

uncertain. If this person was a modern human who descended from temperate areas, as predicted by the 'Out of Africa' hypothesis<sup>2</sup>, then the Russian Arctic was occupied by *Homo sapiens sapiens* shortly after the first newcomers entered Europe<sup>23,24</sup>. On the other hand, if the person was a Neanderthal, then these humans expanded much further north than hitherto assumed, implying that their stage of cultural development was not a barrier to colonization of this Arctic habitat. Whoever she or he was, the findings from Mamontovaya Kurya provide evidence that the European part of the Arctic was inhabited by humans long before the Neanderthals vanished from the continent soon after 28,000 yr BP<sup>20,25,26</sup>. □

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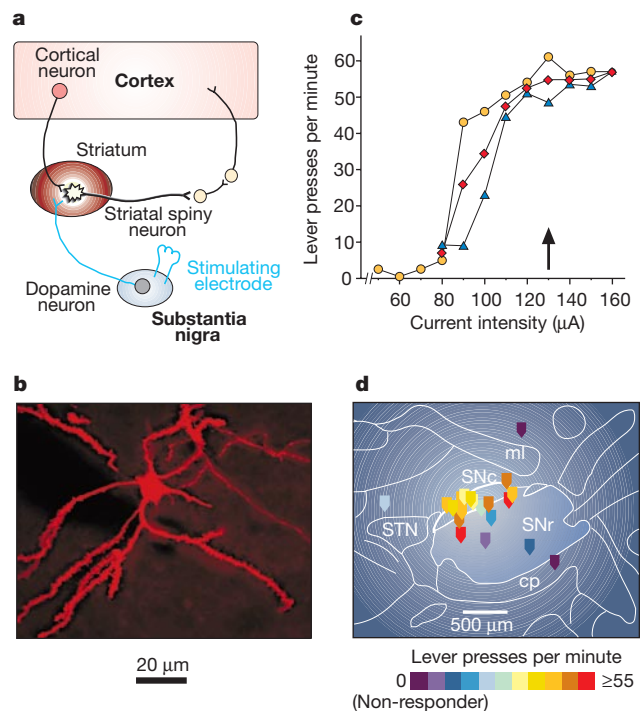
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**A cellular mechanism of reward-related learning**

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Positive reinforcement helps to control the acquisition of learned behaviours. Here we report a cellular mechanism in the brain that may underlie the behavioural effects of positive reinforcement. We used intracranial self-stimulation (ICSS) as a model of reinforcement learning<sup>1</sup>, in which each rat learns to press a lever that applies reinforcing electrical stimulation to its own substantia nigra<sup>2,3</sup>. The outputs from neurons of the substantia nigra terminate on neurons in the striatum in close proximity to inputs from the cerebral cortex on the same striatal neurons<sup>4</sup>. We measured the effect of substantia nigra stimulation on these inputs from the cortex to striatal neurons and also on how quickly the rats learned to press the lever. We found that stimulation of the substantia nigra (with the optimal parameters for lever-pressing behaviour) induced potentiation of synapses between the cortex and the striatum, which required activation of dopamine receptors. The degree of potentiation within ten minutes of the ICSS trains was correlated with the time taken by the rats to learn ICSS behaviour.

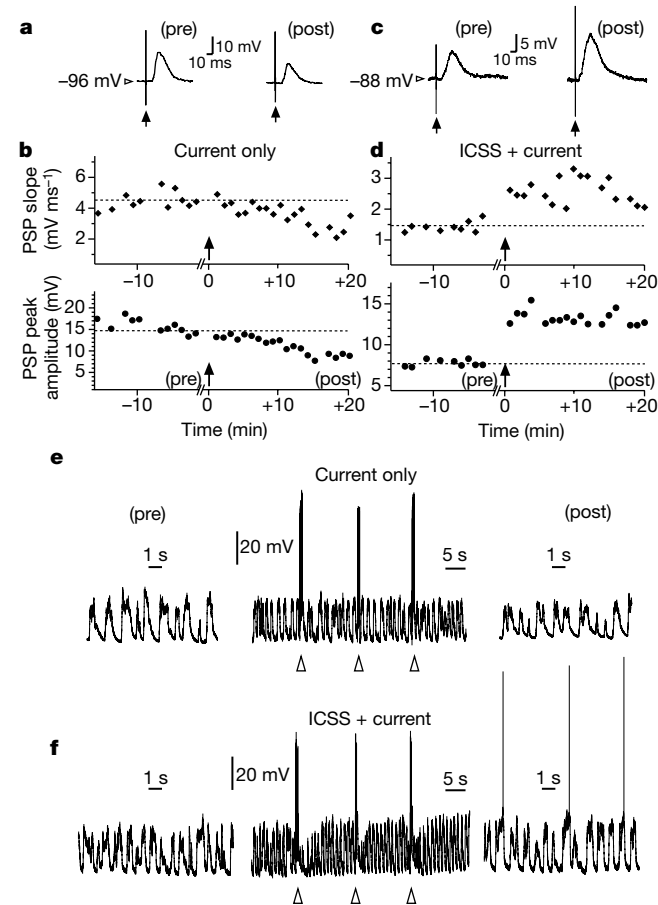


**Figure 1** Intracranial self-stimulation of the nigrostriatal system. **a**, Overview of the circuit studied. **b**, Confocal micrograph of a striatal spiny neuron injected with biocytin during intracellular recording (streptavidin-Texas Red label). **c**, Lever-pressing rate for one rat in response to increments (yellow circles) and decrements (blue triangles) in substantia nigra stimulus intensity. Arrow indicates the optimal current that just maximized the average rate (red diamonds). **d**, Approximate midpoint of the final stimulating electrode positions (sagittal section at mediolateral +1.9 mm; ref. 30). Arrowheads coded by maximum lever-pressing rate. SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; cp, cerebral peduncle; ml, medial lemniscus.

We propose that stimulation of the substantia nigra when the lever is pressed induces a similar potentiation of cortical inputs to the striatum, positively reinforcing the learning of the behaviour by the rats.

Recent electrophysiological studies have identified circuits in the brain which carry specific signals about past and future rewards<sup>5</sup>. The dopamine neurons in the pars compacta of the substantia nigra show short, phasic activation after the presentation of food or liquid rewards<sup>6,7</sup> and are believed to be important in reward-related learning. Nigral dopamine neurons project predominantly to the striatum, where changes in neural activity associated with reward-related learning have been described<sup>8,9</sup>. Determining the effect of short, phasic activation of the dopamine neurons on neural information processing in the striatum is, therefore, a crucial step towards understanding the cellular mechanism of reward-related learning.

We first established ICSS behaviour in male rats using stimulating electrodes permanently implanted in the substantia nigra (Fig. 1a, d). In these behavioural experiments we measured the time taken to establish ICSS (range, 2 to 240 min) and determined the optimal current intensity<sup>10,11</sup> (range, 90 to 275  $\mu$ A; Fig. 1c) and maximum lever-pressing rate (range, 18 to 56 presses per min) for each animal. Over the following two days, we extinguished the newly learned

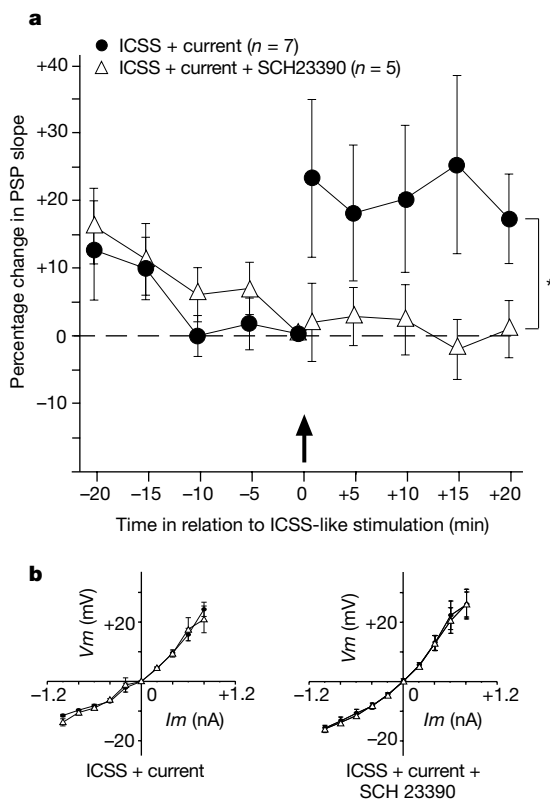


**Figure 2** Effect of treatment protocols on corticostriatal responses. Data is shown from representative striatal neurons in a control rat (**a, b, e**) and a rat experienced in intracranial self-stimulation (ICSS) (**c, d, f**). **a, c**, Post-synaptic potentials (1-min average) just before and 20 min after intracellular current injection alone (**a**) or in conjunction with ICSS-like stimulation (**c**). Arrows indicate stimulus artefact. **b, d**, Slope (diamonds) and peak amplitude (circles) of the post-synaptic potential (PSP) (1-min averages) in relation to application of the protocols (arrows). **e, f**, Membrane potential fluctuations of the neurons before, during and 20 min after the protocols. Protocol application indicated by open arrowheads (action potentials truncated).

behaviour by dissociating lever-pressing from substantia nigra stimulation.

After the behavioural sessions, the same animals were anaesthetized and prepared for *in vivo* electrophysiological recording. Intracellular records were obtained from striatal neurons identified as spiny projection neurons on the basis of typical membrane potential fluctuations<sup>12,13</sup> (Fig. 2e, f), verified in some cases by histological examination (Fig. 1b). The efficacy of corticostriatal synaptic inputs to these neurons was measured from post-synaptic potentials (PSPs; Fig. 2a, c) evoked by control stimulation of the contralateral cerebral cortex<sup>14,15</sup>. These measurements were made at regular intervals before and after ICSS-like stimulation.

In the electrophysiological experiments, ICSS-like stimulation was applied to the substantia nigra electrodes. Stimulus trains contained the same number of pulses and were delivered at the same frequency as used for ICSS, and for each recorded cell were of the current intensity found to be most effective at supporting ICSS behaviour for each individual rat. Activity of the corticostriatal pathway during ICSS-like stimulation was provided by spontaneous cortical input. This input causes large-amplitude membrane potential fluctuations in striatal spiny cells<sup>12</sup>; however, spiny neurons are highly polarized and a proportion of them do not fire action potentials spontaneously<sup>16</sup>. Therefore, to simulate the phasic activation of striatal neurons that occurs during movement<sup>17,18</sup>, we paired the substantia nigra stimulation with an intracellular current injection sufficient to induce action potential firing. To control for the effect of current injection and spontaneous corticostriatal input, a comparable level of intracellular current



**Figure 3** Group average effect of ICSS-like stimulation on corticostriatal responses and cellular properties. **a**, Changes in PSP slope (as percentage of baseline) in both groups that received ICSS-like stimulation. Baseline (dashed line) is average of 5 min of PSPs before application of stimulus protocol (arrow). Asterisk, significantly different between ICSS (no drug) and the ICSS (SCH 23390) group at +20 min ( $P < 0.02$ ). **b**, Group average current-voltage relation before (circles) and 20 min after (triangles) the protocols. The voltage at each point is normalized to membrane potential at zero current. All graph points are group mean  $\pm$  standard error of the mean, s.e.m.

**Table 1 Cellular properties of recorded neurons**

	Time*	ICSS+ current (no drug)†	ICSS+ current+ SCH 23390†	Current only†
Input resistance (MΩ)	Pre	26.0 ± 6.8	30.5 ± 11.9	25.0 ± 8.9
	Post	24.2 ± 8.8	31.3 ± 12.4	24.0 ± 9.0
Membrane potential (mV)	Pre	-90.1 ± 3.3	-91.1 ± 2.1	-87.4 ± 8.2
	Post	-90.9 ± 1.8	-91.6 ± 1.6	-87.2 ± 7.9
Baseline PSP slope (mV ms <sup>-1</sup> )		2.46 ± 0.76	3.07 ± 0.50	2.96 ± 1.05
Baseline PSP peak amplitude (mV)		13.4 ± 5.6	17.5 ± 6.5	15.4 ± 4.4
Protocol depolarization (mV)		-51.3 ± 7.9	-57.7 ± 6.8	-50.7 ± 6.4
ICSS-like stimulus intensity (μA)‡		181 ± 66	144 ± 43	

Data are mean ± s.d.

\* There were no significant differences between values before 'pre' and 20 min after 'post' application of the treatment protocols (paired *t*-test, *P* > 0.05). All comparisons based on at least five cells per group.

† There were no significant differences between treatment groups (one way ANOVA, *P* > 0.05).

‡ The same as the optimal current intensity applied to the substantia nigra during ICSS.

injection was applied to cells in a group that received no ICSS-like stimulation.

Our results revealed a clear potentiation of corticostriatal synaptic efficacy following stimulation of the substantia nigra with the optimal ICSS parameters. As illustrated in Fig. 2a and b, control cells (current injection and spontaneous corticostriatal input only) showed depression of PSPs. In the control group as a whole, the average effect was depression (-15.8 ± 5.1% at 20 min, *n* = 7). In contrast, ICSS-like stimulation reversed the inherent tendency towards depression, inducing potentiation of up to 97% (Fig. 2c and d). The average effect of ICSS-like stimulation (Fig. 3a) was potentiation of the PSP slope (+17.2 ± 6.7% at 20 min, *n* = 7), which differed significantly from the control group at all time points following the treatment protocols (*P* < 0.001). Changes in synaptic responses in each group were not secondary to changes in general cellular properties, because the latter were not affected by the treatment protocols (Table 1). We conclude that the changes in synaptic responses reflect modulation of synaptic efficacy in the corticostriatal pathway. Although synaptic plasticity has been previously demonstrated in the corticostriatal pathway *in vivo*<sup>15,27</sup> the induction of synaptic potentiation by stimulation that affects behaviour is, to our knowledge, a new finding.

To determine whether the effects of substantia nigra stimulation were mediated by dopamine, the dopamine receptor antagonist SCH 23390 was applied to a group that received ICSS-like stimulation. Potentiation was not observed in these neurons. The average effect of ICSS-like stimulation in the dopamine antagonist group (+1.1 ± 4.3% at 20 min, *n* = 5) was significantly different (*P* < 0.02) from the no-drug ICSS group (Fig. 3a). Cellular properties were not affected by the drug or by ICSS-like stimulation (Fig. 3b and Table 1). These data demonstrate that stimulation of the substantia nigra at a current intensity that is optimal to support

ICSS in the same animal, and using the same electrodes, reliably induces dopamine-dependent potentiation of corticostriatal PSPs. It is probable that the same potentiation would have been induced at corticostriatal synapses during ICSS in an awake animal.

Although the most effective ICSS sites are close to dopamine cell bodies<sup>19</sup> (also see Fig. 1d) the substrate directly activated by the ICSS electrode remains unclear<sup>20,21</sup>. It has been suggested that activation of descending myelinated fibres afferent to the dopamine neurons is required<sup>22</sup>. But our results do indicate that the final outcome of substantia nigra ICSS is dopamine-dependent potentiation. This effect is on corticostriatal synaptic efficacy rather than cortical excitability, because the contralateral cortex used to evoke test responses does not receive a crossed dopaminergic input from the substantia nigra<sup>23</sup>.

Recent theories of reinforcement learning<sup>24,25</sup> propose that dopamine acts heterosynaptically to facilitate synaptic plasticity at corticostriatal synapses. Such potentiation of the corticostriatal pathway can lead to increased probability of firing in striatal output neurons, as shown in Fig. 2f. The corticostriatal synapses are a key control point in a re-entrant loop involving the motor cortex and striatum<sup>26</sup> (Fig. 1a), so dopamine-dependent potentiation of these synapses may serve as a cellular mechanism for the learning of behavioural responses.

Because the intracellular recording and ICSS experiments were performed in the same animals, we were able to investigate whether there was any correlation between the magnitude of changes in synaptic efficacy induced by ICSS-like stimulation and behavioural variables. Our combined behavioural-electrophysiological analysis revealed that the degree of potentiation induced by ICSS-like stimulation was negatively correlated with the time taken to learn ICSS. This was observed at time points tested up to 10 min following the stimulus trains (+1 min: *r* = -0.91, *P* < 0.01; +5 min: *r* = -0.78, *P* < 0.05; +10 min: *r* = -0.80, *P* < 0.05) (Fig. 4a). No correlation was observed at later time points (+15 min: *r* = -0.62; +20 min: *r* = -0.46; not significant, NS), even though potentiation persisted for at least 20 min. In contrast to the correlation with the time taken to learn ICSS, there was no correlation between the degree of potentiation and the maximum lever-pressing rate at any time point (+1 min: *r* = -0.16; +5 min: *r* = -0.28; +10 min: *r* = -0.08; +15 min: *r* = -0.12; +20 min: *r* = 0.15, NS) (Fig. 4b). Thus there is a temporally specific relationship between the changes in corticostriatal synaptic efficacy induced by substantia nigra stimulation and the learning of ICSS behaviour, but not the subsequent performance of the behaviour.

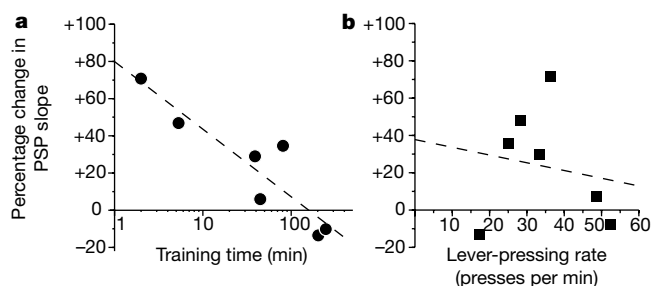
The correlation observed between PSP changes and the rate of acquisition of the ICSS behaviour suggests that enhanced information transmission through the corticostriatal circuit is an important factor in the acquisition of lever-pressing behaviour. We propose that this may be due to selective strengthening of particular pathways through the corticostriatal circuit, as previously proposed<sup>28</sup>. The correlation with the initial degree of potentiation implies that potentiation may influence immediate activities related to achieving ICSS, such as approach to the lever following a priming stimulation. These mechanisms may be generalized to other forms of learning facilitated by positive reinforcement. □

## Methods

### Intracranial self-stimulation methods

All procedures were approved by the University of Otago's Committee on Ethics in the care and Use of Laboratory Animals.

Twenty male Wistar rats (230–385 g) were implanted for ICSS. Rats were anaesthetized with pentobarbitone (60 mg kg<sup>-1</sup> intraperitoneally) and placed in a stereotaxic frame in the flat skull position. Prophylactic antibiotic was administered (Strepicin, 0.25 ml subcutaneously) and surgery performed using an aseptic technique. A bipolar stimulating electrode with tips separated by 0.7 mm was positioned at the level of the substantia nigra pars compacta (medial tip aimed for anteroposterior -4.8 mm, mediolateral 1.3 mm relative to bregma; dorsoventral 7.7 mm from brain surface). At least three days were allowed for post-operative recovery.



**Figure 4** Relationship between changes in synaptic efficacy and ICSS learning and performance. **a**, Correlation between degree of potentiation induced at +1 min following ICSS-like stimulus trains and ICSS training time (*r* = -0.91, *P* < 0.01). **b**, No correlation between degree of potentiation induced at +1 min following ICSS-like stimulation and maximum lever-pressing rate (*r* = -0.16, *P* = 0.73). For both graphs, each point is from a single animal in the no-drug ICSS group.

Rats were trained to perform ICSS in a behavioural chamber with a lever which, when pressed, immediately triggered delivery of a single stimulus train (100 Hz, 0.5 ms biphasic pulses, 500 ms train duration) to the substantia nigra electrode. Priming stimulus trains were administered by the experimenter when the animal was close to the lever, in order to facilitate approach and chance contact with the lever. All training was performed using the same training techniques for each animal. The training time was the total period of time that the rat was in the chamber with access to the lever, until lever-pressing commenced (at least 20 self-initiated presses in two consecutive minutes). Two animals did not reach the criterion within five days and were not used in further experimental procedures.

In the remaining ICSS responders ( $n = 18$ ), response rate versus current intensity data was collected daily until the currents required to support minimum and maximum lever-pressing rates (optimal current) were stable to within  $\pm 10\%$  for three consecutive sessions. Each animal then underwent two days of extinction where the animals were allowed free access to the lever with the self-stimulation circuit disabled. In addition, non-contingent stimulus trains were applied by the experimenter at 5-min intervals when the animal was away from the lever, in order to dissociate lever-pressing from the delivery of stimulus trains. Successful extinction was defined as a failure to approach the lever within the interval between two successive primes. This was successfully achieved in all animals.

## Electrophysiological recording methods

Electrophysiological data was obtained from 12 of the 18 ICSS-experienced rats and 5 additional control animals. Each rat was anaesthetized with urethane ( $1.4\text{--}1.6\text{ g kg}^{-1}$  intraperitoneally), supplemented with ketamine ( $10\text{ mg kg}^{-1}$  intramuscularly) and xylazine ( $2\text{ mg kg}^{-1}$  intramuscularly). An electrode was implanted in all animals in the medial agranular cortex contralateral to the recording site (anteroposterior  $+10.6$  to  $12.7\text{ mm}$ , mediolateral  $-2.0\text{ mm}$  relative to interaural line; dorsoventral  $1.6$  to  $2.0\text{ mm}$  from brain surface). In control rats, a bipolar stimulating electrode was positioned in the substantia nigra at the same coordinates as the permanently implanted electrode in the ICSS-experienced rats but this electrode was not used for ICSS-like stimulation.

Intracellular records were made from striatal neurons with microelectrodes pulled from  $3.0\text{-mm}$  diameter glass and filled with  $1\text{ M K-acetate}$  containing  $4\%$  biocytin. Post-synaptic potentials evoked by cortical test stimuli ( $0.1\text{ Hz}$ ,  $0.1\text{ ms}$  biphasic pulses,  $300$  to  $990\text{ }\mu\text{A}$ ) were routinely recorded for  $20\text{ min}$  before and  $20\text{ min}$  after the application of a treatment protocol. In ICSS-experienced rats, this consisted of six ICSS-like stimulus trains administered at ten-second intervals at the animal's optimal current intensity (Table 1).

In five experiments, the dopamine D1/D5 receptor antagonist SCH 23390 ( $40\text{ }\mu\text{g kg}^{-1}$  intraperitoneally in  $0.1\text{ ml } 0.9\%$  NaCl) was administered approximately  $30\text{ min}$  before the application of ICSS-like stimulus trains. This dose was based on our preliminary behavioural experiments (data not shown) and the reports of others<sup>29</sup>, which show it is sufficient to attenuate the rewarding effect of ICSS. Each ICSS-like stimulus train was paired with a current pulse just above the threshold for action potential firing ( $1.3 \pm 0.5\text{ nA}$ ) of similar intensity to control rats that received only current injection ( $1.1 \pm 0.2\text{ nA}$ ). Cellular properties of the recorded neurons were measured as previously described<sup>15</sup>. Post-synaptic potentials were compared between treatment groups by a repeated measures analysis of variance (ANOVA) (treatment effect: degrees of freedom,  $d.f. = 2$ ,  $F = 5.1$ ,  $P < 0.05$ ; no time effect or interaction). Post-hoc tests between individual groups were performed using a Bonferroni analysis (overall level of significance  $P < 0.05$ ). Substantia nigra electrode positions were verified in unstained vibratome sections. There were no systematic differences in electrode positions between groups.

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# Mobilization of a *Drosophila* transposon in the *Caenorhabditis elegans* germ line

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Transposons have been enormously useful for genetic analysis in both *Drosophila* and bacteria. Mutagenic insertions constitute molecular tags that are used to rapidly clone the mutated gene. Such techniques would be especially advantageous in the nematode *Caenorhabditis elegans*, as the entire sequence of the genome has been determined. Several different types of endogenous transposons are present in *C. elegans*, and these can be mobilized in mutator strains (reviewed in ref. 1). Unfortunately, use of these native transposons for regulated transposition in *C. elegans* is limited. First, all strains contain multiple copies of these transposons and thus new insertions do not provide unique tags. Second, mutator strains tend to activate the transposition of several classes of transposons, so that the type of transposon associated with a particular mutation is not known. Here we demonstrate that the *Drosophila* mariner element *Mos1* can be mobilized in *C. elegans*. First, efficient mobilization of *Mos1* is

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