

SHORT COMMUNICATION

Cocaine-experienced rats exhibit learning deficits in a task sensitive to orbitofrontal cortex lesions

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Abstract

Addictive drugs, such as cocaine, cause long-lasting neural changes in prefrontal cortex. It has been hypothesized that these changes affect the behavioural control mediated by orbitofrontal cortex. To test this hypothesis, rats were given injections of cocaine (30 mg/kg/d, i.p.) or vehicle for 14 days and then trained after a 2-week withdrawal period in an odor discrimination task sensitive to the effects of orbitofrontal cortex lesions. We found that cocaine-treated rats, who demonstrated long-lasting sensitization to the locomotor activating effects of cocaine, failed to show normal changes in response latency during discrimination learning and were also slower than controls to acquire serial reversals. These behavioural impairments are identical to the effects of orbitofrontal cortex lesions in this task and show that cocaine exposure in rats can cause long-lasting effects on orbitofrontal-dependent functions. Notably, these effects were not correlated with increases in locomotor activity linked to cocaine-induced psychomotor sensitization observed before or after training, suggesting that the brain changes underlying the behavioural effects in the discrimination task are different from those mediating psychomotor sensitization.

Introduction

Exposure to psychostimulants results in persistent structural and functional changes in a set of interconnected brain regions, including the ventral tegmental area, nucleus accumbens and regions within the prefrontal cortex (Everitt & Wolf, 2002). These areas are implicated in processing information about the rewarding effects of drugs (Wise, 1996), but they are also critical to normal behaviour, leading to the proposal that these brain changes, particularly their effects on functions that depend on orbitofrontal cortex (OFC), may account for important aspects of cocaine addiction (Jentsch & Taylor, 1999; Robinson & Berridge, 2000; Volkow & Fowler, 2000). Consistent with this idea, cocaine users and cocaine-experienced monkeys exhibit deficits in OFC-dependent behaviours (Grant *et al.*, 2000; Bechara *et al.*, 2001; Jentsch *et al.*, 2002; Coffey *et al.*, 2003), and these deficits are accompanied by metabolic changes in OFC (Breiter *et al.*, 1997; London *et al.*, 2000; Volkow & Fowler, 2000; Bolla *et al.*, 2003).

Although these reports are valuable, human studies cannot reveal whether OFC dysfunction is a cause or an effect of cocaine use, and damage to other brain regions can cause impairments in the tasks that have been used in these studies (Jones & Mishkin, 1972; Stern &

Passingham, 1995; Bechara *et al.*, 1999; Bussey *et al.*, 1999; Cardinal *et al.*, 2001; Hampton & Murray, 2002). In addition, OFC deficits in primates are difficult to link to brain changes documented in rats after cocaine exposure (Pierce *et al.*, 1998; Robinson & Kolb, 1999; Thomas *et al.*, 2001; Trantham *et al.*, 2002; Bowers & Kalivas, 2003). Indeed, studies in rats often focus on changes in medial rather than orbital prefrontal cortex and their involvement in the well-documented psychomotor sensitizing effects of cocaine (Pierce & Kalivas, 1997; Pierce *et al.*, 1998). Little is known about the effects of cocaine on the structure and function of OFC in rats.

To test whether cocaine exposure in rats causes long-lasting changes in OFC-dependent functions, and to explore the relationship between such behavioural changes and the psychomotor sensitizing effects of cocaine, we tested cocaine-experienced rats in a discrimination task in which OFC lesions produce distinctive impairments (Schoenbaum & Setlow, 2003; Schoenbaum *et al.*, 2003). In this task, rats learn to respond to odor cues to obtain reward and avoid punishment, and to modify these responses when the cue–outcome associations are reversed. Like primates with damage to OFC, rats with OFC lesions are impaired at such flexible responding in this task (Schoenbaum *et al.*, 2003). Here, we report that cocaine-experienced rats exhibit a pattern of impairments identical to OFC-lesioned rats in this task and that these impairments are dissociable from drug-induced increases in locomotor measures reflecting the development and expression of persistent psychomotor sensitization.

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Materials and methods

Subjects

Male Long-Evans rats (300–350 g; Charles River Laboratories, Wilmington, MA, USA) were housed individually on a 12-h light–dark cycle with free access to food and water except during discrimination testing when water access was restricted to 30 min/day. Testing was conducted at Johns Hopkins and conformed to National Institutes of Health guidelines; data were analysed at the University of Maryland School of Medicine.

Sensitization

Locomotor activity was monitored using eight plexiglas chambers (25 cm on a side) equipped with activity monitors (Coulbourn, Allentown, PA, USA). The rats were divided into two groups that were matched for their spontaneous activity levels during a 1-h pretreatment session. Subsequently, one group ($n = 11$) received daily i.p. injections of 30 mg/kg cocaine HCl (NIDA) for 14 days; the other group ($n = 12$) received injections of similar volume of a 0.9% saline solution. After each injection, the rats were monitored in the activity chambers for 1 h before being returned to their home cages. After this 14-day treatment phase, the rats underwent a 2-week withdrawal period and then were tested on the odor discrimination task for ≈ 6 weeks. At the end of behavioural testing, rats were challenged with ascending doses of cocaine. For this test, rats in both groups received i.p. injections of 0.9% saline and 7.5, 15.0 or 30.0 mg/kg cocaine. After each injection, rats were monitored in the activity chambers for 1 h as before.

Behavioural testing

Testing began 14 days after cocaine treatment ended and took ≈ 6 weeks for all rats to complete. The apparatus and training schedule were identical to that used previously (Schoenbaum *et al.*, 2003). Behavioural testing occurred in four square aluminium chambers (45 cm/side). Odors were presented at a 2.5-cm odor port in the wall of each box below a pair of panel lights. Fluids were presented at a well located on a ledge below. The task was computer-controlled. When the panel lights were lit, nosepoke into the port resulted in delivery of an odor cue. Each odor problem consisted of two odors. One odor (S1+) indicated that a response at the well would result in delivery of a 10% sucrose solution; the other odor (S2–) indicated that the same response would result in delivery of a 0.02-M quinine solution. If no response was detected at the well within 3 s, the trial was counted as a no-go. Rats were required to learn four different problems (D1–D4) to a criterion of 18 correct responses in 20 trials. After learning these four problems, rats were required to learn two serial reversals of the last problem (D4). During behavioural testing, the rats' preference for the two outcomes (sucrose and quinine) was also assessed by presenting them with bottles containing sucrose and quinine in their home cages for 10 min.

Results

Development and expression of cocaine psychomotor sensitization

Locomotor activity counts during cocaine treatment are presented in Fig. 1A. Cocaine-treated rats did not differ from controls initially but exhibited increased locomotor activity thereafter. A two-factor ANOVA (treatment \times session) revealed significant effects of treatment ($F_{1,21} = 124$, $P < 0.001$) and session ($F_{14,294} = 23.1$, $P < 0.001$) and a significant interaction between the two factors ($F_{14,294} = 67.8$, $P < 0.001$). Locomotor activity counts following ascending challenge doses of cocaine after a period of withdrawal are presented in Fig. 1B. Rats previously treated with cocaine showed significantly more

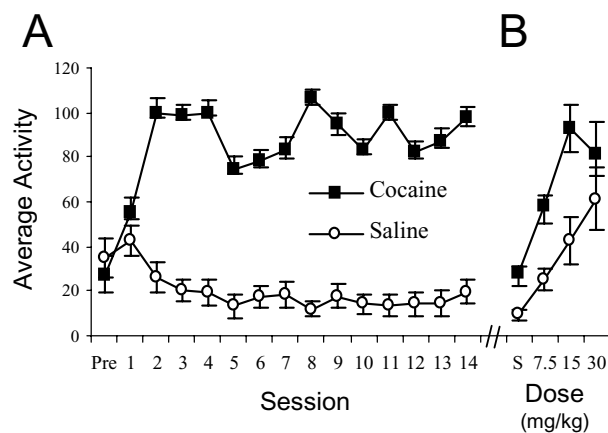


FIG. 1. Locomotor activity in cocaine-treated (■) and control (○) rats, (A) during the 2-week sensitization induction before behavioral training and (B) during dose-response testing after behavioral training. Average activity counts are shown for each 1-h session, which followed each cocaine or saline injection. Counts are measured in 5-min blocks and averaged across the session.

locomotor activity, such that the dose–response curve was shifted to the left. A two-factor ANOVA (treatment \times dose) revealed significant effects of treatment ($F_{1,21} = 11.7$, $P < 0.01$) and dose ($F_{3,63} = 24.13$, $P < 0.001$) and a trend towards a significant interaction between them ($F_{3,63} = 2.18$, $P = 0.09$).

Discrimination learning

Fourteen days after the final cocaine injection, rats began odor discrimination training (Fig. 2A). All rats achieved criterion performance on the four problems. A two-factor ANOVA (treatment \times odor problem) revealed a significant effect of problem ($F_{3,63} = 80.8$, $P < 0.001$), reflecting a reduction in trials-to-criterion across problems, but no effect of treatment condition. Subsequent analyses focused on performance during acquisition of the three nonshaping odor problems (D2–D4). Although control and cocaine-treated rats acquired these problems at the same rate, cocaine-treated rats developed differences in response latency on negative-go vs. positive-go trials to a lesser degree and more slowly than controls (Fig. 2B). A three-factor ANOVA (treatment \times odor problem \times phase) revealed no significant effect of treatment on latency difference, but there was a significant effect of phase ($F_{2,42} = 13.9$, $P < 0.001$) and a significant interaction between treatment and phase ($F_{2,42} = 3.72$, $P < 0.05$). *Post hoc* testing indicated that the latency difference increased significantly by the late phase in controls but not until the postcriterion phase in cocaine-treated rats. Even postcriterion, the difference in cocaine-treated rats was much smaller than that in controls, although this comparison did not reach significance ($P = 0.10$). This difference was largely a result of changes in response latency on the negative-go trials (Fig. 2B, inset). Consistent with this interpretation, a three-factor ANOVA (treatment \times valence \times phase) revealed a significant interaction between treatment, valence and phase ($F_{2,42} = 3.70$, $P < 0.05$). Importantly, neither the development of a latency difference in the late phase nor actual latency measures (data not shown) were correlated with the change in locomotor activity exhibited by the cocaine-treated rats either before or after training (Table 1).

Reversals

As shown in Fig. 2C, cocaine-treated rats were impaired on the initial reversal (S1–/S2+) and on a second reversal back to the original contingencies (S1+/S2–). A three-factor ANOVA (treatment \times contingency \times reversal) showed significant effects of treatment

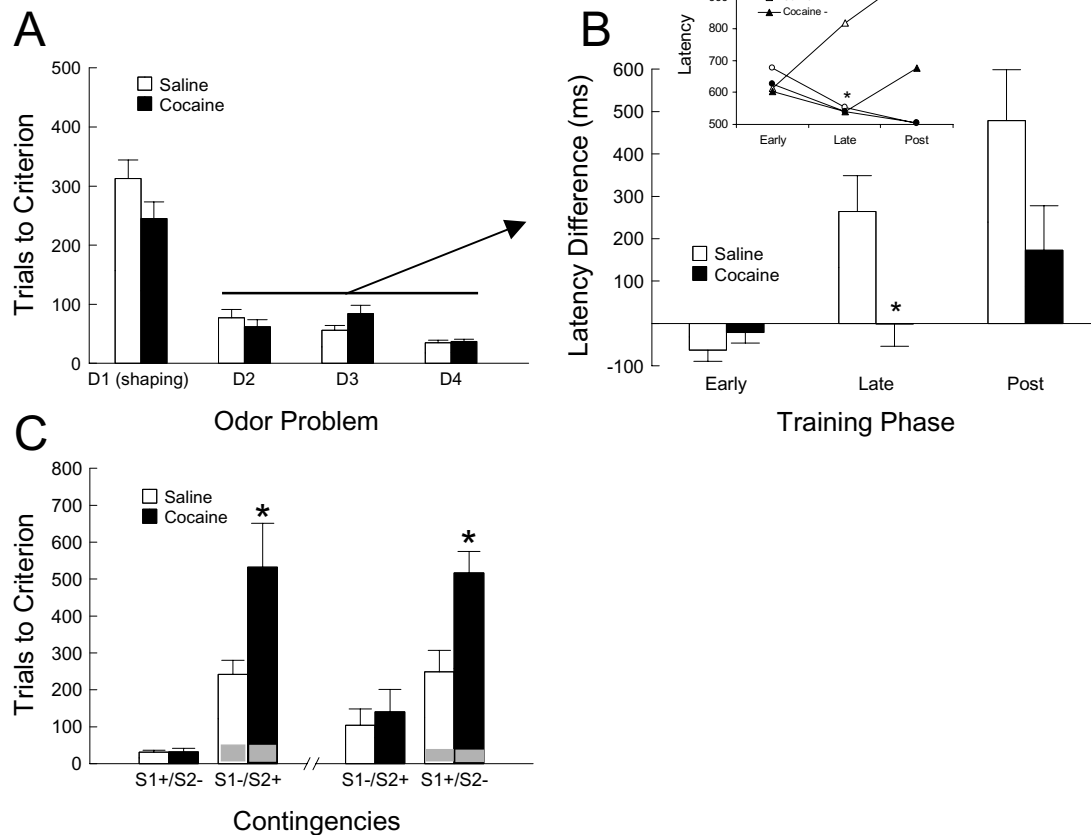


FIG. 2. Acquisition of successive odor discrimination problems and reversals by cocaine-treated (black bars) and control (white bars) rats, 14 days after the final cocaine treatment. (A) Rate of acquisition of each odor discrimination problem (D1, D2, D3 and D4) is represented as the trials it took for each rat to meet a criterion of 18 correct responses in a moving block of 20 trials. (B) The difference in latency (ms) to respond at the fluid well on negative-go minus positive-go trials, averaged over acquisition of the second (D2), third (D3) and fourth (D4) discrimination problems; no-go trials were excluded. The inset shows latencies on positive and negative trials separately for comparison. (C) Rate of acquisition of two serial reversals of the final odor discrimination problem (D4). Performance is shown for both the retention and reversal phases of training, represented as the trials required for each rat to meet a criterion of 18 correct responses in a moving block of 20 trials. Grey areas on reversal days indicate the trials required to reach 50% performance as a measure of perseveration (* $P < 0.05$).

($F_{1,21} = 10.4$, $P < 0.01$) and reversal ($F_{1,21} = 85.9$, $P < 0.001$), and a significant interaction between treatment and reversal ($F_{1,21} = 15.4$, $P < 0.001$). A two-factor ANOVA (treatment \times reversal session) comparing the trials required to reach 50% performance after reversal

TABLE 1. Correlations between the mean reversal performance (trials-to-criterion), latency difference (late phase), and changes in cocaine-induced locomotor activity (locomotor activity after exposure to cocaine minus baseline locomotor activity) before and after discrimination training

| | Reversal performance | | Latency difference | |
|--------------------------------|----------------------|----------|--------------------|----------|
| | <i>r</i> | <i>p</i> | <i>r</i> | <i>p</i> |
| Pre-training, day 14, 30 mg/kg | 0.17 | 0.59 | 0.12 | 0.70 |
| Post-training | | | | |
| 0 mg/kg | -0.05 | 0.88 | 0.06 | 0.84 |
| 7.5 mg/kg | 0.10 | 0.76 | -0.02 | 0.96 |
| 15 mg/kg | -0.25 | 0.44 | -0.11 | 0.72 |
| 30 mg/kg | -0.33 | 0.29 | -0.22 | 0.48 |

Data are from the last day of cocaine exposure (day 14) prior to discrimination training and from a post-training test for the expression of locomotor sensitization, conducted \approx 6 weeks after the last exposure to cocaine. The probability of getting the associated *r*-value by chance is denoted by *p*.

showed no significant effect or interaction with treatment (Fig. 2C, grey areas). Reversal performance (mean trials-to-criterion across both reversals) showed no correlation with the changes in locomotor activity (cocaine-induced activity minus baseline activity) exhibited by the cocaine-treated rats either before or after training (Table 1).

Sucrose/quinine preferences

During a two-bottle preference test, both groups of rats showed a strong preference for sucrose over quinine. Control rats consumed 11.2 mL of sucrose and 2.8 mL of quinine, whereas cocaine-treated rats consumed 8.9 mL of sucrose and 2.1 mL of quinine. A two-factor ANOVA (treatment \times outcome type) revealed a significant effect of outcome ($F_{1,21} = 63.0$, $P < 0.001$) but no effect or interaction involving treatment.

Discussion

It is well documented that psychostimulant exposure results in persistent structural and functional changes in brain regions, such as prefrontal cortex, important for behavioural control (Everitt & Wolf, 2002). These observations suggest that changes in these brain regions, and particularly in the behavioural control mediated by OFC, may account for important aspects of addiction (Jentsch & Taylor, 1999; Volkow & Fowler, 2000), and that normal learning processes that

depend on these brain regions may be altered as a result of drug exposure. Our results demonstrate such an effect in a task sensitive to deficits in OFC-dependent processing.

Cocaine exposure is associated with the disruption of OFC-dependent functions in rats and primates

The idea that cocaine exposure disrupts OFC function has received support from findings in primates. Cocaine users and cocaine-experienced monkeys exhibit metabolic abnormalities in OFC (Breiter *et al.*, 1997; London *et al.*, 2000; Volkow & Fowler, 2000; Bolla *et al.*, 2003) and deficits in rapidly changing established response patterns to reflect changes in expectations of reward and in discounting of information about outcome magnitude across delays (Grant *et al.*, 2000; Bechara *et al.*, 2001; Jentsch *et al.*, 2002; Coffey *et al.*, 2003). These functions depend on processing in OFC (Bechara *et al.*, 1997; Mobini *et al.*, 2002; Bohn *et al.*, 2003; Chudasama & Robbins, 2003; Schoenbaum *et al.*, 2003).

Here we confirm and extend these reports using a task in which the effects of lesions in several limbic and prefrontal regions have been characterized and are known to differ (Schoenbaum & Setlow, 2003; Schoenbaum *et al.*, 2003). This contribution is of value because deficits in gambling, reversal and delayed discounting tasks can reflect damage outside of OFC, including areas of amygdala and accumbens, which are altered by cocaine, and even perirhinal cortex (Jones & Mishkin, 1972; Stern & Passingham, 1995; Bechara *et al.*, 1999; Bussey *et al.*, 1999; Cardinal *et al.*, 2001; Hampton & Murray, 2002). The pattern of deficits exhibited by cocaine-treated rats in the odor discrimination task used here is identical to that exhibited by rats with OFC lesions in this task and is unlike that caused by lesions of either basolateral amygdala or nucleus accumbens, which affect latency changes but fail to cause impairments in reversal learning (Schoenbaum & Setlow, 2003; Schoenbaum *et al.*, 2003). As we discuss in the next section, the failure of cocaine-treated rats to exhibit differential changes in response latency during discrimination learning and the subsequent impairment in rapid reversal learning can be understood as an inability to guide behaviour according to the motivational value of predicted outcomes (Schoenbaum *et al.*, 2003). As a result, the most parsimonious explanation for these deficits is a unitary effect of cocaine exposure on OFC-dependent processing of motivational information. Whether the actual brain changes that account for this effect are in OFC or in afferent and/or efferent regions remains to be determined.

Our findings also provide a link between studies showing that OFC-mediated behavioural control is impaired in human addicts and monkeys after cocaine exposure (Grant *et al.*, 2000; Bechara *et al.*, 2001; Jentsch *et al.*, 2002) and studies showing that cocaine treatment produces long-lasting structural and functional changes in the rodent brain (Pierce *et al.*, 1998; Robinson & Kolb, 1999; Thomas *et al.*, 2001; Trantham *et al.*, 2002; Bowers & Kalivas, 2003). Although these studies have typically examined the effects of cocaine on structure and function in medial prefrontal cortex, at least two published reports show that addictive drugs affect orbital regions (Robinson *et al.*, 2002; Ferrario *et al.*, 2003). These reports show substantial differences between neural changes observed in medial and orbital regions in response to addictive drugs. Thus, cocaine exposure may exert different effects on different parts of prefrontal cortex.

Interestingly, deficits in OFC-dependent functions in the current task were not directly related to the psychomotor stimulant effects of cocaine. This finding suggests that the neural changes that account for these phenomena are not the same and can presumably be dissociated. Indeed, psychomotor sensitization is associated primarily with changes in a circuit of structures including the caudate, nucleus

accumbens, ventral tegmental area and dorsal (but not ventral or orbital) prefrontal regions (Pierce & Kalivas, 1997; Pierce *et al.*, 1998; Thomas *et al.*, 2001).

Disruption of OFC-dependent functions reflects an inability to use motivational value to guide responding

Changes in OFC-dependent functions as a result of cocaine exposure are particularly intriguing, because changes within OFC or disruption of OFC-mediated functions due to changes elsewhere in the brain could contribute to the loss of behavioural control that is characteristic of addiction (Jentsch & Taylor, 1999; Volkow & Fowler, 2000). Evidence suggests that deficits observed after OFC lesions are due to an inability to guide behaviour according to the motivational value of predicted outcomes (Gallagher *et al.*, 1999).

The deficits exhibited by cocaine-treated rats can be understood on a similar basis. The ability to rapidly modify responding during reversals, when the associations between cues and outcomes are switched, is likely to be supported by learning about the value of the predicted outcome. Indeed, damage to OFC prevents rapid changes in encoding of cue significance in amygdala (Saddoris *et al.*, 2003). Similarly, latency to respond after sampling a cue is sensitive to the value of the predicted outcome (Holland & Straub, 1979). For example, response latencies have been shown to reflect reward magnitude during discrimination learning, effects which are abolished by NMDA receptor blockade in OFC (Bohn *et al.*, 2003). Moreover, Sage & Knowlton (2000) reported that rats trained to complete trials to obtain food in a win-stay version of the radial-arm maze exhibited normal choice behaviour, but longer trial completion times (latencies) after the food was devalued.

Lacking this form of behavioural control, the responding of the cocaine-treated rats after reversal resembles the 'habit-like' behaviour of addicts, who continue to take drugs or relapse when exposed to drug cues despite the adverse outcomes (Robbins & Everitt, 1999; Volkow & Fowler, 2000). This feature of addiction may reflect changes, in OFC or in structures that modulate OFC function, that disrupt addicts' ability to use representations of the motivational value of probable outcomes to guide their behaviour.

Divergent effects of cocaine exposure on processing of motivational value

The proposal that cocaine exposure impairs the use of motivational value to guide behaviour is notable in light of evidence that psychostimulants also enhance some aspects of the motivational properties attributed to cues. Prior exposure to psychostimulants potentiates the normal increase in instrumental responding during presentation of the conditioned stimulus in a Pavlovian-to-instrumental transfer (PIT) task (Wyvell & Berridge, 2001) and enhances the normal increase in responding for conditioned reward caused by amphetamine (Taylor & Horger, 1999). These effects reflect enhanced rather than impaired processing of the motivational value of cues in the cocaine-treated animals.

Psychostimulant exposure may have divergent effects on processing of different components of motivational value. The dissociation between behavioural effects in our task and the locomotor sensitizing effects of cocaine would be consistent with this account. Moreover, there is a neuroanatomical dissociation between the substrates that support PIT and amphetamine-induced potentiation of conditioned reward, behaviours which are both enhanced by psychostimulant pretreatment, and the substrates that support many other types of learned behaviours that reflect motivational information (Everitt *et al.*, 2000; Holland & Gallagher, 2003). Psychostimulants may increase the efficacy of processing in the former circuit, which Everitt *et al.* (2000) have referred to as 'representation of affect', while diminishing the

efficacy of processing in the latter for learning about value that is 'specific to the unconditioned stimulus'. By this account, reversal impairments in cocaine-experienced rats could reflect an imbalance in the control of behaviour between cue-triggered reward seeking and cue-evoked representations of outcome. Such an effect would be consistent with a recent report that cocaine-exposure impairs the formulation of a conditioned place preference (Udo *et al.*, 2004), a form of learning which is likely sensitive to reinforcer devaluation (Yin & Knowlton, 2002).

Alternatively, psychostimulant exposure may increase the efficacy of learning about the value of predicted outcomes through effects on limbic regions, while simultaneously making it more difficult for prefrontal areas to access that information. In other words, normal or even enhanced representations of predicted outcomes would be present but inaccessible to control certain behaviours. Such a scenario is consistent with recent evidence that limbic and prefrontal regions play different roles in acquiring vs. expressing motivational information (Pickens *et al.*, 2003). Although there is insufficient evidence to distinguish between these possibilities at present, experiments examining the effect of psychostimulant exposure (and the timing of that exposure) in tasks that tap into these two components of motivational value could distinguish between these accounts.

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Abbreviations

OFC, orbitofrontal cortex; PIT, Pavlovian-to-instrumental transfer.

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