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Working memory training triggers delayed chromatin remodeling in the mouse corticostriatothalamic circuit

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ABSTRACT

Working memory is a cognitive function serving goal-oriented behavior. In the last decade, working memory training has been shown to improve performance and its efficacy for the treatment of several neuropsychiatric disorders has begun to be examined. Neuroimaging studies have contributed to elucidate the brain areas involved but little is known about the underlying cellular events. A growing body of evidence has provided a link between working memory and relatively long-lasting epigenetic changes. However, the effects elicited by working memory training at the epigenetic level remain unknown.

In this study we establish an animal model of working memory training and explore the changes in histone H3 acetylation (H3K9,14Ac) and histone H3 dimethylation on lysine 27 (H3K27Me2) triggered by the procedure in the brain regions of the corticostriatothalamic circuit (prelimbic/infralimbic cortex (PrL/IL), dorsomedial striatum (DMSt) and dorsomedial thalamus (DMTh)).

Mice trained on a spontaneous alternation task showed improved alternation scores when tested with a retention interval that disrupts the performance of untrained animals. We then determined the involvement of the brain areas of the corticostriatothalamic circuit in working memory training by measuring the marker of neuronal activation c-fos. We observed increased c-fos levels in PrL/IL and DMSt in trained mice 90 min after training. These animals also presented lower immunoreactivity for H3K9,14Ac in DMSt 24 h but not 90 min after the procedure. Increases in H3K27Me2, a repressive chromatin mark, were found in the DMSt and DMTh 24 h after the task.

Altogether, we present a mouse model to study the cellular underpinnings of working memory training and provide evidence indicating delayed chromatin remodeling towards repression triggered by the procedure.

1. Introduction

Working memory is a key cognitive function required to perform complex tasks such as reasoning, comprehension and learning. Several neuropsychiatric disorders show working memory deficits, which are indeed predictive of psychosocial and occupational impairment (Nuechterlein et al., 2004; Bajs et al., 2011; Kasper et al., 2012). During the last years it has been shown that training can improve working memory performance (Carretti et al., 2007; Akerlund et al., 2013). The efficacy of training for the treatment of several neuropsychiatric disorders has begun to be examined. There is growing evidence about the utility of training in the treatment of children suffering attention deficit disorder (Rapport et al., 2013) fetal alcohol spectrum disorder (Loomes et al., 2008) or intellectual disability (Söderqvist et al., 2012), as well as for persons with schizophrenia (Hubacher et al., 2013) or recovering from brain injury (Lundqvist et al., 2010; Johansson and Tornmalm, 2012).

Abbreviations: cAMP, cyclic adenosine monophosphate; c-fos, FBJ murine osteosarcoma viral oncogene homologue; cGMP, cyclic guanosine monophosphate; CREB, cAMP response element-binding protein; D1-R, dopamine receptor D1; DLSt, dorsolateral striatum; DMSt, dorsomedial striatum; DMTh, dorsomedial thalamus; DUSP4, dual specificity protein phosphatase 4; ERG2, ETS-related gene 2; ERK1/2, extracellular signal-regulated kinase 1 and 2; Fyn, proto-oncogene tyrosine-protein kinase Fyn; GluN2B, NMDAR subunit 2B; HAT, histone acetyltransferase; HDAC, histone deacetylase; H3K9,14Ac, acetylated histone H3 on lysines 9 and 14; H3K27Me2, dimethylated histone H3 on lysine 27; ITI, intertrial interval; LTP, long-term potentiation; NMDAR, N-methyl-D-aspartate receptor; PCAF, p300/CBP associated factor; PDE, cyclic nucleotide phosphodiesterase; PKA, cAMP-dependent protein kinase; PKG, cGMP-dependent protein kinase; PrL/IL, prelimbic/infralimbic cortex; STEP, striatal-enriched protein tyrosine phosphatase.

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Some advances have been made in the comprehension of the neural basis of such training-mediated improvement. At the brain level, neuroimaging studies in healthy controls demonstrated changes in the brain activity of task relevant areas (i.e. striatum and prefrontal and parietal cortices) as a result of training (Jansma et al., 2001; Olesen et al., 2004; Dahlin et al., 2008). However, the direction of these changes has not been clearly established. In fact, some authors have reported increments in brain activation (Olesen et al., 2004; Bäckman and Nyberg, 2013) while others show both increments and decrements associated with working memory training (Kelly et al., 2006). On the other hand, at the cellular level, there are virtually no data concerning the modifications induced by training in these brain areas.

Since training is essentially an environmentally-linked experience, its neurobiological substrate may be searched among those thought to induce long-term changes in the components of the neuronal circuits implicated in behavioral control. Several mechanisms could explain such long-lasting effects of experience. Among them, in the last years the relationship between neuronal plasticity and epigenetic mechanisms has begun to be explored (see review by Maze et al., 2013). The most studied epigenetic mechanisms with regard to memory processes are DNA methylation and post-translational modifications of histone proteins (e.g. acetylation or methylation). In particular, histone acetylation produces changes in DNA–histone interactions that lead to a transcriptionally-active open conformation of chromatin and the recruitment of additional chromatin regulatory proteins (Kuo et al., 1998; Shahbazian and Grunstein, 2007). Conversely, histone methylation can have diverse consequences on gene expression. For example, trimethylation of H3 on lysine 4 is an active chromatin mark and dimethylation on lysine 9, a repressive one (Gupta et al., 2010). Histone acetylation is mediated by histone acetyltransferases (HATs). Four classes of histone deacetylase (HDAC I–IV) remove acetyl groups from the protein, from which class I HDACs (HDAC-1, HDAC-2 and HDAC-3) appear to have a role in cognition. On the other hand, since the discovery of the first histone lysine methyltransferase in the year 2000, a great variety of methylating and demethylating enzymes have been identified. In contrast to the enzymatic machinery in charge of histone acetylation, histone methyltransferases and demethylases show residue specificity (Lilja et al., 2013; Morris and Monteggia, 2013; Parkel et al., 2013).

With respect to the relationship between covalent modifications of histone proteins and working memory most studies have employed an approach consisting in inducing modifications on the epigenetic machinery and then evaluating performance. While HDAC-1, 2 and 3 all seem to be implicated in different forms of hippocampus-dependent episodic memory (Guan et al., 2009; Hawk et al., 2011; McQuown et al., 2011; Bahari-Javan et al., 2012), only HDAC-2 has been linked with working memory. Conditional HDAC-2 knock-out mice show an improvement in an attentional set-shifting task, which explores an essential component of working memory (Morris et al., 2013), as well as in the spatial working memory non-matching-to-place task in the T-maze and in the Morris water maze (Guan et al., 2009). Interestingly, these animals also show enhanced synaptic plasticity. In this latter work, HDAC-2 overexpressing animals exhibit opposite effects on the performance at these working memory paradigms. The effect of manipulations on histone acetylating enzymes has been investigated as well. Indeed, knock-out mice for a histone acetyltransferase with a role in the CREB/CBP pathway (i.e. p300/CBP associated factor, PCAF), presented impaired performance at a spontaneous alternation task in a Y-maze (Duclot et al., 2010). As regards histone methylation, as far as we know, there is no available evidence on how its manipulation impacts on working memory performance.

Although a relationship between training-induced improvement and epigenetic marks in relevant brain areas could be hypothesized, no direct evidence is available yet. For these reasons, in this work we study the changes on histone H3 acetylation and methylation, two of the most studied histone post-translational modifications, triggered by training on a working memory task in the structures of the corticostriatothalamic circuit.

2. Material and methods

2.1. Animals

Adult male C57BL/6 mice (7–9 weeks of age, Bioterio Central de la Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina) were used for the behavioral tests. Animals were housed in groups of 4–6 in standard polycarbonate cages in an air-conditioned and humidity controlled room (21 ± 1 °C, 50%) with food and water supplied ad libitum and under a 12:12 h light/dark cycle (lights on at 8:00 a.m.). Experiments were conducted according to the Guide for the Care and Use of Laboratory Animals eighth edition (2011) provided by the National Institutes of Health, USA and guidelines provided by local authorities (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Argentina) and were approved by the Ethical Committee of the School of Medicine (Facultad de Medicina, Universidad de Buenos Aires, Argentina, Resolution Number 2969/2013). The minimum possible number of animals was used to achieve statistical significance. All efforts were made to minimize animal suffering.

2.2. Behavioral procedures and experimental groups

2.2.1. Apparatus

The apparatus was constructed based on Takao et al. (2008) with some modifications. The maze was made of white polished plastic and consisted of a start compartment (10 × 6 cm^2), a central arm (44 cm long), two goal arms (each 22 cm long) and two L-shaped auxiliary arms with a 38-cm and a 20-cm long branches. All arms were 6-cm wide and walls were 15-cm high. Guillotine doors separated each compartment and could be operated by the experimenter through a system of pulley strings.

2.2.2. Spontaneous alternation task

The procedure for the working memory test was adapted from Van der Staay et al. (2008). Briefly, mice were habituated to the maze for three consecutive days (habituation sessions). For this purpose mice were placed in the maze for 5 min along with their littermates the first day and individually the second and third day. The next day (test session) consisted of one forced-choice trial followed by 10 successive free-choice trials. In forced-choice trials either the left or right goal arm was blocked while in free-choice trials both goal arms were accessible. The goal arm blocked in the forced-choice trial was counterbalanced among animals within an experimental group. Each trial began with the opening of the start compartment's guillotine door. After crossing the central arm, the mouse could choose between the goal arms. As soon as the animal had completely entered one goal arm (including its tail) the guillotine door was lowered. The mouse remained confined for 5 s and was then let return to the start compartment through the auxiliary arms for the next trial. The inter-trial interval (ITI) was 5 s (ITI-5, Fig. 1). A session was terminated when the animal completed the free trials or 20 min had elapsed. During the sessions animals were not handled by the experimenter.

In order to establish more demanding experimental conditions with which to compare the performances of trained and untrained animals, two additional ITIs were tested: 30 and 60 s (ITI-30 and ITI-60 respectively, Fig. 1). Additionally, by this means we could confirm that the behavior observed relied on working memory mechanisms. Longer inter-trial intervals produced a decrease in the percent spontaneous alternation to chance levels (50% alternation).

The whole test session was recorded with a CCD camera (Sony, USA) and analyzed using Noldus Ethovision ® XT 7.0. The percent spontaneous alternation in arm choice during the 10 free-choice trials was then

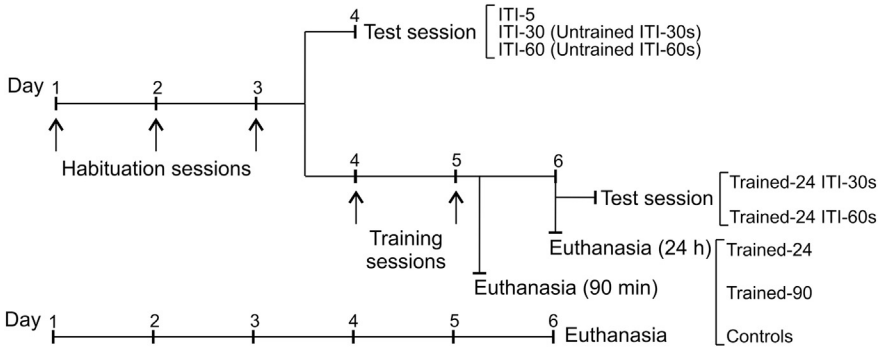

Fig. 1. Experimental procedures. C57BL/6 mice underwent three 5-min habituation sessions in the T-maze. On day 4, a group of animals were tested on the spontaneous alternation task using three different intertrial intervals: 5, 30 and 60 s (ITI-5, ITI-30, ITI-60 respectively). A separate group of animals carried out two training sessions on days 4 and 5, and were then either euthanized at different time points: 90 min or 24 h (Trained-90, Trained-24 respectively), or tested the following day with a 30-s or 60-s intertrial interval (Trained-24 ITI-30s, Trained-24 ITI-60s). The latter animals were compared with those tested with these same intertrial intervals on day 4 (Untrained ITI-30s, Untrained ITI-60s). Control animals remained in their cages during the whole procedure (Controls).

calculated as: (number of alternations in arm choice / total number of free choices) × 100. To check arm preference, the number of choices to the right was registered. The control group consisted of animals not exposed to the T-maze alternation test and that remained in their cages (Fig. 1).

2.2.3. Training protocol

We develop a novel procedure to train working memory in mice. After the three-day habituation described above, a separate group of mice underwent a two-session training procedure. These sessions consisted of 1 forced-choiced trial followed by 10 free-choice trial with an ITI of 5 s and were carried out once per day (two days). The group of animals performing this alternation task was then divided in two as follows (Fig. 1): a group returned to their home cages until the next day, when the efficacy of working memory training was evaluated, and the other was euthanized by transcardiac perfusion to extract tissue for immunohistochemical assays at either 90 min or 24 h after training.

The efficacy of working memory training was evaluated in terms of improvement in the performance in the spontaneous alternation task under the more challenging conditions of ITI-30 and ITI-60.

The sessions were recorded as explained above. The percent spontaneous alternation and the arm preference were calculated in the same manner.

2.3. Tissue extraction and preparation

Animals were deeply anesthetized with a mixture of ketamine hydrochloride and xylazine hydrochloride (200 mg/kg and 28 mg/kg i.p., respectively) either 90 min or 24 h after the test session of the training protocol. Once the palpebral reflex had been lost, the animals were transcardially perfused with saline solution containing 30 IU heparin followed by the fixating solution (4% paraformaldehyde in 0.1 M sodium phosphate buffer pH 7.4). Brains were then removed, post-fixed in the paraformaldehyde solution overnight at 4 °C and then cryoprotected in 30% sucrose in 0.1 M phosphate buffer (pH 7.4) at 4 °C until sectioned. Serial coronal sections (30 μm) were obtained using a freezing microtome (SM 2000 R, Leica CE) and stored at −20 °C in the same cryoprotectant solution until use. Sections containing the prelimbic/infralimbic cortex (PrL/IL, 1.78 mm to 1.98 mm from bregma), the dorsomedial striatum (DMSt, 0.86 mm to 1.10 mm from bregma) and the dorsomedial thalamic nucleus (DMTh, −1.46 mm to −1.70 mm from bregma) were selected according to the atlas of G. Paxinos and K.B.J. Franklin (2004).

2.4. Immunohistochemical assays: c-fos, H3K27Me2 and H3K9,14Ac

Immunohistochemical assays were adapted from Sifonios et al. (2009). Free-floating coronal sections from five or six animals per experimental group were washed in 0.01 M phosphate buffered saline pH 7.4 (PBS). The tissue intended for the staining of methylated or acetylated H3 was also incubated 25 min at 95 °C in 0.01 M sodium citrate buffer pH 6.0 and left to cool down at room temperature for 20 min before proceeding. Endogenous peroxidase was then inactivated in a 10-min incubation in 3% H_2O_2 in PBS. The sections were then rinsed 5 min in PBS and incubated with the blocking solution (0.1% Triton X-100, 3% normal goat serum, 0.01 M PBS) for 1 h at room temperature. Next, the slices were incubated with one of the following primary antibodies: anti c-fos (rabbit polyclonal antibody, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), anti dimethyl-histone H3 (K27) (rabbit monoclonal antibody, Millipore, TM, Billerica, MA, USA) or anti acetyl-histone H3 (K9,14) (rabbit polyclonal antibody, Millipore, TM, Billerica, MA, USA) diluted 1:1500, 1:1000 or 1:5000 respectively in 0.01 M PBS, 0.1% Triton X-100 and 3% normal goat serum overnight at 4 °C. Then, brain sections were washed four times for 5 min with washing solution (0.025% Triton X-100 in 0.01 M PBS) and incubated with a biotinylated anti rabbit IgG secondary antibody (Sigma Aldrich, Saint Louis, MO, USA) diluted 1:250 in 0.01 M PBS, 0.3% Triton X-100 and 3% normal goat serum for 1 h at room temperature. The tissue was then washed four times for 5 min with washing solution and incubated with ExtrAvidin–Peroxidase complex (Sigma Aldrich, Saint Louis, MO, USA) in a 1:500 dilution in 0.01 M PBS, 0.3% Triton X-100 and 3% normal goat serum for 1 h at room temperature. Next, the slices were rinsed once again by means of four 5-minute washes and incubated in 0.1 M sodium acetate buffer pH 5.5 for 5 min with agitation. After that, brain sections were incubated in acetate buffer containing 0.035% 3,3′-diaminobenzidine, 2.5% nickel ammonium sulfate and 0.1% H_2O_2. The enzymatic reaction was stopped by washing the sections first with acetate buffer and then with distilled water. Sections were mounted onto gelatin-coated glass slides and air-dried. Then they were cover-slipped using Canada balsam for light microscope observation. No immunohistochemical labeling was observed when the primary antibody was omitted.

2.5. Image capture and analysis

Sections immunostained for c-fos, H3K27Me2 or H3K9,14Ac were viewed in a Nikon Eclipse 50i light microscope coupled with high resolution CCD camera (MicroFire® model S99808, Optronics, Goleta, CA,

USA) and ExploraNova's (La Rochelle, France) mapping software Mercator Pro. In all cases, PrL/IL, DMSt, or DMTh were delimited according to previous studies (Voorn et al., 2004; Van De Werd et al., 2010) using this mapping software.

In the case of c-fos immunostained sections, a 10× objective was used. Live images were intensity-thresholded and an automatic counting procedure was performed. The whole counting procedure was repeated five times to check its repeatability. c-Fos positive element counts were normalized to 1 mm^2 considering the delimited surface area. For sections immunostained for histone H3 modifications, 3 to 5 random 236 μm × 140 μm probes were generated and images of them were captured using a 40× objective under the same conditions. Images were analyzed employing the ImageJ software (National Institutes of Health, available at http://rsb.info.nih.gov/ij/). Images were thresholded and the relative immunoreactive area (thresholded area / total area × 100) and optical density measured for each probe set as previously described (Sifonios et al., 2009). To test the reliability of the sampling procedure and the thresholding, the whole procedure was repeated five times for one brain section, obtaining a variation coefficient < 10%.

2.6. Statistical analysis

Behavioral data were expressed as the mean percent spontaneous alternation ± standard error. The data set passed Shapiro–Wilk's modified normality test (data not shown). Mean values were compared with chance levels (50% alternation) using Student's *t*-test. Arm preference was evaluated analyzing the number of choices to the right. This variable also passed the normality test and the mean was compared with the no preference condition (50% of choices to the right) using Student's *t*-test. Groups tested at different ITIs (ITI-5, ITI-30 and ITI-60, Fig. 1) were compared using a one-way ANOVA followed by Tukey's post-hoc test. Trained and untrained animals whose behavior was assessed using two ITI were compared using a two-way ANOVA. Since the interaction between factors was significant, simple effects were evaluated with Student's *t*-test.

For immunohistochemistry experiments, averages of c-fos-positive nuclei counts or relative immunoreactive area and OD of H3K27Me2- or H3K9,14Ac-stained tissue sections (two cortices, striata or thalami per section from five animals per group) were obtained. The mean values ± standard error of these averages in three to four experiments for each group were calculated. Comparisons between experimental groups were carried out using Student's *t*-test.

All statistical analyses were performed with the GraphPad Prism 3.1 (GraphPad Software Inc.). Differences were considered significant when the p value was lower than 0.05.

3. Results

3.1. Training improved performance in a working memory task using a more demanding retention interval

In order to study working memory performance, mice underwent a spontaneous alternation task in a T-maze, a spatial working memory paradigm. Choices to the right were analyzed to discard arm preference. Animals' choices were equally distributed between both arms (ITI-5: $t = 1.000$, $p > 0.10$; ITI-30: $t = 0.388$, $p > 0.10$; ITI-60: $t = 0.2076$, $p > 0.10$; $n = 9$ animals per group). Animals spontaneously alternated above chance level (81.1%, $t = 8.854$, $p < 0.0001$, $n = 9$, Fig. 2A) with a 5-s intertrial interval. As a further control and to confirm that working memory was indeed required for the spontaneous alternation behavior to express, another group of animals performed the behavioral task under two conditions which are more demanding upon working memory, i.e. a 30-s and a 60-s intertrial interval. These groups did not alternate differently from chance level (ITI-30: 54.4%, $t = 1.079$, $p > 0.05$, $n = 9$; ITI-60: 63.4%, $t = 2.172$, $p > 0.05$, $n = 9$; Fig. 2A) and showed

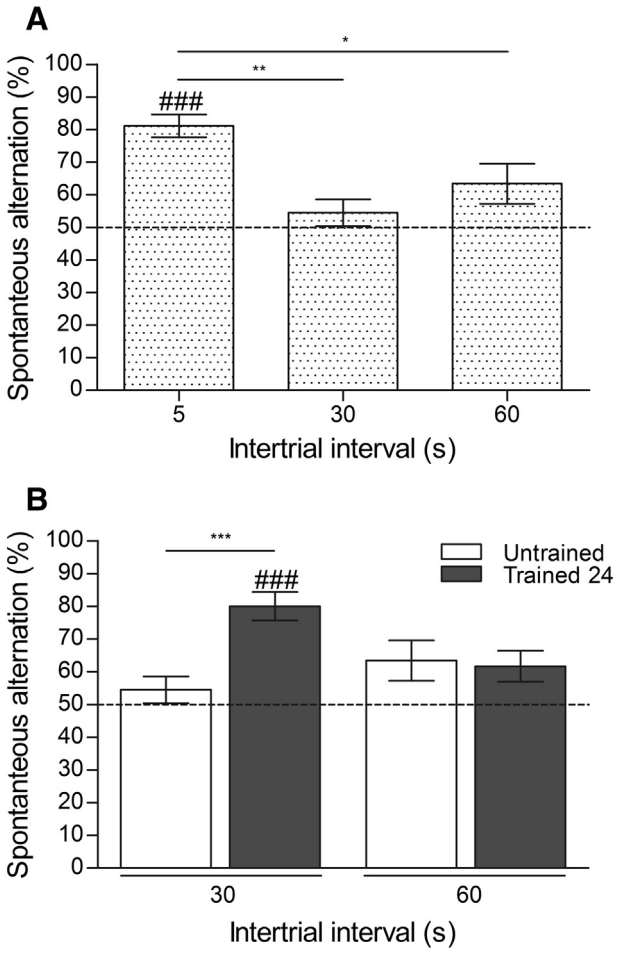

Fig. 2. Training improved performance in a working memory task using a more demanding retention interval. (A) Percent spontaneous alternation of C57BL/6 mice in a T-maze using three different intertrial interval (ITI) durations: 5, 30 or 60 s ($n = 9$ per group). The data are expressed as mean ± SEM of percent alternation. Animals alternated above chance level (50% alternation, dashed line) when the ITI was 5 s, as opposed to the longer ITI conditions where the animals significantly reduced their spontaneous alternation to chance level. (B) Trained animals improved their performance in the spontaneous alternation task compared with untrained animals when tested using a 30-s ITI but not when the ITI was 60 s. The data are expressed as mean ± SEM of percent alternation of 7–9 animals per group. ### $p < 0.001$ vs. 50%, Student's *t*-test. * $p < 0.05$, ** $p < 0.01$, one-way ANOVA followed by Tukey's post-hoc test. *** $p < 0.001$, Student's *t*-test.

a statistically significant difference from ITI-5 ($F_{2, 24} = 8.2$, $p < 0.01$; ITI-5 vs. ITI-30, $p < 0.01$; ITI-5 vs. ITI-60, $p < 0.05$). The dependence of the performance upon the retention time is indicative that the task requires working memory function.

In a separate experiment, animals performed a working memory training procedure consisting of two sessions of 1 forced-choice trial + 10 free-choice trials using a 5-s ITI, and were then subjected to a test session with either a 30-s or a 60-s ITI. A statistically significant interaction between training and ITI duration was detected ($F_{1, 27} = 6.94$, $p < 0.05$). Trained animals improved their percent spontaneous alternation compared with untrained animals when tested using a 30-s ITI ($t = 4.219$, $p < 0.001$, $n = 7$–9 animals per group) but not when ITI was 60 s ($t = 0.2027$, $p > 0.10$, $n = 6$–9 animals per group). These data suggest a retention interval-dependent improvement in working memory performance associated with training (Fig. 2B).

3.2. Working memory training produced neuronal activation in components of the corticostriatothalamic circuit

The study of the expression of immediate early genes has been used before to map the activity of brain areas in different behavioral

paradigms. Immunostaining for c-fos was carried out in the brain regions of the corticostriatothalamic circuit associated with working memory (PrL/IL, DMSt and DMTh) in control and trained animals, 90 min after training (the reported time for maximal c-fos activation) (Fig. 3). Mice that had performed the training procedure (Trained-90) showed significant increases of c-fos in PrL/IL and DMSt when compared with the controls (PrL/IL: $t = 4.329$, $p < 0.01$, $n = 5–6$ animals per group; DMSt: $t = 2.681$, $p < 0.05$, $n = 5–6$ animals per group, Fig. 3C). No changes were seen in the DMTh ($t = 0.4693$, $p > 0.10$, $n = 5–6$ animals per group, Fig. 3C) or the DLSt ($p > 0.10$, data not shown), used as a further control for the specificity of the dorsomedial striatal activation. These results indicate that there is neuronal activation within the cortical and striatal components of the circuit as a consequence of training.

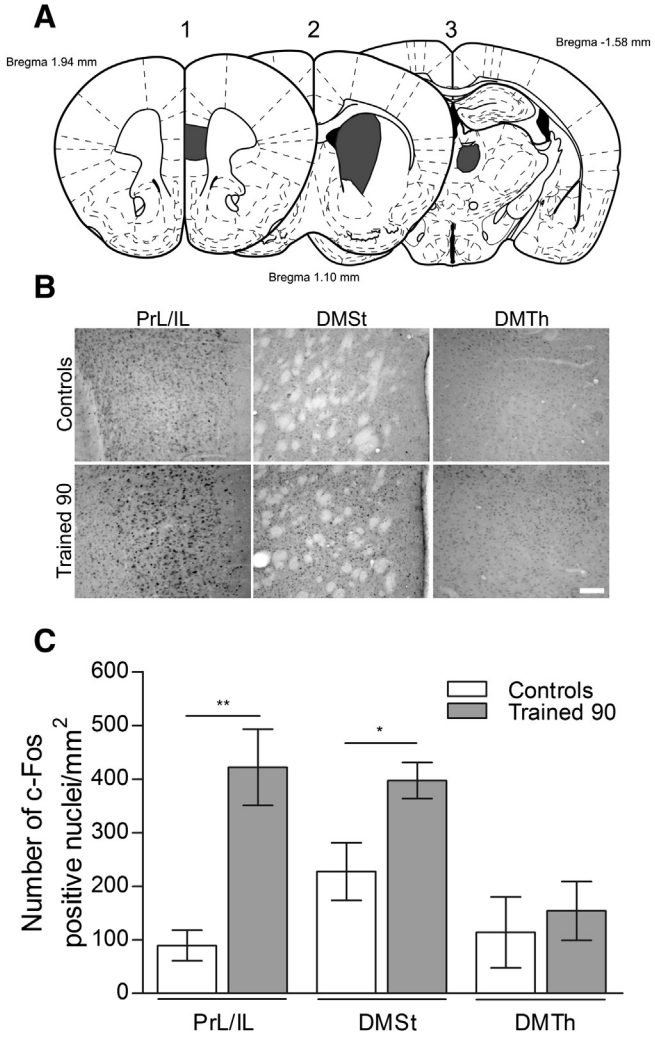

Fig. 3. Neuronal activation triggered by training on the spontaneous alternation task in the corticostriatothalamic circuit. (A) Brain sections containing the structures of the corticostriatothalamic circuit analyzed are shown: the prelimbic/infralimbic cortex (1, PrL/IL, 1.78 mm to 1.98 mm from bregma), the dorsomedial striatum (2, DMSt, 0.86 mm to 1.10 mm from bregma) and the dorsomedial thalamic nucleus (3, DMTh, −1.46 mm to −1.70 mm from bregma). The shaded area indicates the zone considered for analysis in the immunostainings. (B) Representative microphotographs taken at 10× of the c-fos immunohistochemical assays, performed in brain sections containing prelimbic/infralimbic cortex, dorsomedial striatum or dorsomedial thalamic nucleus of C57BL/6 of controls and trained mice ($n = 5–6$ per group). (C) Quantification of the immunostainings. The data are expressed as the mean number of c-fos positive nuclei per $mm^2 \pm$ SEM. Animals were euthanized 90 min after the task, based on the time reported for c-fos' peak. * $p < 0.05$, ** $p < 0.01$. Student's *t*-test. PrL/IL: prelimbic/infralimbic cortex, DMSt: dorsomedial striatum, DMTh, dorsomedial thalamic nucleus. Scale = 100 μm.

3.3. Training on a working memory task triggers delayed changes in histone methylation and acetylation

Two epigenetic marks on chromatin thought to modulate gene expression in opposite directions were analyzed in these same regions and groups at two time points: 90 min and 24 h after training.

The relative immunoreactive area for the repressive dimethylated histone H3 (H3K27Me2) was found to be unaltered in the structures analyzed 90 min after training on a spontaneous alternation task (PrL/IL: $t = 0.1120$, DMSt: $t = 2.110$, DMTh: $t = 0.7811$, $p > 0.05$, $n = 5–6$ animals per group, Fig. 4A and B). However, 24 h after training a significant increase in H3K27Me2 immunostaining was observed in the dorsomedial striatum and the dorsomedial thalamic nucleus (DMSt: $t = 3.652$, $p < 0.01$, DMTh: $t = 3.474$, $p < 0.01$, $n = 5–6$, Fig. 4C and D). No changes in the levels of H3K27Me2 were found in the prelimbic/infralimbic cortex at this time point ($t = 0.7811$, $p > 0.10$, $n = 5–6$, Fig. 4C and D).

Relative immunoreactive area for the activating acetylated histone H3 (H3K9,14Ac) did not change in the three brain regions involved 90 min after the training procedure (PrL/IL: $t = 0.7010$, DMSt: $t = 0.02933$, DMTh: $t = 0.1096$; $p > 0.10$, $n = 5–6$, Fig. 5A and B). In contrast, 24 h after training, a significant decrease in the immunoreactive area for H3K9,14Ac was observed in the dorsomedial striatum with respect to control animals ($t = 2.963$, $p < 0.05$, $n = 5–6$, Fig. 5C and D). At this time point, no changes were detected in the prefrontal cortex or the dorsomedial thalamic nucleus (PrL/IL: $t = 0.1361$, DMTh: $t = 0.8605$; $p > 0.10$, $n = 5–6$, Fig. 5C and D).

Optical density was also measured for both markers and found unaltered through all experimental groups and regions analyzed (data not shown).

4. Discussion

4.1. Validation of the spontaneous alternation in a T-maze as a working memory task

In order to explore the histone post-translational changes associated with working memory training, we first set the conditions of the spontaneous alternation task in a T-maze, a paradigm that assesses spatial working memory (Lalonde, 2002; Van der Staay et al., 2008). Given that by definition this type of memory only remains active for a short period of time (Tetzlaff et al., 2012), we first challenged its persistence by increasing the delay between trials. Animals were retained in the start compartment 5, 30 or 60 s between trials and their spontaneous alternation was assessed. While spontaneous alternation was the predominant behavior with a 5-s intertrial interval, alternation dropped to chance level when this was increased to 30 or 60 s. This observation validated the employment of the 5-s intertrial interval and the use of the behavioral procedure itself as a paradigm of working memory. Additionally, the experiment provided us with conditions in which performance was disrupted. These conditions were then utilized to test the efficacy of the training procedure.

4.2. Working memory training elicits an improvement in the spontaneous alternation in a T-maze

Next, the conditions of the training protocol were established. Mice were exposed to a two-day training procedure on the working memory task with an intertrial interval of 5 s. The following day, the performance of these animals was evaluated under more demanding experimental conditions, that is intertrial intervals of 30 and 60 s, which have been previously shown to interfere with the spontaneous alternation behavior.

We observed that animals previously trained on the T-maze paradigm showed spontaneous alternation as the predominant behavior with a 30-s but not with a 60-s intertrial interval. This could indicate

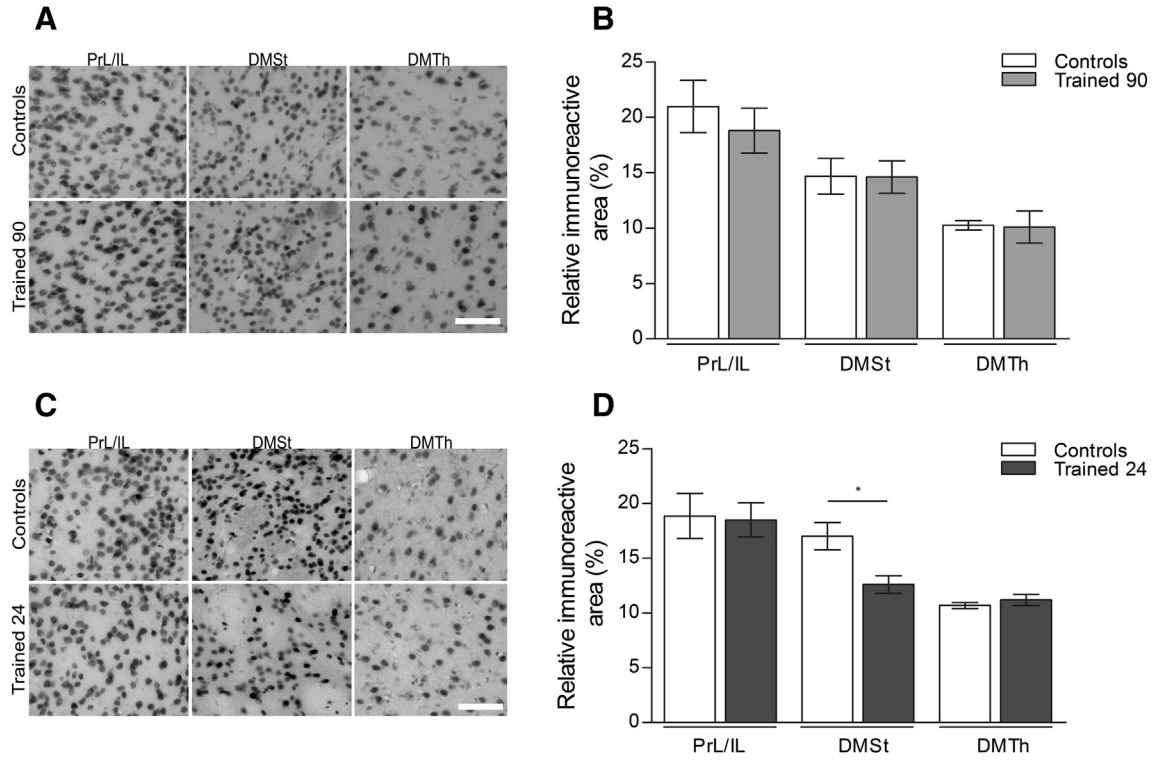

Fig. 4. Histone H3 dimethylation on lysine 27 (H3K27Me2) analysis after training on a spontaneous alternation task. *Panels A and C* show representative microphotographs taken at 40× of the immunohistochemical assays for H3K27Me2 in 30 μm brain sections containing prelimbic/infralimbic cortex, dorsomedial striatum or dorsomedial thalamic nucleus of C57BL/6 control mice and animals euthanized 90 min or 24 h after training on a spontaneous alternation task (trained-90 and trained-24, respectively) (n = 5–6 per group). On *panels B and D*, the quantification of the immunostainings is shown. The data are expressed as relative immunoreactive area (%) ± SEM. At the earlier time point (i.e. 90 min), no differences between the groups were observed for this histone modification in the structures studied. In addition, statistically significant increases were found in the dorsomedial striata and in the dorsomedial thalamic nuclei of mice euthanized 24 h after the training procedure in comparison with the control group. No changes were detected in the prelimbic/infralimbic cortex. $^{**}p < 0.01$. Student's *t*-test. PrL/IL: prelimbic/infralimbic cortex, DMSt: dorsomedial striatum, DMTh, dorsomedial thalamic nucleus. Scale = 50 μm.

that working memory training has allowed the mice to overcome the interference of longer retention times. It would also be interesting to test the efficacy of a more intensive training protocol at the 60-s intertrial interval. Once again, the dependence on the duration of the intertrial interval suggests that the improvement in performance was not due to automatic alternation behavior.

Efficacy of training for improving working memory performance has been shown in healthy people as well as in persons suffering diverse mental or neurological disorders. In healthy adults early reports go back to 1980, when Ericcson and colleagues reported a significant improvement in digit recall after exhaustive training (Ericcson et al., 1980). Since then, different training strategies were proposed and applied not only to healthy human beings but also to persons with attention deficit disorder, schizophrenia, intellectual disability and individuals who suffered from a brain injury (Comblain, 1994; Hubacher et al., 2013; Lundqvist et al., 2010; Rapport et al., 2013; Söderqvist et al., 2012; Subramaniam et al., 2014).

Training approaches can be broadly classified according to their focus on domain general or domain specific components of the working memory system (i.e. strategy training or core task training respectively) (Morrison and Chein, 2011). The approach we employed in our work could be considered as a model of the core task training approach, since animals are trained in the same task in which the efficacy of training is later tested. It would be very interesting to test whether the increased capacity observed in the animals can be generalized to another task sharing the neural substrate with that employed in the spontaneous alternation in the T maze.

The model of working memory training presented here is a simple, novel and non-rewarded procedure in which the associated cellular events can be studied in mice. So far, working memory training had only been studied in human beings employing neuroimaging. Although very interesting evidence has been provided on the pattern of brain activation and the involvement of dopamine D1 receptors (Olesen et al., 2004; Dahlin et al., 2008; McNab et al., 2009), there is an important gap in the literature regarding the consequences of working memory training at the cellular level. The model reported here could be a useful means of studying different processes such as the activation of signaling cascades, synaptic plasticity and changes in the electrophysiological properties of neurons of the corresponding circuit and in the patterns of gene expression.

4.3. Neuronal activation is increased in the prefrontal cortex and the dorsomedial striatum but not in the dorsomedial thalamus 90 min after training in mice

The expression of some immediate-early genes such as c-fos has been long known to be triggered by sustained neuronal activation (Chaudhuri et al., 2000; Guzowski et al., 2005). In the past decades, this approach has been successfully used to map brain regions that become active after behavioral tasks (Vann et al., 2000; Touzani et al., 2003; Shires and Aggleton, 2008; Matsuo et al., 2009; Barbosa et al., 2013; Fouquet et al., 2013). Therefore, in order to determine the brain areas to be explored in the search for epigenetic marks elicited by working memory training, we studied the expression of c-fos in regions previously reported to be activated by such cognitive challenge in trained animals.

We report increased c-fos expression in the trained-90 group both in the prefrontal cortex and the dorsomedial striatum with respect to control animals. This finding suggests that neuronal activation occurs in these areas as a result of working memory training. Therefore, it is worth investigating whether these structures are the scenery of events

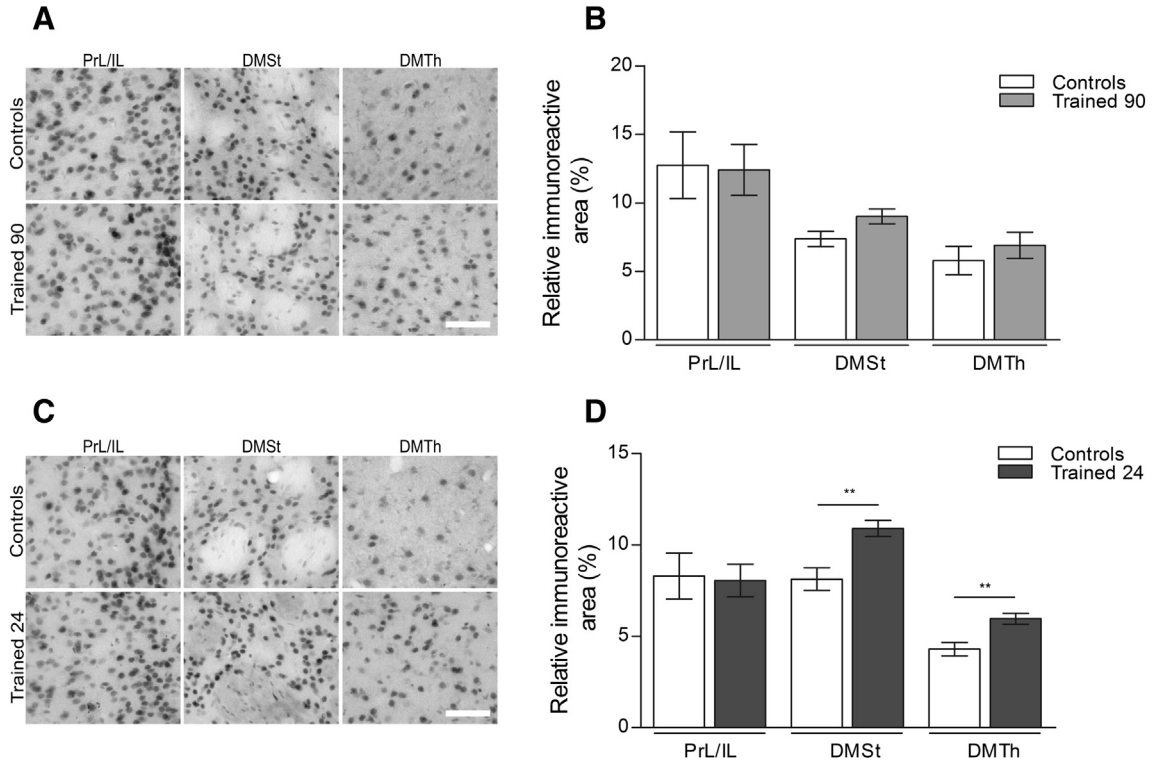

Fig. 5. Histone H3 acetylation analysis after training on a spontaneous alternation task. *Panels A and C* show representative microphotographs taken at 40× of the immunohistochemical assays for acetylated histone H3 (H3K9,14Ac) in 30 μm brain sections containing prelimbic/infralimbic cortex, dorsomedial striatum or dorsomedial thalamic nucleus of C57BL/6 control mice and animals euthanized 90 min or 24 h after training on a spontaneous alternation task (trained-90 and trained-24, respectively) (n = 5–6 per group). On *panels B and D*, the quantification of the immunostainings is shown. The data are expressed as relative immunoreactive area (%) ± SEM. Optical density was also measured (data not shown) and found unaltered through all experimental groups and regions analyzed. At the earlier time point (i.e. 90 min), no difference between the experimental groups was detected in any structure analyzed. A statistically significant difference was observed in the dorsomedial striatum in trained-24 with respect to control animals. In the prefrontal cortex or the dorsomedial thalamus, no difference was detected between the groups. * $p < 0.05$. Student's *t*-test. PrL/IL: prelimbic/infralimbic cortex, DMSt: dorsomedial striatum, DMTh, dorsomedial thalamic nucleus. Scale = 50 μm.

at the neuronal level associated with training-induced working memory improvement.

The data provided here are consistent with previous publications. Increments in c-fos expression in the prefrontal cortex have been reported by researchers who employ a different visuospatial working memory task (i.e. the radial-arm maze) (Vann et al., 2000; Touzani et al., 2003; Matsuo et al., 2009; Méndez-López et al., 2009). We now demonstrate that these increments are also observed in animals trained on a spontaneous alternation task, therefore confirming that the prefrontal cortex is a key structure in this kind of cognitive challenges. In addition, neuroimaging studies carried out in human beings provide further evidence in this same direction (D'Ardenne et al., 2012; Tanida et al., 2012). As regards the potential function of the peak of c-fos in the prefrontal cortex, the evidence suggests that it could be part of the cellular events involved in learning. Indeed, blockade of the expression of c-fos in the medial prefrontal cortex during the acquisition of a fear conditioning paradigm reduces conditioned fear-induced immobility (Morrow et al., 1999).

On the other hand, despite the growing evidence from functional neuroimaging indicating that the dorsomedial striatum is consistently recruited during various stages of working memory tasks, the role of this structure in working memory performance or training has been hardly studied in rodents (Lewis et al., 2004; Murty et al., 2011). A recent study demonstrates that the dorsomedial striatum is critically involved in the use of spatiotemporal representations to perform goal-directed navigation (Fouquet et al., 2013), a sort of exploratory behavior rather similar to that required for successfully performing the spontaneous alternation in the T-maze. The results presented here contribute to the evidence on the role of the dorsomedial striatum in working memory training.

Contrarily to what was observed in the cortex and the striatum, we observed no changes in c-fos expression in the dorsomedial thalamic nucleus. The lack of activation of this nucleus was unexpected, since lesion studies demonstrated its participation in cognitive challenges (Jenkins et al., 2002; Parnaudeau et al., 2013). However, in accordance with our results, other authors failed to observe changes in c-fos expression in the dorsomedial thalamus of intact hemispheres of animals performing a radial-arm maze task. Interestingly, these authors documented increments in c-fos or Zif268 expression in 12 brain areas including other thalamic nuclei (Jenkins et al., 2006).

4.4. Training on a working memory task induces late changes in both H3 methylation and acetylation in the dorsomedial striatum and the dorsomedial thalamus, but not in the prefrontal cortex

Once we demonstrated that working memory training induces an improvement in performance in the T maze alternation task, we investigated whether it triggers changes in histone methylation and acetylation at two time points.

As a first approach, we chose an active and a repressive chromatin mark. As regards the repressive forms of histone methylation, H3 methylation on K9, K27 and K36 have been studied in the brain, in particular di- and trimethylation (Tsankova et al., 2006; Hunter et al., 2009; Gupta et al., 2010). Among these, changes in H327Me2 in response to environmental interventions have been shown to last up to a month (Tsankova et al., 2006). On the other hand, H3 acetylation on K9 and K14 has been extensively studied in cognition, although modifications in different forms of acetylation in H4 and H2B have also been reported (Levenson et al., 2004; Fischer et al., 2007; Peleg et al., 2010; Bousiges et al., 2013). Since to the best of our knowledge there are no reports

associating any specific histone modification with working memory training, we chose to first study one of the repressive forms of H3 methylation (H3K27Me2) and the more common form of H3 acetylation, an active chromatin mark. Further studies should continue this first attempt to characterize the pattern of histone modification following working memory training to provide a more complete picture of the changes taking place.

We found no changes in either histone methylation (H3K27Me2) or acetylation (H3K9,14Ac) in any of the three structures probed 90 min after the training procedure. This suggests that changes at the level of histone tail covalent modification do not occur early after the training procedure even in the structures where neuronal activation has been detected by increases in c-fos.

In the prefrontal cortex, the levels of H3K27Me2 and H3K9,14Ac remain unchanged 24 h after training. The lack of changes in the prefrontal cortex was unexpected given the importance traditionally attributed to this structure in cognitive functions such as working memory and in particular as a consequence of working memory training in human and non-human primates (Meyer et al., 2011; Qi and Constantinidis, 2013; Vartanian et al., 2013; Wass et al., 2013). However, we cannot rule out an effect of training in a time frame different to that we examined or the involvement of other histone modifications.

In addition, H3K27Me2 was found to be increased in the dorsomedial thalamic nucleus 24 h after training. Conversely, at this time point no changes in H3K9,14Ac were detected. In the dorsomedial striatum, training had an effect both on H3K27Me2 and H3K9,14Ac, but in opposite directions: histone dimethylation on K27 increased whereas acetylation decreased.

Our observations are the first showing changes in histone post-translational modifications triggered by training on a working memory task. The fact that these modifications are associated with enhanced working memory performance is of great interest, although further experiments are required to establish to what extent and how these molecular events account for the improvement of cognitive behavior in response to training.

No reports of a linkage between any kind of histone methylation and working memory performance have been reported so far; however, there is extensive evidence strongly suggesting a connection between histone acetylation and changes in working memory performance. Indeed, pharmacological and genetic manipulations that negatively affect histone deacetylase activity were shown to have positive effects both on working memory tasks and plasticity-related parameters, as well as on other cognitive paradigms (Levenson et al., 2004; Guan et al., 2009; Morris et al., 2013a,b, Morris and Monteggia, 2013). Additionally, knock-out mice for a histone acetyltransferase involved in CREB/CBP pathway presented deficits in working memory (Duclot et al., 2010). Recently, virus-induced overexpression of HDAC-1 in the prefrontal cortex has been shown to lead to working memory dysfunction as well (Jakovcevski et al., 2013). Furthermore, the effect of hyperacetylating interventions has also been studied at the synaptic level. Histone acetylation has been shown to facilitate plastic changes (Monsey et al., 2011) which, as emerge from the positive effects of HDAC inhibition on working memory, are most likely needed for cognitive performance (Guan et al., 2009). With this background, we predicted an increment of H3 acetylation in trained animals.

The results presented here appear to contradict the reports reviewed above, in which increases in bulk histone acetylation are consistently associated with cognitive enhancement. The decrease in the active mark H3K9,14Ac we observe combined with an increase in the repressive H3K27Me2 suggests that working memory training shifts the global balance of gene expression towards repression in the dorsomedial striatum. However, it must be noticed that how these changes affect the function of specific neural circuits will depend both on the identity of the genes targeted and the role of the structure in the circuit.

In particular, it has been proposed that the dorsomedial striatum could provide a dynamic gating mechanism responsible for the selection of relevant working memory representations (e.g. plans, goals, task-relevant sensory stimuli, partial products of ongoing processing, etc.) according to their reinforcement value (Hazy et al., 2007; Murty et al., 2011). In this model, the firing of neurons of the direct and indirect pathways respectively provide Go and NoGo signals that allow this selection process. Therefore, it could be hypothesized that cellular processes leading to enhanced corticostriatal neurotransmission could improve the filtering function of the dorsomedial striatum, thus making working memory performance better.

Given that we observe a shift towards repression in global gene expression, if the changes reported here in histone acetylation and methylation are part of the mechanism of training-induced working memory enhancement, it could be suggested that genes coding for proteins that negatively affect corticostriatal neurotransmission in the dorsomedial striatum are repressed.

Two interesting targets to test for are the members of the family of the phosphodiesterases (PDE) and the striatal-enriched protein tyrosine phosphatase (STEP). These proteins are key in the modulation of glutamatergic neurotransmission by dopamine acting on the D1-R. PDEs degrade cyclic nucleotides such as cAMP and cGMP, leading to decreased activation of PKA and PKG, whose effector pathways are thought to regulate long-term corticostriatal synaptic efficacy (see review by Threlfell and West, 2013). In fact, an inhibitor of PDE10A, which is highly expressed in striatal MSNs, facilitates spontaneous and evoked corticostriatal transmission (Threlfell et al., 2009). The phosphatase STEP is known to de-phosphorylate some key proteins of these effector pathways, such as ERK1/2, GluN2B and Fyn (see review by Goebel-Goody et al., 2012). In recent works, pharmacological inhibition of these enzymes has been shown to reverse working memory deficits, suggesting that they could have an important role in this cognitive function (Van der Staay et al., 2008; Xu et al., 2014).

Furthermore, the strengthening of corticostriatal synapses could also be part of the mechanism leading to enhanced corticostriatal neurotransmission. The predominant form of long-term synaptic plasticity in the dorsomedial striatum is NMDAR-dependent long-term potentiation (Partridge et al., 2000). Interestingly, STEP knock-out mice show striatal upregulation of several genes relevant to synaptic plasticity such as ERG2 or DUSP4 (Reinhart et al., 2014). This means that the downregulation of this protein could enhance corticostriatal transmission acting on the signaling cascade and triggering long-term synaptic plasticity.

It is important to note that the speculations presented above focus on the medium-sized spiny neurons, which represent the 95% of the striatal neurons (Kemp and Powell, 1971). These GABAergic neurons receive cortical and thalamic input and are the only projection neurons in the striatum (see review by Kreitzer, 2009). We cannot rule out changes in the remaining 5% percent of neurons (mainly GABAergic and cholinergic interneurons) but the method conducted here is not sensitive enough to detect changes in these minor populations. However, astrocytes could alternatively be the cell type where the changes in histone acetylation and methylation occur. Astroglia is thought to be an important component of the tripartite synapse and modulate synaptic transmission through different mechanisms (e.g. reuptake transporters, degradation of neurotransmitters, secretion of molecules that regulate plasticity) (Goubard et al., 2011; Villalba and Smith, 2011; see review by Clarke and Barres, 2013). However, as far as we know, there are no reports on astrocytic molecules whose repression could result in working memory improvement.

It is interesting to point out that interventions of another nature have been shown to produce a similar sequence of events in the striatum than the one we report here. Martin et al. (2012) showed that the administration of a single non-toxic dose of methamphetamine produces both increases in the transcripts of c-fos early after the treatment (1–2 h) and a shift towards gene repression in the ventral striatum 24 h later (134 genes downregulated out of 197 showing differential expression). Moreover, when the authors measured global H3 acetylation at

this time point, they found that this chromatin mark was decreased. These observations are comparable to ours. It can be therefore suggested that these events are part of a general response of the striatum ultimately leading to plastic changes.

The link between c-fos and subsequent changes in chromatin marks in the striatum has not been yet established. However, some studies have provided clues that might help unravel the subject. A recent work reports a direct interaction between Fos protein and HDAC3, leading to changes in the latter's enzymatic activity (Rawat et al., 2015). Additionally, another member of the Fos family, delta FosB, regulates the expression of the methyltransferase G9a in the striatum in response to cocaine (Maze et al., 2010). These works indicate that the products of immediate early genes are capable of regulating the epigenetic machinery.

With respect to the dorsomedial thalamic nucleus, it has been long known to have dense excitatory connections with the prefrontal cortex (Kuroda et al., 1998). Recently, inhibition of this brain area has been associated with impaired working memory (Parnaudeau et al., 2013). Here, we report an increase in H3K27Me2 in the dorsomedial thalamus, which suggests that the expression of some genes is downregulated. However, it is difficult to propose candidate genes, since this nucleus receives excitatory and inhibitory inputs from the prefrontal cortex and from the output nuclei of the basal ganglia respectively, along with afferent projections from other subcortical nuclei (Kuroda and Price, 1991; Kuroda et al., 1998).

The time course of the changes in histone methylation and acetylation provides information about the dynamics of the events triggered by working memory training. The levels of these chromatin marks are not different from controls 90 min after the procedure, but changes are detected 24 h later. The activation of a series of molecular events preceding the changes in histone methylation and acetylation following training is likely.

This is not the first time that experience is observed to trigger late changes in histone acetylation or methylation status. Environmental enrichment induces methylation of H3 on the lysine 4 (H3K4Me1), an active mark, in the cortex 24 h after the procedure (Fischer et al., 2007). The levels of H3K4Me1 remained increased up to two weeks later. Additionally, H3K9 acetylation was found to be increased in this structure only two weeks after the procedure. The time course for the changes in the histone modifications observed by us is comparable with that reported by Fischer et al. as a result of environmental enrichment. This suggests that these changes have a considerable latency and can be fairly long-lasting. Interestingly enough, in both cases they are associated with cognitive improvement.

Indeed, and in particular with respect to the potential association between the epigenetic changes we report and working memory training effects, some evidence is available concerning the endurance of working memory training in humans. In healthy children, for example, improvement in diverse cognitive item (i.e. metacognition, integration skills, working memory updating as well as reading and listening comprehension) persist for at least eight months, according with the results presented by Carretti et al. (2014). Similar results were obtained by training young or older adults (Borella et al., 2013; McAvinue et al., 2013; Thompson et al., 2013), people with schizophrenia (Bowie et al., 2012) or children with attention-deficit/hyperactivity disorder (Hovik et al., 2013). It seems reasonable to propose that long-lasting chromatin remodeling changes could be at least one of the underlying mechanisms of such long term effect of training.

5. Conclusion

In summary, here we provide a mouse model to investigate the cellular underpinnings of working memory training. As far as we know this is the first study linking enhanced working memory performance as a result of training with chromatin remodeling in the corticostriatothalamic circuit. Enduring changes (24 h) in H3 acetylation in the dorsomedial striatum as well as in H3 dimethylation in the dorsomedial striatum and the dorsomedial nucleus of the thalamus were found. These changes suggest a shift towards repression in the global balance of gene expression. Further comprehension of their physiological significance requires the identification of the genes involved. In the meantime, it is interesting to point that working memory training is capable of promoting relatively long-lasting changes in histone acetylation and methylation in critical components of the participating neural circuit.

Acknowledgments

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