, M.J., Finlay, J.M., 1994. Stress-induced sensitization of dopamine and norepinephrine

efflux in medial prefrontal cortex of the rat. J. Neurochem. 63, 575–583.
Harvey, B.H., Brand, L., Jeeva, Z., Stein, D.J., 2006. Cortical/hippocampal monoamines, HPA-axis changes and aversive behavior following stress and restress in an animal model of post-traumatic stress disorder. Physiol. Behav. 87, 881–890.
Jackson, M.E., Moghaddam, B., 2006. Distinct patterns of plasticity in prefrontal cortex neurons that encode slow and fast responses to stress. Eur. J. Neurosci. 24, 1702–1710.
Kim, D.H., Zhao, X., 2005. BDNF protects neurons following injury by modulation of caspase activity. Neurocrit. Care 3, 71–76.
Kitraki, E., Kremmyda, O., Youlatos, D., Alexis, M., Kittas, C., 2004. Spatial performance and corticosteroid receptor status in the 21-day restraint stress paradigm. Ann. N. Y. Acad. Sci. 1018, 323–327.
Lahtinen, H., Miettinen, R., Ylinen, A., Halonen, T., Riekkinen sr., P.J., 1993. Biochemical and morphological changes in the rat hippocampus following transection of the fimbria-fornix. Brain Res. Bull. 31, 311–318.
Lee, K.J., Kim, S.J., Kim, S.W., Choi, S.H., Shin, Y.C., Park, S.H., Moon, B.H., Cho, E., Lee, M.S., Choi, S.H., Chun, B.G., Shin, K.H., 2006. Chronic mild stress decreases survival, but not proliferation, of new-born cells in adult rat hippocampus. Exp. Mol. Med. 38, 44–54.
Li, S., Carmichael, S.T., 2006. Growth-associated gene and protein expression in the region of axonal sprouting in the aged brain after stroke. Neurobiol. Dis. 23, 362–373.
Lippert-Grüner, M., Maegele, M., Garbe, J., Angelov, D.N., 2007a. Late effects of enriched environment (EE) plus multimodal early onset stimulation (MEOS) after traumatic brain injury in rats: ongoing improvement of neuromotor function despite sustained volume of the CNS lesion. Exp. Neurol. 203, 82–94.
Lippert-Grüner, M., Maegele, M., Pokorny, J., Angelov, D., Svestkova, O., Wittner, M., Trojan, S., 2007b. Early rehabilitation model shows positive effects on neural degeneration and recovery from neuromotor deficits following traumatic brain injury. Physiol. Res. 56, 359–368.
Liston, C., Miller, M.M., Goldwater, D.S., Radley, J.J., Rocher, A.B., Hof, P.R., Morrison, J.H., McEwen, B.S., 2006. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J. Neurosci. 26, 7870–7874.
Luine, V., 2002. Sex differences in chronic stress effects on memory in rats. Stress. 5, 205–216.
Luine, V., Villegas, M., Martinez, C., McEwen, B.S., 1994a. Repeated stress causes reversible impairments of spatial memory performance. Brain Res. 639, 167–170.
Luine, V., Villegas, M., Martinez, C., McEwen, B.S., 1994b. Stress-dependent impairments of spatial memory: role of 5-HT. Ann. N. Y. Acad. Sci. 746, 403–404.
Luine, V., Martinez, C., Villegas, M., Magarinos, A.M., McEwen, B.S., 1996. Restraint stress reversibly enhances spatial memory performance. Physiol. Behav. 59, 27–32.
M'Harzi, M., Willig, F., Costa, J.C., DeLaCour, J., 1988. d-Amphetamine enhances memory performance in rats with damage to the fimbria. Physiol. Behav. 42, 575–579.
Maegele, M., Lippert-Grüner, M., Ester-Bode, T., Garbe, J., Bouillon, B., Neugebauer, E., Klug, N., Lefering, R., Neiss, W.F., Angelov, D.N., 2005. Multimodal early onset stimulation combined with enriched environment is associated with reduced CNS lesion volume and enhanced reversal of neuromotor dysfunction after traumatic brain injury in rats. Eur. J. Neurosci. 21, 2406–2418.
Magarinos, A.M., McEwen, B.S., 1995. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: comparison of stressors. Neuroscience 69, 83–88.
Magarinos, A.M., Verdugo, J.M., McEwen, B.S., 1997. Chronic stress alters synaptic terminal structure in hippocampus. Proc. Natl. Acad. Sci. U. S. A. 94, 14002–14008.
Malá, H., Alsina, C.G., Madsen, K.S., Sibbesen, E.C., Stick, H., Mogensen, J., 2005. Erythropoietin improves place learning in an 8-arm radial maze in fimbria-fornix transected rats. Neural Plast. 12, 329–340.
Marmigere, F., Givalois, L., Rage, F., Arancibia, S., Tapia-Arancibia, L., 2003. Rapid induction of BDNF expression in the hippocampus during immobilization stress challenge in adult rats. Hippocampus 13, 646–655.
Mogensen, J., Wörtwein, G., Gustafson, B., Ermens, P., 1995. L-nitroarginine reduces hippocampal mediation of place learning in the rat. Neurobiol. Learn. Mem. 64, 17–24.
Mogensen, J., Christensen, L.H., Johansson, A., Wörtwein, G., Bang, L.E., Holm, S., 2002. Place learning in scopolamine-treated rats: the roles of distal cues and catecholaminergic mediation. Neurobiol. Learn. Mem. 78, 139–166.
Mogensen, J., Lauritsen, K.T., Elvertorp, S., Hasman, A., Moustgaard, A., Wörtwein, G., 2004a. Place learning and object recognition by rats subjected to transection of the fimbria-fornix and/or ablation of the prefrontal cortex. Brain Res. Bull. 63, 217–236.
Mogensen, J., Miskowiak, K., Sørensen, T.A., Lind, C.T., Olsen, N.V., Springborg, J.B., Malá, H., 2004b. Erythropoietin improves place learning in fimbria-fornix transected rats and modifies the search pattern of normal rats. Pharmacol. Biochem. Behav. 77, 381–390.
Mogensen, J., Moustgaard, A., Khan, U., Wörtwein, G., Nielsen, K.S., 2005. Egocentric spatial orientation in a water maze by rats subjected to transection of the fimbria-fornix and/or ablation of the prefrontal cortex. Brain Res. Bull. 65, 41–58.
Mogensen, J., Hjortkjær, J., Ibervang, K.L., Stedal, K., Malá, H., 2007. Prefrontal cortex and hippocampus in posttraumatic functional recovery: spatial delayed alternation by rats subjected to transection of the fimbria-fornix and/or ablation of the prefrontal cortex. Brain Res. Bull. 73, 86–95.
Murakami, S., Imbe, H., Morikawa, Y., Kubo, C., Senba, E., 2005. Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. Neurosci. Res. 53, 129–139.
Nibuya, M., Takahashi, M., Russell, D.S., Duman, R.S., 1999. Repeated stress increases catalytic TrkB mRNA in rat hippocampus. Neurosci. Lett. 267, 81–84.
Orsini, C., Ventura, R., Lucchese, F., Puglisi-Allegra, S., Cabib, S., 2002. Predictable stress promotes place preference and low mesoaccumbens dopamine response. Physiol. Behav. 75, 135–141.
Paxinos, G., Watson, Ch., 1986. The Rat Brain in Stereotaxic Coordinates, 2nd ed. Academic Press, Inc.
Pham, K., Nacher, J., Hof, P.R., McEwen, B.S., 2003. Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. Eur. J. Neurosci. 17, 879–886.
Puglisi-Allegra, S., Imperato, A., Angelucci, L., Cabib, S., 1991. Acute stress induces time-dependent responses in dopamine mesolimbic system. Brain Res. 554, 217–222.
Radecki, D.T., Brown, L.M., Martinez, J., Teyler, T.J., 2005. BDNF protects against stress-induced impairments in spatial learning and memory and LTP. Hippocampus 15, 246–253.
Radley, J.J., Rocher, A.B., Miller, M., Janssen, W.G., Liston, C., Hof, P.R., McEwen, B.S., Morrison, J.H., 2006. Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. Cereb. Cortex 16, 313–320.
Rage, F., Givalois, L., Marmigere, F., Tapia-Arancibia, L., Arancibia, S., 2002. Immobilization stress rapidly modulates BDNF mRNA expression in the hypothalamus of adult male rats Neuroscience 112, 309–318.
Sandi, C., Davies, H.A., Cordero, M.I., Rodriguez, J.J., Popov, V.I., Stewart, M.G., 2003. Rapid reversal of stress induced loss of synapses in CA3 of rat hippocampus following water maze training. Eur. J. Neurosci. 17, 2447–2456.

Scaccianoce, S., Lombardo, K., Angelucci, L., 2000. Nerve growth factor brain concentration and stress: changes depend on type of stressor and age. Int. J. Dev. Neurosci. 18, 469–479.

Scaccianoce, S., Mattei, V., Del, B.P., Gizzi, C., Sorice, M., Hiraiwa, M., Misasi, R., 2004. Hippocampal prosaposin changes during stress: a glucocorticoid-independent event. Hippocampus 14, 275–280.

Shansky, R.M., Rubinow, K., Brennan, A., Arnsten, A.F., 2006. The effects of sex and hormonal status on restraint-stress-induced working memory impairment. Behav. Brain Funct. 2, 8.

Shors, T.J., Weiss, C., Thompson, R.F., 1992. Stress-induced facilitation of classical conditioning. Science 257, 537–539.

Smith, M.A., Makino, S., Kvetnansky, R., Post, R.M., 1995. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J. Neurosci. 15, 1768–1777.

Smith, D.H., Chen, X.H., Pierce, J.E., Wolf, J.A., Trojanowski, J.Q., Graham, D.I., McIntosh, T.K., 1997. Progressive atrophy and neuron death for one year following brain trauma in the rat. J. Neurotrauma 14, 715–727.

Smith, D.G., Davis, R.J., Gehlert, D.R., Nomikos, G.G., 2006. Exposure to predator odor stress increases efflux of frontal cortex acetylcholine and monoamines in mice: comparisons with immobilization stress and reversal by chlordiazepoxide. Brain Res. 1114, 24–30.

Stein, D.G., 2005. The case for progesterone. Ann. N. Y. Acad. Sci. 1052, 152–169.

Trneckova, L., Armario, A., Hynie, S., Sida, P., Klenerova, V., 2006. Differences in the brain expression of c-fos mRNA after restraint stress in Lewis compared to Sprague–Dawley rats. Brain Res. 1077, 7–15.

Vaynman, S., Ying, Z., Gomez-Pinilla, F., 2004. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur. J. Neurosci. 20, 2580–2590.

Ventura, R., Cabib, S., Puglisi-Allegra, S., 2001. Opposite genotype-dependent mesocorticolimbic dopamine response to stress. Neuroscience 104, 627–631.

Vyas, A., Mitra, R., Shankaranarayana Rao, B.S., Chattarji, S., 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J. Neurosci. 22, 6810–6818.

Watanabe, Y., Gould, E., McEwen, B.S., 1992. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res. 588, 341–345.

Wörtwein, G., Saerup, L.H., Charlottenfeld-Starpov, D., Mogensen, J., 1995. Place learning by fimbria-fornix transected rats in a modified water maze. Int. J. Neurosci. 82, 71–81.

Wright, R.L., Conrad, C.D., 2005. Chronic stress leaves novelty-seeking behavior intact while impairing spatial recognition memory in the Y-maze. Stress. 8, 151–154.