Novelty, but Not Operant Aversive Learning, Enhances Fos and Egr-1 Expression in the Medial Prefrontal Cortex and Hippocampal Areas of Rats

Angélica Yochiy, Luiz R. G. Britto, and Maria H. L. Hunziker
University of São Paulo

Immediate early genes (IEGs) are presumed to be activated in response to stress, novelty, and learning. Evidence supports the involvement of prefrontal and hippocampal areas in stress and learning, but also in the detection of novel events. This study examined whether a previous experience with shocks changes the pattern of Fos and Egr-1 expression in the medial prefrontal cortex (mPFC), the hippocampal cornus ammonis 1 (CA1), and dentate gyrus (DG) of adult male Wistar rats that learned to escape in an operant aversive test. Subjects previously exposed to inescapable footshocks that learned to escape from shocks were assigned to the treated group (EXP). Subjects from Group Novelty (NOV) rested undisturbed during treatment and also learned to escape in the test. The nonshock group (NSH) rested undisturbed in both sessions. Standard immunohistochemistry procedures were used to detect the proteins in brain sections. The results show that a previous experience with shocks changed the pattern of IEG expression, then demonstrating c-fos and egr-1 induction as experience-dependent events. Compared with NSH and EXP an enhanced Fos expression was detected in the mPFC and CA1 subfield of Group NOV, which also exhibited increased Egr-1 expression in the mPFC and DG in comparison to NSH. No differences were found in the DG for Fos, or in the CA1 for Egr-1. Novelty, and not the operant aversive escape learning, seems to have generated IEG induction. The results suggest novel stimuli as a possible confounding factor in studies on Fos and/or Egr-1 expression in aversive conditions.

Keywords: medial prefrontal cortex, hippocampus, inescapable footshock, stress, immediate early genes

Immediate-early genes (IEGs), a class of genes that are rapidly and transiently activated in neurons (Farifär, Zangenehpour, & Chaudhuri, 2004; Herdegen & Leah, 1998), are believed to be induced by different types of stress, including that derived from footshocks (Morrow, Elsworth, Inglis, & Roth, 1999; Senba & Ueyama, 1997). However, some evidence has indicated that the novelty of the stressor and not the stressor per se may have an important role in the IEG expression, implying that factors such as stress, sensory stimulation, or motor activity may not inevitably lead to IEG induction in the brain (Nikolaev, Werka, & Kaczmarek, 1992; Tischmeyer & Grimm, 1999).

Novelty detection is considered a prerequisite for learning (Tischmeyer & Grimm, 1999; Tulving, Markowitsch, Craik, Habib, & Houle, 1996) and a memory-dependent process, because it implies the comparison of a particular stimulus to others previously retained in the brain (Montag-Sallaz, Welzl, Kuhl, Montag, & Schachner, 1999). Several brain regions have been implicated in novelty detection (Ranganath & Rainer, 2003; Yamaguchi, Hale, D’Esposito, & Knight, 2004), but the hippocampus (Knight, 1996; Nyberg, 2005; Yamaguchi et al., 2004) and the prefrontal cortical areas (Daffner et al., 2000; Dias & Honey, 2002) are considered essential components in the processing of novelty.

The IEGs c-fos and egr-1 are widely used as markers of brain neuronal activity (Farifär et al., 2004). Activation of c-fos has been repeatedly associated with learning processes (Aggleton & Brown, 2005), but novel stimuli have also been indicated as an important factor in triggering Fos protein expression (Albasser, Poirier, & Aggleton, 2010; Handa, Nunley, & Bollinow, 1993; Nikolaev, Werka, et al., 1992; Papa, Pellicano, Welzlz, & Sadile, 1993; Radulovic, Kammermeier, & Spiess, 1998; Rinaldi, Romeo, Agustin-Pavon, Oliverio, & Mele, 2010). In the medial prefrontal cortex (mPFC), increased Fos expression was suggested to have a role in acquisition of aversive learning (Morrow et al., 1999). In the hippocampus, Fos and Egr-1 proteins have been proposed as markers of novelty and retrieval, respectively (Radulovic & Tronson, 2010). Induction of egr-1 seems to be essential for the transition from short- to long-term retention and retrieval in mutant mouse, evidence of a major role in plasticity and learning (Alberini, 2009; Jones et al., 2001). However, Egr-1 regulation by novelty is another possibility (Davis, Bozon, & Laroche, 2003; Tischmeyer & Grimm, 1999).

Studies have been organized to discriminate between experimental effects and the consequences of other concomitant factors,
but some questions have been raised by the fact that the strongest
IEG induction occurs during the early phases of behavioral train-
ing, when a learning process is commonly taking place
(Tischmeyer & Grimm, 1999). In addition to differences between
behavioral protocols, species, and techniques that have been held
accountable for discrepancies among results, novelty studies have
usually used complex sets of stimuli and apparatus, making it
difficult to determine whether an increased IEG expression was
consequence of exposure to stress, novelty, or the effect of an
enhanced locomotor activity (Montag-Sallaz et al., 1999). Oppos-
ing viewpoints also surround the concept and the use of the term
“stress” (Koolhaas et al., 2011), and the fact that some studies
address novelty as a type of stress may represent another source of
confusion.

Within the context of the aforementioned considerations, the
purpose of the present study was to investigate whether a previous
experience with inescapable shocks changes the pattern of Fos and
Egr-1 expression in the mPFC, hippocampal cornus ammonis 1 (CA1),
and dentate gyrus (DG) of rats that learned to escape from
aversive stimuli (footshocks) in an operant aversive learning test.
The data are expected to contribute to the understanding of mo-
olecular brain changes related to a previous aversive experience and
the operant learning under exposure to (stressful) aversive events.

Methods

Subjects

The subjects were 42 male Wistar rats, experimentally naïve,
obtained from the Animal Facilities of the Institute of Biomedical
Sciences (University of São Paulo). The animals were raised in
plastic cages, a maximum of six rats per cage, in a temperature-
and light-controlled room (22 ± 1 °C, 12/12-hr light/dark cycle,
lights on at 7:00 a.m.) at the Institute of Psychology (University of
São Paulo). The subjects were housed in individual cages starting
at the age of 90 days and then were weighed weekly. The rats
(350–440 g) remained in their cages for at least 1 week before the
beginning of adaptation procedures. The behavioral sessions were
conducted between 8:00 a.m. and 2:00 p.m. Food and water were
provided ad libitum in the home cage. The experimental proce-
dures were approved by the Animal Research Ethics Committee
(Protocol # 010.2008) of the Institute of Psychology, University of
São Paulo.

Apparatus

Two chambers were used in the experiment. The treatment
chamber, 21.5 cm long, 21.5 cm wide, and 21.5 cm high, was made
of transparent acrylic and aluminum. The grid floor, made of 0.3
cm stainless steel rods spaced 1.3 cm apart, was connected to a
113–33 electric shock generator (Lehigh Valley). The test cham-
ber, a 50.0 cm long, 15.5 cm wide, and 20.0 cm high shuttle box,
was made of transparent and opaque black acrylic. A partition of
black acrylic divided the chamber into two compartments of equal
size. This central wall had a 7.5-cm-high by 6-cm-wide rectangular
opening placed at 8 cm above the grid floor. The opening base
was provided with metal rods on both sides of the wall to avoid
perching. Each compartment had an independent grid floor, also
made of 0.3 cm stainless steel rods spaced 1.3 cm apart, which
were connected to a BRS Foringer 901 electric shock generator
and a scrambler. When the animal’s weight depressed the grid
floor, a microswitch was activated, then registering the presence of
the subject inside that compartment. The animal had to jump from
one side to the other to turn off the shock delivered through the
metal rods of the grid floor and at the base of the rectangular
opening. The chambers were placed inside wood boxes that re-
mained open during all sessions. Only one animal was handled at
a time. The chambers were cleaned after each session with ethanol
solution to minimize olfactory cues for the next subject. Computer
software especially developed for this type of experiment using
Delphi 6 (Borland Software Corp., Scotts Valley, California) was
used to control the sessions and collect the data. Statistical anal-
yses were performed using GraphPad Prism 5 (GraphPad Soft-
ware, San Diego, California) e Statistica v. Eight (StatSoft Inc.,
Tulsa, OK). A p value of less than .05 was considered statistically
significant.

Behavioral Procedures

The behavioral procedures started with a period of adaptation, a
preexposure for 3 days to the experimental conditions. The sub-
jects were placed inside the treatment and test chambers, 30 min in
each apparatus, without being disturbed. They were then trans-
ported to another room where the handling required for adminis-
tering the anesthesia on a later stage was simulated. After com-
pleting 30 min in this room the subjects returned to their home
cages. The 3-day preexposure period (adaptation procedure) aimed
at avoiding the interference of commonly available environmental
stimuli in the expression of Fos and Egr-1 proteins.

In the fourth day, one set of rats (group pre-EXP) received
treatment with 60 inescapable 1.0-mA footshocks lasting 10 s
each, applied at an average interval of 1.0 min, with an intertrial
interval (ITI) of 10–110 s. The subjects were then submitted to an
operant escape test 24 hr later, a 30-trial FR1 escape contingency
for jumping with maximum footshock duration of 10 s (ITI
= 10–110 s). Another set of animals (group pre-NOV) rested inside
the treatment chamber with no shock and was also submitted to the
escape test 24 hr later. The subjects should have similar escape
performance in the test to allow the comparison between groups.
Therefore, to be allocated to groups novelty (NOV) or experienced
(EXP), subjects from groups pre-NOV and pre-EXP had to provide
escape latencies below 5 s in at least 20 of 30 trials in the operant
escape test. Subjects from nonshock control group (NSH) were
submitted to the same adaptation procedure inside the chambers
followed by treatment and test sessions, but without being exposed
to shocks. One hour after the beginning of the test session, all
subjects were deeply anesthetized with ketamine (Dopalen, Vet-
brands) and xylazine (Anasedan, Vetbrands) for transcardiac per-
fusion. Subjects with behavioral responses in the escape test that
could affect the correct measurement of latencies, for example,
perching to avoid aversive stimuli (despite the metal rods on both
sides of the rectangular opening base), and subjects that failed to
reach the performance criterion were excluded from the present
experiment. A detailed discussion on the FR1 operand escape
contingency applied in the test can be found in Hunziker and
Santos (2007).
Immunohistochemistry Procedures

Transcardiac perfusion was performed with saline followed by 4% (wt/vol) paraformaldehyde (PFA), 400 ml each, both solutions prepared with 0.1 M phosphate buffer (PB). The brains were removed and postfixed in 4% (wt/vol) PFA for 4 hr and maintained in 30% (wt/vol) sucrose in PB under refrigeration (4 °C) for cryoprotection. Coronal 30-μm sections of the frozen brains were obtained on a sliding microtome and collected in PB. Incubation of the free-floating sections with rabbit antisera against Fos (Calbiochem, EMD Biosciences, La Jolla, CA) and Egr-1 (Santa Cruz Biotechnology, Santa Cruz, CA) proteins for 12–16 hr followed, diluted in PB containing 0.3% (vol/vol) Triton X-100 at 1:1,000 and 1:500, respectively. The sections were then incubated with biotinylated antirabbit 1:200 (Vector Laboratories, Burlingame, CA) and avidin-biotin-peroxidase complex (ABC Elite, Vector Laboratories) for 2 hr each. A reaction of 0.05% (wt/vol) 3′-diaminobenzidine with 0.01% (vol/vol) hydrogen peroxide revealed the Fos and Egr-1 proteins. All steps were performed at room temperature (22 °C) incubations in slow rotation, with brain sections rinsed in PB between procedures. After being mounted on gelatin-coated slides and dried on a hot plate (40 °C, 48 hr), the free-floating sections were immersed in 0.05% (wt/vol) osmium tetroxide solution to intensify the staining, then dehydrated in graded series of ethanol solutions (70%, 90%, and 100%, vol/vol) and xylene, and finally coverslipped with drops of Permount (Fisher, Pittsburgh, PA).

National Institutes of Health Image software (Bethesda, MD) was used in the positive-nuclei counting procedure. The system was adjusted to detect and capture cell nuclei exhibiting a signal-to-noise ratio above 3. Paxinos and Watson’s rat brain atlas (Paxinos & Watson, 2005) helped in the identification of the medial prefrontal area (predominantly prelimbic and infralimbic cortices) and hippocampus (dorsal CA1 and the dentate gyrus). In the counting procedure, at least four sections of each brain region were examined per animal.

Results

Behavioral Data

Subjects from Groups NOV and EXP should have similar escape performances in the test to allow the comparison of data, which was achieved when only subjects that provided latencies below 5 s in at least 20 of 30 trials in the test were allocated to the groups. Statistical analysis of the data using two-way ANOVA for repeated measures followed by Bonferroni post hoc test indicated no distinction between mean latencies of Groups NOV and EXP in the operant test, $F(1,45) = 0.17$, $p > .05$, no systematic differences between groups and trials, $F(5,45) = 1.35$, $p > .05$, and changes of mean latencies throughout the successive trials, $F(5,45) = 3.18$, $p < .05$. Mean latencies and the respective standard errors of the mean (SEM) from Groups NOV and EXP are shown in Figure 1. Data from Group NSH is not available for comparison because in that experimental condition the subjects were not submitted to the aversive, operant escape contingency.

Figure 1. Mean latencies (seconds) of escape jumping responses, grouped in blocks of five trials, from subjects that learned the escape contingency when exposed to the operant aversive test with footshocks (Group NOV) and subjects that learned to escape the same contingency after being exposed to inescapable footshocks during treatment (Group EXP). Standard error bars (±SEM) are depicted in only one side of the mean latencies to provide a clear unobstructed view.

Fos and Egr-1 Data Analysis

One-way ANOVA followed by Tukey-Kramer post hoc test and unpaired Student’s $t$ tests were performed on Fos- and Egr-1-labeled nuclei data after the exclusion of outliers (Tukey’s outlier rule). One-way ANOVA detected the higher density of Fos-positive nuclei, $F(2,13) = 9.80$, $p = .002$, in the mPFC of Group NOV ($n = 6$) in comparison to Groups NSH ($n = 6$, $p < .01$) or EXP ($n = 4$, $p < .05$). The $t$ tests confirmed the increased Fos expression in the mPFC of Group NOV in comparison to Groups NSH, $t(10) = 3.57$, $p = .005$, and EXP, $t(8) = 2.74$, $p = .026$, and the absence of difference between Groups NSH and EXP, $t(8) = .54$, $p = .604$.

A similar pattern of Fos expression was detected for the CA1 area, $F(2,13) = 7.79$, $p = .006$. A higher density of Fos protein was revealed in the CA1 region of Group NOV ($n = 6$) in comparison to the other two groups (NSH, $n = 6$, $p < .05$; EXP, $n = 4$, $p < .01$). Student $t$ tests confirmed the presence of differences in Fos expression in the CA1 area of Group NOV in comparison to Group NSH, $t(10) = 2.64$, $p = .025$, and Group EXP, $t(8) = 2.94$, $p = .019$, but also between Groups NSH and EXP, $t(8) = 2.80$, $p = .023$. No significant difference in Fos expression was found between groups in the DG, $F(2,13) = .32$, $p = .730$, a result that was confirmed by $t$ tests: NSH vs. NOV, $t(10) = .47$, $p = .646$; NOV vs. EXP, $t(8) = .35$, $p = .732$, NSH versus EXP, $t(8) = .81$, $p = .441$. 
Multiple comparisons detected no significant difference in 
Egr-1 expression between groups in the mPFC, \( F(2, 13) = 3.34, 
\ p = .067 \). However, when \( t \) tests were applied, a significant 
difference was detected between Groups NSH and NOV, \( t(10) = 2.27, \ p = .047 \), but not between Groups NOV and EXP, \( t(8) = 1.97, \ p = .084 \), or Groups NSH and EXP, \( t(8) = .53, \ p = .612 \). In 
the DG, a significant difference in Egr-1 expression, \( F(2, 13) = 5.54, \ p = .018 \), between Groups NOV and NSH \( (p < .05) \) was 
detected, which was confirmed by \( t \) test, \( t(10) = 3.20, \ p = .010 \). 
No significant difference in Egr-1 expression was found in the DG 
between Groups NOV and EXP or Groups NSH and EXP, results 
also confirmed by \( t \) test, \( t(8) = 2.03, \ p = .076 \); \( t(8) = .23, \ p = .820 \), respectively. In the CA1 subfield, the lack of change in Egr-1 
expression was revealed either by ANOVA, \( F(2, 13) = .34, \ p = .714 \), or \( t \) tests, NSH vs. NOV, \( t(10) = .19, \ p = .854 \); NOV vs. 
EXP, \( t(8) = .52, \ p = .619 \); NSH versus EXP, \( t(8) = .49, \ p = .174 \).

The analysis of Fos and Egr-1 data is depicted in Figure 2. 
Digital images of Fos and Egr-1 expression in the brain areas are 
provided, respectively, in Figures 3 and 4. The patterns of distrib-
ution of Fos and Egr-1 mean values in the different groups are 
available in Figure 5.

**Discussion**

In the present study Fos and Egr-1 proteins were used as 
markers of neuronal activity in brains of rats submitted, or not, to 
a previous aversive experience. The measurements were per-
formed following an operant aversive learning test in which the 
subjects should provide similar behavioral performance to allow 
the comparison of data. Statistical analysis found no significant 
differences between escape performances of Groups NOV and

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**Figure 2.** In the top row, an increased Fos expression \((\pm SEM)\) was found in the medial prefrontal cortex 
(mPFC) and hippocampal cornus ammonis 1 (CA1) areas of Group Novelty (NOV) in comparison to groups 
non-shock (NSH) and experienced (EXP) and in the CA1 subfield of Group NSH in comparison to Group EXP, 
but not between groups in the dentate gyrus (DG). In the bottom row, significant Egr-1 results \((\pm SEM)\) were 
detected in the mPFC (Student’s \( t \) test) and DG of Group NOV in comparison to Group NSH, but not between 
groups in the CA1 area \((p < .05)\). **\( p < .01 \).**
EXP. It was therefore assumed that both groups similarly learned the contingency.

Lower mean values exhibited in the first block of latencies in comparison to the second block (see Figure 1) can be explained by a higher burst of activity immediately after the shock onset (Kirk & Blampied, 1985). These respondent motor reactions initially elicited by aversive stimuli (Dallemagne & Richelle, 1970) may have helped the subjects to pass faster through the central opening in the first trials, generating the lower latencies. Therefore, the operant performance might be better represented if the first block of latencies is not taken into account.

The learning contingency with escapable footshocks was a novel event for NOV subjects as they had no previous experience with aversive stimuli. Subjects from Group EXP had prior experience with shocks, but without having had the opportunity to learn the operant escape contingency. The results show that despite the similar behavioral performances during the escape test, Groups NOV and EXP generated different patterns of Fos and Egr-1 expression (Figures 2–4). NSH data show baseline Egr-1 levels greater than Fos levels (see Figure 5), results supported by other studies (Farifar et al., 2004; Herdegen & Leah, 1998). The amount of change of Fos and Egr-1 expression in brain regions of NOV and EXP subjects compared with NSH (control group), as well as between the experimental groups, can be visualized in Figure 5.

Enhanced Fos expression was found in the mPFC and CA1 subfield of Group NOV in comparison to Groups NSH and EXP. A slight increase in Fos was also revealed in the CA1 of Group NSH in comparison to Group EXP. Increased Fos expression has been found in the prefrontal cortex (PFC) of mice (Rinaldi et al., 2010) and rats (Handa et al., 1993) exposed to novel stimuli in conditions supposed to be nonaversive. Therefore, these results might suggest that novelty is an important factor in triggering Fos expression in the mPFC and CA1 regions under nonaversive and clearly aversive conditions.

Increased Egr-1 expression was also detected in the mPFC and DG of subjects from Group NOV in comparison to Group NSH. Statistical analysis of Egr-1 data revealed p values near .05 in t test comparisons (mPFC, $p = .084$; DG, $p = .076$) when Groups NOV and EXP were compared, raising the question of whether it would be ethically justifiable to expose a greater number of animals to inescapable shocks in the pursuit of statistical significance.

Egr-1 upregulation found in associative learning and after long-term potentiation (LTP) (Alberini, 2009; Jones et al., 2001) suggests that the enhanced Egr-1 expression revealed in the present experiment might reflect the occurrence of parallel mechanisms, possibly required for long-term retention of information, as novelty detection per se may be insufficient for long-term retention of information on novel events (Tulving et al., 1996). Studies that found LTP induction related to novelty in the DG (Davis, Jones, & Derrick, 2004; Straube, Korz, Balschun, & Frey, 2003) apparently support this assumption.

Whether the PFC is involved in the acquisition of aversive learning (Morrow et al., 1999), retrieval and not acquisition of information (Dalley, Cardinal, & Robbins, 2004), the present results support the mPFC involvement in the acquisition of novel events, but not the acquisition of operant aversive learning. The results indicate Fos and Egr-1 proteins as nuclear markers of novelty and acquisition of novel events, respectively, strengthening the idea that an increased Egr-1 expression in the hippocampus.

![Figure 3. Digital images of Fos-positive nuclei detected in the medial prefrontal cortex (mPFC, top row) and hippocampal cornus ammonis 1 region (CA1, bottom row) in coronal brain sections of rats from groups nonshock (NSH), novelty (NOV), and experienced (EXP). The images depict the enhanced Fos expression detected in the mPFC and CA1 area of Group NOV in comparison to the other two groups and in the dorsal CA1 subfield of Group NSH in comparison to Group EXP.](image_url)
might be more related to novelty than learning (Tischmeyer & Grimm, 1999; Davis et al., 2003).

Differential modulation between CA1 and DG, as detected in the present study, has been found by other studies. For instance, decreased and increased firing rates were registered in the CA1 and DG interneurons of rats, respectively, under the same novel condition (Nitz & McNaughton, 2003). In another study, increased and decreased Fos expression was found, respectively, in the CA1 and DG areas after exposure to novel environment (Albasser et al., 2010). Finally, environmental novelty was associated to an increased expression of Fos in the CA1, but not in the DG, in a study of neuroplasticity (VanElzakker, Fevurly, Breindel, & Spencer, 2008). The present results support neither a relationship between an increased Egr-1 expression in the CA1 and novelty detection (Alberini, 2009; Davis et al., 2003), nor an increased Fos expression in the DG associated with a novel environment (Aggleton & Brown, 2005).

Comparable patterns of activation were exhibited by Groups NSH and EXP (see Figure 5), notwithstanding the exposure of EXP subjects to aversive stimuli in the treatment and test sessions, and the lack of experience with footshocks of subjects from Group NSH. The present data support that a prior aversive experience may change the pattern of Fos and Egr-1 expression in brain areas of rats that learned to escape from an aversive test and substantiate the assumption that an increased gene expression may not be always related to the subject’s performance during the task (Nikolaev, Kaminska, Tischmeyer, Matthies, & Kaczmarek, 1992).

Although the objective initially set for the present study has been achieved and the evidence has led to the effect of novelty in the mPFC and hippocampus, the present findings might be interpreted as if the previous experience with shocks had adversely affected IEG induction in the test. As different types of novel stimuli, stressors, and learning conditions have been described, each one possibly activating specific brain mechanisms, other possible explanations for the present results cannot be excluded without further investigation.

**Novelty and the Prefrontal and Hippocampal Areas**

Studies have frequently related PFC and CA1 subfields to novelty, which gives support to the present findings. The PFC is involved in a neural circuit that gives rise to a positive deflection in electroencephalographic studies, termed novelty P3 or P3a (Ranganath & Rainer, 2003). P3a event-related potentials (ERPs), which have a more frontocentral scalp distribution than P3b ERPs (more restricted to the temporoparietal region), were reported after involuntary orientation to an unanticipated new event in humans (Friedman, Cycowicz, & Gaeta, 2001; Knight & Scabini, 1998). Damage to PFC has been correlated with reduced attention to novel events and to a decreased or disrupted P3a response, so that it has been hypothesized that novelty P3 response might reflect neural processes related to attention to novel events (Daffner et al., 2000; Knight & Scabini, 1998). P3a-like potentials recorded in other mammalian species indicate the hippocampal-neocortical circuitry as an essential component in novelty detection (Knight, 1996).

The CA1 subfield has been identified as anatomically constructed to function as a mismatch detector (Langston, Stevenson, Wilson, Saunders, & Wood, 2010) and the CA1 neurons as comparators of present and past experience, allowing the distinction between information processed or not by the hippocampal circuit (Hunsaker & Kesner, 2009). A selective reduction of ERPs to

![Figure 4](image-url)
novel but not to already known verbal stimuli detected in patients with hippocampal sclerosis indicates the hippocampal involvement in the processing of novelty (Friedman et al., 2001; Grunwald, Lehnertz, Heinze, Helmstaedter, & Elger, 1998). Damage to the CA1 in patients resulted in normal P3b amplitudes and in P3a reductions over the prefrontal regions (Knight, 1996). Postmortem examination of patients with impaired recognition memory (the ability of detecting the prior occurrence of stimuli) revealed bilateral lesions limited to the CA1 subfield and CA1-subicular border zone (Reed & Squire, 1997). A profound impairment in the ability to remember in rats with CA1 lesion indicates the subfield as a critical area for processing temporal information (Hoge & Kesner, 2007). However, patients with prefrontal damage and rats with mPFC lesions have also exhibited difficulties in remembering the temporal order of information (Dalley et al., 2004; Hoge & Kesner, 2007).

The Previous Aversive Experience

Acute aversive stimuli are supposed to induce c-fos and egr-1 in several brain structures, but decreased responses have been reported when the exposure to aversive stimuli is repeated (Tischmeyer & Grimm, 1999). For instance, prior exposure of mice to footshocks suppressed c-fos induction in some areas of the brain including the CA1 area (Radulovic et al., 1998), and an enhanced c-fos and egr-1 mRNA expression was detected in the rat hippocampi after a single, but not long-term avoidance training sessions, although c-fos induction was found to be preserved in the presence of novel stimuli (Nikolaev, Kamińska, et al., 1992; Nikolaev, Werka, et al., 1992).

Fos upregulation was also reported in the CA1 of rats exposed for the first time to a maze in comparison to repeatedly exposed or unexposed control rats (Papa et al., 1993). Successive presentations of novel stimuli also reduced the magnitude of novelty P3 responses in the mPFC (Friedman et al., 2001; Ranganath & Rainer, 2003). Jackson and Moghaddam (2006) examined the neuronal responses to restraint stress in the mPFC of rats and the changes after a subsequent exposure to the same contingency 2 hr later. The reduced neuronal responsiveness was concluded to indicate a disconnection of prefrontal neurons from the aversive stimulus, which could be important to preserve the organism’s ability to emit adaptive responses under stress.

The present results thus show that a previous experience with inescapable footshocks changed the pattern of Fos and Egr-1 expression in some brain regions and consequently demonstrate c-fos and egr-1 induction as experience-dependent events. Despite the similar behavioral operant performance in the aversive learning task, subjects from Groups NOV and EXP presented distinct levels of IEG expression, which suggests that similar operant behavioral performances may not generate the same pattern of Fos and Egr-1 expression in some areas of the brain.

Similar patterns of Fos and Egr-1 expression were detected between Groups NSH and EXP, so that more efforts are needed to reveal where the aversive conditions applied to the treated (EXP) group may have generated distinctive Fos and/or Egr-1 activation.
Given that all subjects from Groups NOV and EXP learned the operant contingency and moved to escape during the test, the higher Fos and Egr-I expression detected in the brain regions apparently indicates that novelty, and not the aversiveness of the event, the locomotor activity or the operant learning, led to changes in the IEG expression.

Finally, the present findings support the assumption that the nPFC, the dorsal hippocampal CA1 and DG might have functional roles in the processing of novel stimuli in aversive conditions and offer for consideration that exposure to novelty might be an important confounding factor in experiments that have investigated c-fos and/or egr-I induction in aversive learning conditions.

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