Reward mechanisms in the brain and their role in dependence: evidence from neurophysiological and neuroimaging studies

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Abstract

This article reviews neuronal activity related to reward processing in primate and human brains. In the primate brain, neurophysiological methods provide a differentiated view of reward processing in a limited number of brain structures. Dopamine neurons respond to unpredictable rewards and produce a global reinforcement signal. Some neurons in the striatum also react to the expectation and detection of reward. Other striatal neurons show reward-related activities related to the preparation, initiation and execution of movement. Orbitofrontal neurons discriminate among different rewards and code reward preferences. In the human brain, regions belonging to a meso-striatal and meso-corticolimbic loop respond to reinforcement stimuli in control subjects. These observations corroborate results obtained in primates. Additionally, reward induces activation in regions specific to task performance. Our results also show a similar pattern of reward-related activation in nicotine and opiate addicts. Thus, in contrast to healthy subjects, typical reward-related regions respond in addicts to monetary reward but not to nonmonetary reinforcement. Reduced activation in performance-related regions is also observed in both groups of dependent subjects. The results of animal and human studies suggest that dopamine and dopamine-related regions are associated with the integration of motivational information and movement execution. Dopamine-related pathological disorders can be associated with movement disorders, such as Parkinson’s disease or with false motivational attributions such as drug dependence.

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1. Introduction

Reward controls goal-directed behavior and involves learning, since it acts as a positive reinforcer. Obtaining reward is in turn associated with pleasant feelings, which give incentive value to the goal-object. Reward can elicit approach and consummatory behavior, and objects signalling reward are labelled with positive motivational value.

1.1. Neural bases of reward

The neural basis of reward has been investigated using numerous experimental approaches including brain lesions, psychopharmacology, electrical self-stimulation, single neuron recording and neuroimaging [9, 17, 26, 37]. Most of these studies indicated that dopamine neurons are involved in reward processing. Dopamine is implicated in approach behavior, evaluation of rewarding outcomes, reward-related learning, and the effect of addictive substances [11, 26, 36]. Some regions of the mesolimbic dopamine system, like the midbrain, striatum and orbitofrontal cortex evidence involvement in reward processing [3, 10, 21], suggesting that these regions belong to a dopamine-related cortico-subcortical loop mediating motivational processes.

1.2. Reward and dependence

Empirical evidence indicates that the reinforcing properties of psychoactive drugs are mediated by the mesocorticolimbic dopamine system. Studies have shown that most psychoactive drugs increase dopaminergic transmission within this system, especially in the nucleus accumbens [18]. Furthermore, psychoactive drugs, including cocaine, amphetamine, nicotine, opiates and ethanol, facilitate intracranial self-stimulation and place preference. They are self-administered in animals and humans [9, 36], confirming that reinforcement mechanisms play a role in drug addiction. These observations suggest that drug addiction is a dopamine-dependent disorder in which the positive reinforcing value of the drug is mediated through the activation of the mesolimbic dopamine system [8].

Based on the previous work of Schultz and coworkers [3, 21], the present project integrated human and animal research to investigate the neural mechanisms involved in reward processing as well as their role in dependence. We investigated reward processing with neurophysiological methods in the primate brain and with \[^{15}O\] Positron Emission Tomography (PET) in the human brain. Interested in the relation between dopamine and reward, but having no direct measure of dopamine, we compared activation in a group of patients with Parkinsonian disease, in which the dopaminergic neurotransmitter system is compromised, with a group of healthy subjects. To explore the relationship between dependence and reward, we included two groups of addicts in our study: opiate addicts and smokers. Assessing differences between drug addicts and non-addicts, a supplementary questionnaire addressed personality features that could influence reward perception.

2. Neurophysiological study

2.1. Material and methods

The activity of single neurons was recorded from extracellular positions with moveable microelectrodes in *Macaca fascicularis* monkeys performing behavioral tasks. The behavioral apparatus as well as most recording, evaluation and histological reconstruction techniques were
similar to those described previously [14]. In addition to neuronal activity, electromyograms from the extensor digitorum communis, arm biceps and masseter muscles, and horizontal and vertical electrooculograms were recorded through chronically implanted electrodes together with neuronal activity.

2.2. Behavioral tasks

We employed different versions of visual tasks with delayed response to compare responses to liquid reward with no reward (Fig. 1 top) [32] and to different liquid or food rewards (Fig. 1 bottom) [33]. In a go–nogo task, an initial instruction picture indicated one of three trial types, namely rewarded movement, rewarded non-movement and unrewarded movement. In a spatial task, the instruction picture contained two types of information: (i) its position indicated the target of an arm movement performed in reaction to a trigger stimulus; (ii) its content indicated which of two liquid or food rewards would be delivered for correct behavior at trial end. Following the appropriate behavioral response, the animal received the reward indicated by the instruction.

Liquid rewards were grenadine, apple, orange and grape juice. Food rewards were raisins (most preferred), small apple morsels (intermediate preferred) and sugar-honey cereal (least preferred). Rewards and target positions alternated randomly in each block of trials, with maximally three consecutive identical trials.

Reward preferences were assessed in separate blocks of trials; instructions for two randomly alternating rewards appeared simultaneously at left and right target positions, allowing the animal to touch the lever of its choice following the trigger stimulus.

2.3. Results

Our analysis demonstrated a considerable variety of neuronal activities coding different aspects of rewarding events. Neurons in the orbitofrontal cortex showed three principal forms of reward-related activity, namely responses to reward-predicting instructions, activations during the expectation period, and responses following the reward (Fig. 2A) [30,34]. Neurons in the striatum were also activated in response to the expectation and detection of reward. Other striatal neurons showed activation related to the preparation, initiation and execution of movements, and many of the responses depended on reward being delivered at trial end [14,32]. Whereas distinct orbitofrontal and striatal neurons showed diverse reward-related activities, dopamine neurons displayed rather homogeneous responses to rewards and reward-predicting stimuli [29]. These responses depended on event unpredictability, as dopamine neurons evidenced increased activity following unpredictable rewards, showed no changes in response to fully predictable rewards and decreased when rewards were omitted [14,29].

In the striatum, an interesting phenomenon consisted of activations preceding the reward in both rewarded trial types irrespective of the go or nogo reaction (Fig. 2A). These activations usually began later than 1 s before the liquid reward, remained present until the reward was delivered and terminated 0.5–1.0 s afterwards, even when the reward occurred before or after the habitual time. Some
related to reward prediction in the striatum: the prediction of liquid reward at trial end influenced all forms of task relationships. In particular, the reward expected at trial end influenced movement preparation, initiation and execution. Many activations following the trigger stimulus or occurring immediately before or during the arm movement were seen in movement but not non-movement trials (Fig. 5).

Another remarkable finding was the predominantly reward-related nature of orbitofrontal activations. These neurons showed a limited spectrum of covariation with behavioral events compared to neurons of the dorsolateral and ventrolateral prefrontal cortex, which process visual features of objects [13,35]. Apparently these orbitofrontal neurons did not primarily code purely physical aspects of reward objects. The physical properties may be coded in more caudal orbitofrontal areas where neurons discriminate well among various rewarding tastes and smells [7,27]. Orbitofrontal neurons discriminated among different liquid or food rewards, according to their motivational value. The preference-related activations of orbitofrontal neurons may serve to identify more or less valued rewards. These activations could facilitate neuronal mechanisms involved in making decisions about immediate behavioral choices leading to rewarding goals, as they indicate the most profitable outcome among available alternatives. Relative information coding would in general allow subjects to reach quick decisions without computing every aspect of the objects present in the environment.

3. Neuroimaging studies

3.1. Subjects

The neuroimaging studies included four groups of subjects: healthy controls, smokers, opiate addicts and Parkinsonian patients. All subjects were right-handed. They were tested for psychiatric, neurological or medical disorders. Candidates with depression were excluded. Normal memory performance and executive functions, tested prior to imaging, were required for participation in the experiment. Only candidates with no drug dependence or abuse were admitted to the group of controls and only nicotine dependence was accepted in the smokers. The opiate-dependent patients were on methadone maintenance supervised by an outpatient clinic of the Division of Substance Abuse (University Hospital of Geneva); they had received a stable dose for least 1 month. They were instructed not to use any substance of abuse other than cigarettes and methadone on the day preceding the test. Subjects could smoke prior to the experiment. The Parkinsonian patients had a diagnosis of idiopathic Parkinson’s disease and were treated with levodopa. They were investigated during the on-state.

The experiment was approved by the Ethics Committees of the Department of Neurology of the University Hospital
of Zurich and of the Psychiatric Department of the University Hospital of Geneva. All subjects gave their informed written consent according to the Declaration of Helsinki.

3.2. Behavioral task

The subjects performed a visuo-spatial recognition task with delayed response during the PET acquisition as illustrated in Fig. 3. Feedback comprised no reinforcement, nonmonetary reinforcement, or monetary reward. The tasks were identical except for the reinforcer used. In the condition with no reinforcement, subjects received nonsense feedback for every response. In the reinforcement conditions, wrong responses were not reinforced. The maximum monetary reward which could be won was 320 sFr (approximately $180 US); the subjects were instructed before the trials that they would receive the sum shown at the end of the session. Thoroughly instructed before the session, the subjects performed the task once under all three conditions during training.

We used ratings of mood and the subjective value of money to control for the effect of reward. Furthermore, we monitored heart rate as a measure of autonomic nervous system function in order to assess the unspecified arousal produced by the task.

3.3. PET-scanning

We measured rCBF with the tracer $^{15}$O; subjects were informed of the condition before each intravenous bolus, which they received immediately after the task began. An interval of 12 min was interposed between scans in order to permit sufficient decay of radioactivity. The measure-

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**A. visuo-spatial recognition task used in the PET-study**

![Diagram of the visuo-spatial recognition task](image)

**B. Types of feedbacks**

- **No Reinforcement**
  - 8 Frs
  - Gesamt 16 Frs

- **Nonmonetary Reinforcement**
  - OK
  - Gesamt 2 OK

- **Monetary Reward**
  - XY
  - Gesamt 123

Fig. 3. Spatial delayed task used in the PET-study. The instruction consisted of three rectangular fields containing five black horizontal streaks displayed simultaneously for 2.5 s on the screen. A blank interrupted one of the streaks at a different position in each field. After 3 s, during which the screen stayed blank, a rectangular field was displayed at one of the initial positions. The subjects were given 1.5 s to decide whether this pattern was identical to and at the same position as the one presented previously. If so, the correct response for the subjects was to press the computer mouse with their right index finger. If not, no action was the correct response. After the response time had elapsed, the picture disappeared. With a further delay of 2.5 s, feedback appeared on the screen. Feedback comprised no reinforcement, nonmonetary reinforcement, or a monetary reward.
ments were made with an Advance tomograph (GE Medical Systems, Waukesha, WI) acquiring in three-di-

mensional mode. Analysis of the images used the SPM96 software [12] implemented in Matlab (Mathworks, Sher-
born, MA, USA). After spatial standardisation, the scans were smoothed with a Gaussian filter of 10 mm FWHM. Proportional scaling preceded comparison of conditions within a group using a fixed effects design for multiple subjects with repetitions.

3.4. Results

3.4.1. Reward activation in the healthy brain

3.4.1.1. Typical reward-related regions. In addition to the striatum and orbitofrontal cortex investigated in the neuro-
physiological study of primates, we found activation in other regions typically associated with reward processes including the midbrain, the dorsolateral cortex, and the cingulate gyrus. Confirming a previous PET study which compared responses to monetary reward and nonmonetary reinforcement [31], we found rCBF increases in the midbrain, the thalamus and in the same Brodmann areas of the frontal and orbitofrontal cortex. All regions, with the exception of the thalamus and striatum, were activated both by the nonmonetary and monetary reinforcement in control subjects (Fig. 4A,B).

Interestingly, the younger subjects showed unilateral activation of the striatum, whereas the older subjects evidenced bilateral activation [19,22]. Furthermore, activation of the thalamus was observed in the younger but not in the older subjects.

3.4.1.2. Additional regions. Activated regions not associ-
ated with the mesolimbic dopaminergic system and reward include the primary motor cortex, the visual cortex, the inferior temporal gyrus, the parietal inferior lobule, and the cerebellum.

3.4.2. Reward activation in the addicted brain

3.4.2.1. Smokers. rCBF increases in the cerebellum were the most apparent feature in smokers. Remarkable is the absence in all contrasts of thalamus and striatal regions and of occipital, temporal or parietal regions (Fig. 4C). The only typical reward-related areas evidencing increases, mainly in specific response to monetary reward, were the left orbitofrontal cortex, right cingulate gyrus and left midbrain [22].

3.4.2.2. Opiate addicts. The main differences between control subjects and opiate addicts concern activation in regions typically associated with reward: the orbitofrontal cortex, the cingulate gyrus, the midbrain and the striatum. In contrast to the control subjects, the opiate addicts exhibited rCBF increases in most of these regions only in the comparison of monetary reward with nonmonetary reinforcement, indicating specific activation in response to monetary reward [23]. Another remarkable difference between control subjects and opiate addicts resides in the number of activated regions not associated with the mesocorticolimbic or meso-striatal dopaminergic systems. Indeed opiate addicts showed less activation in these regions.

3.4.2.3. Reward activation in Parkinsonian patients. The Parkinsonian patients showed a qualitatively different pattern of rCBF increases than the controls [19]: rCBF increases were found mostly in the comparison of monetary reward with nonmonetary reinforcement. However, the most striking difference is the lack of striatal rCBF increases in the patients. In contrast, other typical reward-related regions did show activation. Thus, the midbrain, the dorsolateral prefrontal cortex and the medial frontal gyrus evidenced increased activation with the level of reinforcement. The cingulate gyrus and the superior frontal gyrus responded specifically to monetary reward. Most of the performance-related regions also reacted specifically to monetary reward in Parkinsonian patients.

3.5. Discussion

3.5.1. Control subjects

Control subjects exhibited activation in regions mediated by dopamine and typically associated with reward pro-
cesses. Additional regions associated rather with visual and motor performance also responded. Thus, the activation of the left primary motor cortex evidenced the motor response of the right hand. rCBF increases in the occipital, parietal and temporal cortex could follow from the differences in reading the words presented as feedback in the three conditions as suggested by Jernigan et al. [16] and Peterson et al. [25]. Activation of the visual cortex and precuneus is consistent with another neuroimaging study suggesting that processing the emotional value of visual stimuli may involve these regions [24]. Finally, increases in the cerebellum evidenced in all comparisons could confirm its role in reading the different verbal feedbacks presented [16]. Alternatively, they could reflect increased arousal associated with attentional processes and the coordination of selective attention as shown in Ref. [1].

The differences found in the activation patterns of young and older subjects, suggesting age-related changes in the neural pathway involved in reward processing, could be explained by the decline of the dopaminergic system with age found by Antonini and Leenders [2].

3.5.2. Dependent subjects

Our results indicate a common pattern of reward-related activation in two forms of dependence: fewer regions of dependent subjects' brains respond to reward. In contrast to the control subjects, typical reward-related regions are activated by monetary reward, but not by nonmonetary
Fig. 4. SPM projections of significantly activated brain areas in comparisons between no reinforcement and monetary reward using a search threshold of $P\leq 0.001$. (A) Regions activated in younger controls: the primary motor cortex, the right dorsolateral prefrontal cortex, right and left orbitofrontal cortex, the left cingulate gyrus, right cingulum, right medial temporal gyrus, left occipital cortex, primary visual cortex, right midbrain, right putamen, right caudate nucleus and right and left cerebellum (adapted from Martin-Soelch). (B) Regions activated in older controls: bilaterally in the striatum, caudate nucleus and anterior cingulate gyrus, and unilaterally in the left cerebellum, midbrain and medial frontal gyrus (adapted from Küng et al.). (C) Regions activated in smokers: the right cingulate gyrus and right and left cerebellum (adapted from Martin-Soelch). (D) Regions activated in Parkinsonian patients: the right medial frontal cortex, the left superior parietal lobule, medial temporal gyrus, and thalamus and right and left cerebellum (adapted from Küng et al.).
reinforcement. Both groups of dependent subjects also evidence reduced activation in performance-related regions. This pattern could indicate that nonmonetary reinforcement has insufficient motivational value to activate reward-related regions, suggesting that they require more stimulation in addicts’ brains.

A particular feature of the smokers is the total lack of striatal activation, which could indicate that chronic tobacco use induces even more dramatic changes in the mesostriatal dopaminergic system than opiate dependence. A recent [(18)F]Fluorodopa PET-study [28] reporting greater dopamine activity in the striatum of smokers than of non-smokers supports this hypothesis. Furthermore, a previous study showed that cigarette smokers prefer immediate rewards to delayed outcomes [4], suggesting that the impact of the monetary gain presented on the screen could be weaker for smokers than nonsmokers, because it involved a delayed outcome.

3.5.3. Parkinsonian patients

The most striking finding in Parkinsonian patients was the lack of striatal activation indicating attenuation of striatal reward processing attributable to the disease-related dopaminergic nigrostriatal deficit. This and the pattern of response specific to monetary reward constitute a similarity between Parkinsonian patients and dependent subjects which supports the hypotheses that drug dependence is a dopamine-related disorder (Fig. 6), and that dopamine is involved in evaluating the salience of motivational stimuli.

4. Questionnaire study

4.1. Material and methods

To investigate how rewarding stimuli are perceived by drug addicts, we assessed sensation-seeking and hedonism. High sensation-seeking has been shown to be related to drug use [38]. Furthermore, links between anhedonia and low sensation-seeking have been demonstrated in depression [5]. Ninety-one former heroin users, stabilised on methadone maintenance treatment (MMT), and 117 healthy students participated in the study. Sensation-seeking was assessed with the Sensation-Seeking Scale Form V. To investigate the association between high sensation-seeking and hedonism, we used an adaptation of the Mood Related Scale originally developed by Lewinsohn and Graf [20].

![Fig. 5. Schematic overview of the forms of reward processing found in fronto-striatal and dopamine system. Top: Orbitofrontal neurons showed three main forms of task-related changes, which were all related to upcoming or past reward. Middle: all forms of task-related activations in the striatum depended on the reward expected at trial end. In addition, striatal neurons showed two forms of activation related directly to time of reward. Bottom: dopamine neurons were activated by unpredictable reward and reward-predicting conditioned stimuli but were depressed by omitted rewards. In the orbitofrontal cortex and striatum, the different forms were found in different neuronal populations, whereas the same dopamine neurons showed the three forms depending on the situations in which rewards and conditioned stimuli occurred or were omitted. Constructed from population histograms, the graphs represent average changes in single neurons. Right: schematic connectivity of involved structures (VA, thalamus, ventroanterior thalamus; SNpr, substantia nigra pars reticulata; GP, globus pallidus). Brain areas investigated in the present studies are shaded (adapted from Schultz et al.).](image-url)
This questionnaire presents activities or reinforcements selected as sources of pleasure by a large range of subjects.

4.2. Results and discussion

Evaluation of the questionnaire confirmed that the MMT subjects exhibited significantly higher levels of sensation-seeking and subjective pleasure than the healthy controls. A relation between greater degrees of hedonism, disinhibition-seeking and drug use was found in MMT women. MMT men demonstrated a strong relation between thrill and adventure-seeking and drug use [6].

5. Conclusions

In the primate brain, neurophysiological methods provide a differentiated view of reward processing in a limited number of brain structures. Dopamine neurons displayed homogeneous responses to rewards and reward-predicting stimuli and involved event unpredictability. Neurons in the striatum also reacted to the expectation and detection of reward. Thus, the reward expected at trial end influenced movement initiation and execution following the instruction stimulus or during the delay preceding the movement. Orbitofrontal neurons discriminated among different rewards and coded reward preferences. These neurons could be involved in assessing the characteristics of individual rewards, thus underlying the perception of rewards.

In the human brain, PET studies demonstrate that regions belonging to a meso-striatal and meso-corticolimbic loop are activated by reinforcement stimuli in control subjects. These observations corroborate the results obtained in primates. Reward induced activation in additional regions specific to task performance. This activation could reflect additional mental effort made to maximize the obtained results, a direct effect of reward on goal-directed behavior. Monetary and nonmonetary reinforcements produced differences in activation. The most conspicuous example was the absence of striatal activation in response to nonmonetary reinforcement, suggesting that this region reacts specifically to reward or salient stimuli.

The patterns of activation in dependent subjects differed noticeably from those in controls. We found a similar pattern of reward-related activation in two major forms of dependence. Thus, typical reward-related regions were activated by monetary reward but not nonmonetary reinforcement, in contrast to the control subjects. Both groups of dependent subjects also evidenced reduced activation in performance-related regions. The patterns indicate that the brains of dependent subjects interpret and react to reward differently than controls’ brains. The differences might reflect substance-specific changes in the brain.

Our questionnaire showed that opiate addicts obtain higher sensation-seeking scores than controls. Since smokers also evidence more sensation-seeking and impulsivity than control subjects, differences in activation patterns between controls and drug dependents support the hypothesis that the brains of dependent subjects need more stimulation in order to be activated. Since psychoactive drugs act as rewards and directly affect regions of the dopaminergic system like the striatum, these differences can be interpreted as results of the addiction process.

Parkinsonian patients also responded rather to monetary reward than to nonmonetary reinforcement. However the most striking feature was the lack of striatal activation. Although the most probable explanation is the disease-
related dopaminergic nigrostriatal deficit, the similarity of the activation patterns between Parkinsonian patients and dependent subjects supports the hypotheses that drug dependence is a dopamine-related disorder and that dopamine is involved in evaluating the salience of motivational stimuli.

The results of animal and human studies provide a comprehensive view of the neural processes associated with reward (Fig. 5). They suggest that dopamine and dopamine-related regions, especially the striatum, are associated with the integration of motivational information and movement execution. Thus, striatal neurons show activity related to the prediction of reward, which influences movement initiation and execution. Dopamine-related pathological disorders can be associated with movement disorders, such as Parkinson’s disease or with false motivational attributions such as drug dependence (Fig. 6).

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