Brief Communication

Cognitive and neural determinants of response strategy in the dual-solution plus-maze task

Elvira De Leonibus,^{1,2,3,4,7,8} Vivian J. A. Costantini,^{1,2,7} Antonio Massaro,^{1,2} Georgia Mandolesi,⁵ Valentina Vanni,⁵ Siro Luvisetto,⁶ Flaminia Pavone,⁶ Alberto Oliverio,^{1,2,6} and Andrea Mele^{1,2,6}

¹Dipartimento di Biologia e Biotechnologie, Università degli Studi di Roma "La Sapienza," 00185 Rome, Italy; ²Centro di Ricerca in Neurobiologia-D. Bovet, Università degli Studi di Roma "La Sapienza," 00185 Rome, Italy; ³Institute of Genetics and Biophysics (IGB), CNR, 80131 Naples, Italy; ⁴Telethon Institute of Genetics and Medicine (TIGEM), 80131 Naples, Italy; ⁵Laboratory of Neuroplasticity, CERC-Fondazione Santa Lucia, 00143 Rome, Italy; ⁶Istituto di Neuroscienze, CNR-CERC, 00143 Rome, Italy

Response strategy in the dual-solution plus maze is regarded as a form of stimulus-response learning. In this study, by using an outcome devaluation procedure, we show that it can be based on both action-outcome and stimulus-response habit learning, depending on the amount of training that the animals receive. Furthermore, we show that deactivation of the dorso-medial and the dorso-lateral striatum with *Botulinum neurotoxin A*, mimicked or abolished, respectively, the effects of practice on the sensitivity of the response strategy to outcome devaluation. These findings have relevant implications for the understanding of the learning mechanisms underlying different overt behaviors in this widely used maze task.

[Supplemental material is available for this article.]

The dual-solution plus-maze task developed by Tolman et al. (1946) has been used as a valuable tool to distinguish between goal-directed actions and habitual responses. In this task, rodents are trained to retrieve food from a consistently baited arm, starting always from the same start box. Using this procedure, they may learn to find food in a particular place in space (place strategy) or to make a particular body turn (response strategy). However, by testing them from the start box used during training does not allow a discrimination of the kind of strategy used by the animals. But the strategy they use can be resolved by submitting them to a probe test from the opposite arm. It has been demonstrated that with increasing training, normal rats shift from a place to a response strategy (RS) (Packard and McGaugh 1996; Packard 1999; Yin and Knowlton 2004). There is a wealth of studies in the literature, both in rats and mice, which adopts the RS to study the neurobiology of stimulus-response (S-R) habit learning (Packard 1999; Passino et al. 2002; Colombo et al. 2003; Compton 2004; Middei et al. 2004a, b; Brightwell et al. 2008; Kheirbek et al. 2009; Moustgaard and Hau 2009; Ferragud et al. 2010). Nevertheless, the kind of learning mechanism underlying RS has never been studied before. Recent experimental evidence in instrumental tasks showed that, independently of the behavior observed, the same response can rely on either action-outcome (A-O) or S-R association, respectively, controlled by reward expectancy or by antecedent stimuli. Thus, a stringent criterion to discriminate the learning mechanism underlying the RS would be to test its sensitivity to reward devaluation (Vanderschuren and Everitt 2004; Yin et al. 2004, 2005a,b; 2006).

Toward this result, in this study food-restricted (80%–85% of their free-feeding weight) CD1 adult male mice (Charles River, Italy) were trained (15 consecutive trials × day, ITI = 40 sec) for 26 d to find a reward (chocolate puffed rice) in a constantly baited arm (e.g., west), always starting from the same start box (south) (Fig. 1A, Training panel). When animals entered the unbaited arm they were confined there for 15 sec (with no reward available) and the response was scored as incorrect trials. Entry into the baited arm was rewarded with one grain of chocolate and scored as a correct trial (Fig. 1A, Training panel). On day 27, the mice were tested for the acquired strategy, releasing them from a novel arm (north) (Fig. 1A, Probe 1 panel). Animals entering the arm where the reward was located during training were designed as “place;” on the contrary, animals making the same turning response as during training were designed as “response” or using response strategy (RS) (Fig. 1A, Probe 1 panel).

As shown in Figure 1B, 82% (22 out of 26 animals, $P = 0.001$) of the animals approached the goal box opposite to the one consistently baited during training. This result confirms that long-lasting training favors the use of RS (a specific body turn) as compared with a place strategy (Packard 1999; Yin and Knowlton 2004).

To test the sensitivity of the RS to reward value change, mice displaying RS on day 27 were submitted for five consecutive days to a reinforcement devaluation procedure by pairing the chocolate reward with Lithium Chloride (LiCl) once the animals were placed in a waiting cage after training (Supplemental material). Control mice (valued) were administered with saline (Fig. 1A, Devaluation panel). This procedure, while inducing taste aversion to the reward, as shown by the significant reduction in chocolate consumption observed both in the waiting cage and in the maze (Supplemental Fig. S1A,B), did not affect the number of correct trials from the training arm (Fig. 1C). In fact, the percentage of correct trials expressed by reward-devalued mice on day 5 of reward

⁷These two authors contributed equally to this work.

⁸Corresponding author.

E-mail deleonibus@igb.cnr.it; fax 39-081-6132706.

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Figure 1. (A) Schematic representation of the apparatus, the training, and the testing procedures with the indication of the start and the goal arm in different stages. The apparatus was a plus maze, consisting of four radial arms (north, south, east, west) with clear Plexiglas walls and a black-opaque Plexiglas floor. The maze was placed in the center of a black square-shaped gazebo measuring 2×2 m and enlightened by a lamp (60 W) positioned directly above the maze. (B) Percentage of mice emitting a place or a response on probe test 1 (day 27) in the dual-solution plus-maze task, showing a preferential use of the response strategy. (C) Percentage of correct trials on day 26 (before devaluation) and on day 31 (on day 5 of devaluation) in the valued and devalued groups. (D) Percentage of mice using a response strategy on probe test 1 (day 27), maintaining their response on probe test 2 (day 32) in the valued and devalued group. Devalued, but not valued mice shifted their response. (E) Percentage of mice using a place or a response strategy after overtraining on probe test 1 (day 61). After 61 d of training most animals use a RS. (F) In overtrained mice the percentage of correct trials on the last devaluation day (day 66) did not differ from percentage of correct trials emitted on last training day (day 61). (G) When response learners mice trained for 61 d were submitted to outcome devaluation, no change in turning response was observed in the second probe test (on day 67). (‡) $P < 0.05$ Place vs. Response on probe test 1 (day 27 or 62); (*) $P < 0.05$ before and after devaluation—day 27 vs. day 32.

devaluation (day 31) did not differ from that of the same group before devaluation or that of the valued controls (outcome $F_{(1,20)} = 1.824$; $P = \text{n.s.}$), days [$F_{(1,20)} = 1.924$; $P = \text{n.s.}$], outcome $\times$ days [$F_{(1,20)} = 2.982$; $P = \text{n.s.}$] (Fig. 1C). This result demonstrates that the turning response emitted by the animals, starting from the familiar start box, is insensitive to reward devaluation, consistent with an S-R habit learning. The same mice were then submitted to an additional probe test (day 32), in which they were released from the start box opposite to the one used during training (Fig. 1A, Probe 2 panel). Most mice in the control group maintained their turning response (Fig. 1D). The behavior of this group confirmed that RS is insensitive to maze arm change, and, therefore, is not guided by spatial information. Unexpectedly, the devalued group, when released from the novel arm, shifted behavior, turning in the opposite direction (Fig. 1D), (χ^2 for the devalued and valued groups being, respectively: $\chi^2 = 5.33$, $P = 0.020$, and $\chi^2 = 0.90$, $P = \text{n.s.}$).

These data show that the RS in the plus maze is insensitive to changes in the reward value in animals released from the training arm, but sensitive to changes from the novel arm. This means that the turning behavior in the two testing conditions has a different sensitivity to reward devaluation and, therefore, might be based on distinct learning mechanisms. Since the north start arm could be distinguished from the south arm only if the animal codified the spatial relationship between all of the other available stimuli in the environment ("context related information"), these data suggest that learned responses (from the training arm), insensitive

to the reward value change during the initial test conditions, became sensitive when a spatial change occurred. Recent findings demonstrated that when hungry rats are trained on single response, test performance is insensitive to devaluation of the contingent outcome. On the contrary, training on a schedule that offers a choice between responses that yield different outcomes prevents the onset of behavioral autonomy (Kosaki and Dickinson 2010). According to these data, RS animals were not sensitive to reward devaluation from the familiar arm because they were not trained for an alternative; on the contrary, when they were released from the opposite arm, they were challenged by the spatial change and able to use a goal-directed behavior against the acquired habit. These findings prompt the suggestion that when changes in the subjects' motivation failed to modify habits, a simultaneous spatial change might favor the desired behavioral modification.

To test whether further practice could yield a complete behavioral autonomy, in the next experiment we overtrained the mice for 61 d (915 trials). As expected, most mice (71%, 15 out of 21, $P = 0.03$) when challenged from the novel arm on day 62 (probe 1), made the same body turn utilized during training (RS) (Fig. 1E). Mice utilizing the RS were then submitted to the reward devaluation procedure for 5 d, as previously described. After devaluation, mice showed reduced food consumption (Supplemental Fig. S1C,D). Despite the acquired taste aversion, the response of the devalued group did not differ from that of the valued controls (Fig. 1F) (Days [$F_{(1,20)} = 6.72$; $P = 0.02$]; no significant differences with post-hoc analysis). However, in this study unlike previously, when tested on day 67 (Probe 2) from the novel arm devalued mice showed a response similar to that of the controls (Fig. 1G) Devalued [$\chi^2 = 0.11$, $P = \text{n.s.}$] and valued group [$\chi^2 = 0.17$, $P = \text{n.s.}$].

These results demonstrate that overtraining makes RS insensitive to both arm-entering and reward-value changes. Furthermore, the difference observed in the sensitivity to reward value changes from the novel arm in the animals trained 26 vs. 61 d provides the first experimental evidence in the literature that RS acquired after extensive training in the plus maze can be either dependent or independent of the value of the reinforcement. This allows for the conclusion that RS can be based on A-O or S-R (Adams and Dickinson 1981; Adams 1982; Balleine 1992) depending on the amount of training the animals receive. A direct implication of this result is that, although the probe test is generally used to infer the kind of learning mechanism used by the animals relying on RS (Packard 1999; Passino et al. 2002; Colombo et al. 2003; Compton 2004; Middei et al. 2004a, b; Brightwell et al. 2008; Kheirbek et al. 2009; Moustgaard and Hau 2009; Ferragud et al. 2010), the turning behavior from the novel arm is not sufficient to define it by itself.

Recent experimental evidence shows that manipulations of the dorso-medial striatum (DMS) impair A-O learning (Yin and Knowlton 2004; De Leonibus et al. 2005; Yin et al. 2005a), while

Figure 2. BoNT/A injection in the dorsal striatum. (A) Reconstruction of coronal sections through the dorsal striatum. Numbers represent the anterior–posterior coordinates relative to the bregma according to the mouse brain atlas (Franklin and Paxinos 1997). (B–E) The robust immunostaining for cleaved SNAP-25 (red labeling) shows the effectiveness of BoNT/A treatment at 7 d (B,C) and 46 d after the injection (D,E). C and E are a high magnification of the white square in B and D, respectively. (F) Staining for cleaved SNAP-25 in control mice injected with saline solution. Scale bar, B, D, and F, 100 μm; C and E, 10 μm.

lesions of the dorso-lateral (DLS) component of the striatum induce deficits in S-R habit learning (Yin and Knowlton 2004; Yin et al. 2005b). Therefore, we tested the involvement of the DMS and DLS in mediating RS sensitivity to outcome value change after 26 and 61 d of training, respectively. With this aim in mind, different groups of animals were injected with the *Botulinum neurotoxin A* (BoNT/A) (Supplemental material) before the beginning of training. BoNT/A is able to induce a long-lasting inhibition of neurotransmitter release by cleaving SNAP-25 (synaptosomal-associated protein of 25 kDa), an essential component of the vesicle fusion machinery (Schiavo et al. 2000; Rossetto et al. 2006; Antonucci et al. 2008). Figure 2 shows the expression levels of the cleaved SNAP-25 in the striatum 7 and 46 d after BoNT/A administrations. The cleaved protein was expressed in the striatum at both time points, confirming, in our conditions, the long lasting effects of the toxin (Schiavo et al. 2000; Rossetto et al. 2006; Antonucci et al. 2008). The analysis of the extension of the immunoreactivity, demonstrated that the mean values of the major axis (dorsoventral) and the minor axis length (medialateral) were 1.1 ± 0.07 and 0.9 ± 0.13 mm, respectively. We estimated a spread of about 1.8 mm in the rostrocaudal direction, thus demonstrating that the effect was limited to the target area.

Consistent with previous findings in the literature (Yin and Knowlton 2004) pretraining DMS (Supplemental Fig. S2A) or DLS (Supplemental Fig. S2C) injection of BoNT/A had no effect or a negligible one on the percentage of correct trials during training (Days [$F_{(1,25)} = 54.07$; $P < 0.0001$] and Treatment [$F_{(1,33)} = 3.92$; $P = 0.056$], respectively, for DMS and DLS). Although DMS deactivation slightly affected the percentage of animals using RS, we could not find any significant difference between the sham (82%) and the DMS group (68%) in the percentage of animals using the RS ($\chi^2 = 1.01$, $P = \text{n.s.}$) (Supplemental Fig. S2B). This is consistent with previous findings showing that DMS

lesions do not affect the use of RS (Yin and Knowlton 2004). Both DMS (BoNT/A-injected) and sham (vehicle-injected) animals showed conditioned taste aversion to chocolate (Supplemental Fig. S1A,B). However, DMS mice generalized food aversion between the waiting cage and the maze more efficiently. RS from the familiar arm was not affected in reward-devalued DMS animals (Day [$F_{(1,33)} = 6.17$; $P = 0.02$]; Day $\times$ Outcome [$F_{(1,33)} = 5.73$; $P < 0.02$]) (Fig. 3A). However, in contrast to devalued sham animals ($\chi^2 = 5.33$; $P = 0.02$) reward-devalued DMS animals maintained their turning response when released from the novel starting box ($\chi^2 = 0.12$; $P = \text{n.s.}$) (Fig. 3B). These findings demonstrate that intact synaptic transmission within the DMS is necessary to maintain the RS sensitive to the outcome value change from the novel arm. As already mentioned, the response observed after 26 d of training in sham reward-devalued animals when released from the novel arm suggests an interaction between motivational and spatial information. As a consequence, the preservation of the RS in devalued DMS mice allows one to speculate that this might be the site where spatial and outcome-related information are linked to the action, making it flexible according to motivational and contextual demands.

The analysis of the effects of DLS deactivation in a group of mice submitted to the 61 d of training shows, consistent with some previous findings (Botreau and Gisquet-Verrier 2010), but not others (Packard and McGaugh 1996; Packard 1999), no impairment in the use of RS in DLS (BoNT/A-injected) animals when compared with sham (vehicle-injected) controls ($\chi^2 = 0.03$, $P = \text{n.s.}$) (Supplemental Fig. S2D). The mice that used RS in the two experimental groups were then submitted to the devaluation procedure. Devalued DLS mice, as the sham group, developed conditioned taste aversion (Supplemental Fig. S1C,D). Nevertheless, on the last day of devaluation, the percentage of correct trials did not differ between the two groups when released from the start box used during training (Days [$F_{(1,20)} = 12.58$; $P = 0.002$]) (Fig. 3C). Finally, devalued DLS mice, in contrast to

Figure 3. Dorsomedial (DMS) and dorsolateral (DLS) striatal deactivation effects on the use of response strategy after devaluation. (A) Percentage of correct trials in sham and DMS BoNT/A-injected groups, valued or devalued, on the last day of training (day 26) or on the last day of devaluation (day 31). (B) Percentage sham or DMS mice using a response strategy on probe test 1 (day 27), maintaining their response on probe test 2 (day 32) in the valued and devalued groups. (C) Percentage of correct trials in sham and DLS BoNT/A-injected groups, valued or devalued, on the last day of overtraining (day 61) or on the last day of devaluation (day 66). (D) Percentage sham or DLS mice using a response strategy after overtraining on probe test 1 (day 62), maintaining their response on probe test 2 (day 67) in the valued and devalued groups. (*) $P < 0.05$ Tukey Honestly Significant Difference (HSD) post-hoc analysis to compare within group before and after devaluation—day 27 vs. day 32, or day 62 vs. day 67.

sham-devalued animals, shifted their response when starting from the novel arm ($\chi^2 = 4.00$, $P = 0.045$) (Fig. 3D). This result indicates that inactivation of DLS prevented the development of RS insensitivity to the interaction between the spatial change and reward devaluation promoted by overtraining. According to the current literature, this region plays a crucial role in S-R learning (Yin et al. 2005b, 2006). Therefore, one should expect impairment in the use of RS independently of the releasing arm or the devaluation procedure. The lack of effects on RS, observed in this study after 61 d of training, as well as after devaluation when mice were released from the familiar arm, suggests that an intact DLS might be required when novel stimulus-response learning is being formed, or when it is generalized to novel situations (e.g., a novel arm); with overtraining, however, its function might be bypassed by the activation of other brain regions (e.g., cerebellum) (Lancioni et al. 2010). The fact that DLS neural deactivation might not affect the acquisition of S-R association per se if the animals have more time to learn implies that this brain region might have a permissive, but not an indispensable role in habit formation under overtraining conditions.

In conclusion, in this study, by using a reward devaluation procedure we showed that animals using the RS, after 26 d of training changed their response when tested again after devaluation of the reward, indicating that they were not relying on S-R learning. Nevertheless, if the animals were overtrained for 61 d, RS became completely independent on the hedonic value of the reward. This suggests that RS acquired in the dual-solution plus-maze task can rely on both A-O and S-R association, depending on the amount of training the animals receive. These findings challenge two general assumptions about the response strategy in the cross maze: (1) that the RS is always a form of S-R, (2) that the kind of learning mechanism that the animal is using from the training arm can be inferred by probing the animal from the novel arm. Finally, we showed that neural deactivation of the DMS and the DLS with BonT/A favored and abolished, respectively, the effects of practice on the sensitivity of the RS to outcome devaluation. Altogether, these results have relevant implications for the understanding not only of the neural basis of habit learning, but also of the learning mechanisms underlying different overt behaviors in this widely used maze task.

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