Pergamon

www.elsevier.com/locate/neuroscience

PII: S0306-4522(00)00019-1

Neuroscience Vol. 96, No. 4, pp. 651–656, 2000

0306-4522/00 $20.00+0.00

COMMENTARY

MESOLIMBOCORTICAL AND NIGROSTRIATAL DOPAMINE RESPONSES TO SALIENT NON-REWARD EVENTS

J. C. HORVITZ*

Department of Psychology, Columbia University, New York, NY 10027, U.S.A.

Abstract—While it has previously been assumed that mesolimbic dopamine neurons carry a reward signal, recent data from single-unit, microdialysis and voltammetry studies suggest that these neurons respond to a large category of salient and arousing events, including appetitive, aversive, high intensity, and novel stimuli. Elevations in dopamine release within mesolimbic, mesocortical and nigrostriatal target sites coincide with arousal, and the increase in dopamine activity within target sites modulates a number of behavioral functions. However, because dopamine neurons respond to a category of salient events that extend beyond that of reward stimuli, dopamine levels are not likely to code for the reward value of encountered events.

The paper (i) examines evidence showing that dopamine neurons respond to salient and arousing change in environmental conditions, regardless of the motivational valence of that change, and (ii) asks how this might shape our thinking about the role of dopamine systems in goal-directed behavior. © 2000 IBRO. Published by Elsevier Science Ltd.

Key words: attention, reinforcement, aversive, voltammetry, single-unit dialysis, salient arousal.

CONTENTS

1. NIGROSTRIATAL AND MESOLIMBOCORTICAL DOPAMINE NEURONS RESPOND TO SALIENT ENVIRONMENTAL CHANGE

According to traditional views, nigrostriatal dopamine (DA) neurons, originating in the substantia nigra (SN) and projecting to the dorsal striatum,[25] play a role in the expression of motor acts,[12,34] while mesolimbic DA neurons, originating in the ventral tegmental area (VTA) and projecting largely to the nucleus accumbens and other ventral striatal regions[25] play a role in reinforcement or incentive motivational processes.[13,22] From these views, it might have been expected that nigrostriatal DA neurons would fire in relation to specific motor acts, and that mesolimbic DA neurons would respond specifically to the presentation of reward stimuli. However, single-unit studies show that DA neurons within the SN do not respond to phasic bodily movements,[68,71] nor do DA neurons within the VTA respond exclusively to reward stimuli.[36] It has previously been noted that mesolimbic DA activity plays a role in behavioral responses to both appetitive and aversive stimuli, and that “reward signal transmission” fails to appropriately characterize DA’s behavioral role.[9,43,62,65] In accordance with this view, the present paper examines evidence showing that mesolimbic, mesocortical and nigrostriatal DA neurons respond to the presentation of salient and arousing environmental stimuli, a category of events that includes but extends beyond that of rewards.

When considering the behavioral function of nigrostriatal and mesolimbocortical DA systems, it is helpful to ask: (i) under what environmental conditions are the systems activated; and (ii) what are the behavioral consequences of that activation? Sections 1–3 of this paper focus on the former question, and answer that nigrostriatal, mesolimbic, and mesocortical DA neurons are activated by salient and arousing environmental stimuli. Section 4 addresses the latter question. If DA release within nigrostriatal, mesolimbic, and mesocortical target sites increases in response to salient environmental change, how should this influence our thinking about the role of these DA systems in goal-directed behavior?

*Tel.: +1-212-854-8945; fax: +1-212-854-3609.
E-mail address: jon@paradox.psych.columbia.edu (J. C. Horvitz).
Abbreviations: DA, dopamine; SN, substantia nigra; VTA, ventral tegmental area.

1.1. Dopamine responses to appetitive events

Nucleus accumbens DA levels are elevated during appetitive behaviors, including feeding,[33,53,59,80] drinking,[82] and copulation.[18,51,56,57] Dorsal striatal DA elevations have also been observed during these appetitive behaviors,[18,48,56,82] although the elevations are generally of a smaller magnitude than those observed within the accumbens. Single-unit responses to food and to conditioned stimuli signaling food delivery have been observed in DA neurons within the VTA and SN,[45,54,55] sites of origin for the mesolimbic and nigrostriatal DA pathways, respectively.[25] These findings, in themselves, are consistent with a DA/reward view. However, the increased accumbens DA concentrations that are observed during feeding sessions are not closely tied to food consumption itself, but to locomotor or exploratory behavior associated with certain feeding schedules.[53] This latter finding raises the possibility that increases in DA activity that are observed during reward-related behaviors might reflect something other than reward consumption.

It is possible to present food reward in a manner which is salient and arousing, or to present it in a less-salient manner. DA neurons respond to food delivery in the former, but not the latter condition. VTA and SN DA neurons reliably respond to food when the time of delivery is unpredictable.[54] DA elevations are generally absent when the food is presented in a predictable manner.[54] The DA response to a reward stimulus appears to require that its presentation be surprising. This again suggests that DA neurons may be responding to something other than reward *per se*. Finally, when a conditioned stimulus, e.g., a light, has come to predict food delivery, DA neurons become less responsive to the food, and respond instead to presentation of the light.[45] This may reflect a shift of incentive value from the food to the light. Alternatively, this may reflect an increase in the salience of the light as it comes to predict food, and a decrease in the salience of the food, as its presentation becomes less surprising.

1.2. Dopamine responses to novel events

Another class of salient and arousing events are novel stimuli. If DA neurons respond to stimulus salience, one would predict that DA neurons should respond to novel events. Microdialysis fails to detect DA elevations following exposure to a novel environmental chamber.[18,56] However, because novel stimuli are subject to habituation, methods that detect phasic changes in DA neuronal activity with better temporal resolution, such as single-unit electrophysiology and voltammetry, are most likely to detect DA responses to novel events.

Single-unit studies show midbrain DA responses to the novel opening of a door compartment of a behavioral apparatus prior to appetitive conditioning, when the animals react to the door opening with target-directed saccades.[45] DA neuronal responses to this event are no longer seen after the ocular reaction has habituated. Consistent with these findings, novelty-induced increases in DA release have been observed within the accumbens shell using fast-scan voltammetry.[60] Mesolimbic DA neurons, then, respond to novel events. These elevations might reflect an animal's expectation of possible reward whenever a novel circumstance is encountered; alternatively, these DA responses may reflect the salience and arousal value of the novel event, regardless of reward expectation.

1.3. Dopamine responses to aversive events

If DA neurons respond to arousing and salient events, and not only to reward-related stimuli, they should also respond to arousing 'aversive' events and to salient sensory stimuli without primary or conditioned motivational properties. In fact, microdialysis and voltammetry studies have shown elevations in DA release in response to aversive events such as foot shock,[70,83] a conditioned signal for foot shock,[83] tail shock,[1,39] tail pinch,[46] restraint stress,[20,37,76] and administration of anxiogenic drugs.[7,52] Single-unit responses to aversive stimuli have been observed in VTA[41] and SN[16] DA neurons. However, in a recent single-unit study, DA responses to aversive or conditioned aversive stimuli were rarely observed.[55] The current debate over the nature of DA responses to aversive events involves data obtained using single-unit, dialysis, and voltammetry techniques; data which are not always in agreement. Some important differences between single-unit and neurochemical (dialysis and voltammetry) measurement techniques are discussed below.

1.3.1. Single-unit versus neurochemical data. Single-unit studies of DAergic neurons record the time of occurrence of individual action potentials, and typically generate peri-event time histograms depicting the relationship between neuronal discharge and the occurrence of a sensory or behavioral event.[36,38,45,69] On the other hand, microdialysis and voltammetry techniques estimate concentrations of extracellular DA within target regions, such as the neostriatum, nucleus accumbens, or prefrontal cortex. Single-unit electrophysiology possesses the attribute of millisecond time resolution of neuronal events, allowing the detection of phasic neuronal responses to environmental events, responses that might not be observable under the (generally) 10-min sampling rate of microdialysis or even under the faster (seconds) resolution of voltammetry.

However, single-unit recordings cannot reveal the final amount of DA released into the extracellular space within terminal regions. The quantity of DA released is known to reflect the influence of a number of factors, including action potential occurrence,[77] presynaptic neuronal inputs[15] and activity at release-modulating autoreceptors at the nerve terminal.[29] The precise time of DA action potential occurrence is measurable using single-unit electrophysiology, but assessment of the final amount of DA release to target regions requires dialysis or voltammetry.

One explanation for the consistently observed DA response to aversive events using dialysis and voltammetry, but not using single-unit methods, is that stress-induced elevations in DA activity result primarily from presynaptic enhancement of DA release by glutamate acting at receptor sites on the DA terminal, rather than from elevated rates of action potential discharge at DA cell bodies. It is known, for instance, that glutamate and other excitatory amino acid inputs to the striatum and nucleus accumbens are capable of enhancing presynaptic DA release.[27,63] However, there is evidence to suggest that elevated rates of DA neuronal firing, rather than presynaptic factors, may be largely responsible for the DA response to aversive events.[16,39,41,85] Striatal DA elevations produced by tail-pinch, for instance, are not attenuated

by infusion of glutamate receptor antagonists into DA terminal sites, but are abolished following tetrodotoxin-induced blockade of action potential propagation along DA axons.[39,85]

An alternative explanation for the consistent observation of DA responses to aversive events using neurochemical, but not single-unit, methods is that DA responses to aversive events may be gradual rather than phasic.[69] A gradual DA response to stress might be difficult to detect using single-unit methods that typically look for changes in action potential likelihood within hundreds of milliseconds after an event has occurred. Further research is needed to characterize precise temporal relationships between the occurrence of aversive events and DA neuronal activation.

1.3.2. Strong versus mild aversive events. The question of whether aversive events produce a DA response (phasic or gradual) appears to depend upon the strength of the aversive event. It has been suggested that elevations in DA activity occur in response to strong, but not mild, aversive stimuli.[14,65] Indeed, mesolimbic and nigrostriatal DA activity is not increased by air puffs to the arm,[55] the taste of hypertonic saline,[55] gentle handling[14] or mild tail pinch.[14,57] DA activity is, however, elevated in response to stronger aversive events such as footshock,[70] tail shock,[1,14,39,58] tail prick,[41] cold ice bath,[40] prolonged restraint,[20,37] and anxiogenic drugs.[7,52] Regardless of the degree to which the DA response to aversive events is gradual or phasic, impulse-dependent or due to presynaptic factors, elevations in DA neuronal firing are generally absent during the presentation of mild aversive stimuli, but are seen in response to strong aversive events that produce greater behavioral activation and/or arousal. This generalization appears to account for a very large number of findings, using a number of different aversive stimuli, and involving dialysis, electrochemical detection, and single-unit recording of DA activity.

1.3.3. The onset versus offset of aversive events. Still, in defense of the view that DA provides a reward signal to target regions, one might suggest that elevations in DA release to aversive events reflect the rewarding or negative reinforcing consequences of aversive event offset. Indeed, neurochemical techniques often lack the temporal resolution to distinguish responses to the onset versus the offset of a brief aversive event. However, even when aversive conditions are present throughout an entire microdialysis sampling period, DA elevations are observed; that is, DA elevations are seen prior to the offset of the aversive event.[11,37,58] DA responses to aversive events are therefore not a response to aversive event offset, but instead, reflect important changes in environmental conditions, even if those changes are of an aversive nature.

1.4. Dopamine responses to salient events without primary or conditioned motivational properties

Strong evidence that DA neuronal responses are elicited by event salience, rather than incentive value, is the finding that DA neurons within the SN respond to salient auditory, visual, somatosensory and olfactory stimuli with neither primary nor conditioned reward or aversive properties.[16,32,72,73] One might imagine that these sensory responses are restricted to SN DA neurons since this system is implicated in sensory motor processes.[12,78] However, VTA DA neurons also respond to non-appetitive events like loud clicks and bright flashes of light,[36] that is, to events whose salience derives from physical sensory characteristics such as rapid onset and high intensity, and not from conditioned reward properties. Further, these salient events cause VTA DA cells to fire in burst mode,[28,36] an activity mode associated with disproportionally large increases in DA release at target sites.[31] Nigrostriatal and mesolimbocortical DA neurons, then, appear to respond to sensory stimuli that are rewarding or aversive, conditioned predictors of rewarding or aversive outcomes, novel, or simply of high intensity. A large category of salient and arousing events appears capable of driving SN and VTA DA neurons.

2. DOPAMINE RELEASE WITHIN NIGROSTRIATAL, MESOLIMBIC AND MESOCORTICAL TARGET SITES

Aversive events increase DA activity both within the nucleus accumbens[7,37,52,76,79,83] (but see Refs 6 and 8) and within the prefrontal cortex.[1,6,37,74,75,79] Similarly, appetitive events elevate DA levels both in the accumbens[4,5,33,49,59] and in the prefrontal cortex.[4,14,74] On the other hand, detectable elevations in DA levels within the dorsal striatum are often absent following appetitive[14,49] and aversive[37] events (but see Refs 1 and 8). One cannot rule out the possibility that specific regions within DA target sites respond differentially to events of differing motivational value, and there is some evidence in support of this possibility.[6,8,49] However, a large research literature suggests that salient and arousing events elevate mesolimbic, mesocortical, and to a lesser degree nigrostriatal, DA activity regardless of the motivational valence of the event.

Using an identical stressor, the magnitude of the observed increase in DA utilization relative to baseline levels is greatest in the prefrontal cortex, less in the accumbens, and least in the neostriatum.[1] Why are large elevations in DA concentration most likely to be observed within the prefrontal cortex? First, there is evidence to suggest that prefrontal DA release may be most strongly elevated during early stages of conditioning, while accumbens DA release may occur predominantly during later stages of conditioning, when conditioned responding emerges.[79] Therefore, the apparent volatility in prefrontal DA levels compared to those in other target regions may reflect the fact that DA responses to appetitive and aversive events are often measured during initial exposure to the event, that is during periods when prefrontal responses are likely to be greatest. Second, high levels of prefrontal DA activity may reflect a relative lack of autoreceptor and other feedback regulatory mechanisms within the prefrontal cortex,[17] mechanisms that act to prevent wide fluctuation in extracellular DA concentrations within other DA target regions.[26,84]

Single-unit recordings of DA neurons in the SN and VTA, sites of origin for the nigrostriatal and mesolimbocortical systems, show that cells originating in these regions are similarly activated by salient environmental stimuli.[36,45,73] It is therefore likely that DA neurons projecting to the striatum, accumbens, and prefrontal cortex all respond to salient sensory events with a burst of action potential discharge, but that the magnitude of the resulting increase in extracellular DA concentration with the prefrontal cortex, accumbens, and dorsal striatum, depends upon presynaptic influences at the nerve terminal and the efficiency of feedback regulatory

mechanisms. Efficient regulatory mechanisms within the striatum[26,84] may prevent long-term fluctuations in extracellular DA concentrations in this region.

Because the neostriatum is associated with sensory-motor processes and the execution of complex motor acts,[2,10] it is not unreasonable to imagine that there is a benefit to tight control of basal DA levels within this region, which would permit phasic DA elevations to occur with some temporal precision, for example, to facilitate switching of response components of a behavioral act.[44] In contrast, because DA within the nucleus accumbens and other limbic target sites is associated with incentive motivational, behavioral or mood states[3,22,62,65] and prefrontal DA modulates working memory function,[30] one might imagine that, within these regions, there is less need for DA fluctuations to occur with great temporal precision. To the contrary, one would imagine that DA modulation of these functions might instead call for a build-up of extracellular DA concentrations over a sustained period of time.

3. DO DOPAMINE NEURONS REPORT A "PREDICTION ERROR" OR A "REWARD PREDICTION ERROR"?

DA neurons signal the occurrence of events that were not expected to occur, and of events that occur at unexpected times.[69] Schultz has described this DA function as the reporting of a "reward prediction error". However the present analysis assumes a more general DA function in reporting "prediction error". The notion that DA specifically signals reward prediction error is based upon the findings that DA neurons (i) respond to unexpected food presentation, (ii) fail to respond to food presented at an expected time, and (iii) show suppressed activity when food fails to be delivered at a time when its delivery was expected (see Ref. 69 for review). These findings can be accounted for by the assumption that changes in DA activity reflect the computation: reward occurrence − reward expectation.[69] Because midbrain DA neurons rarely respond to aversive events such as airpuffs to the arm or saline to the mouth, it is possible that DA cells specifically report the occurrence of unexpected rewards.[55] However, as described in Section 1.3.2 above, DA activity appears to increase in response to strong and arousing aversive stimuli; responses to mild aversive events are less frequently observed. According to the present analysis, DA neurons are activated by a large category of arousing events that (as described above) include novel stimuli, unexpected rewards, aversive stimuli, high intensity visual and auditory events. DA activity is, on the other hand suppressed by events that are associated with reduced arousal or decreased anticipatory excitement, including the actual consumption of food reward[61] and the omission of expected reward.[69]

4. IMPLICATIONS FOR BEHAVIORAL FUNCTION

The function of DA activity within specific brain sites has been examined with respect to a number of behavioral processes, including associative learning and reinforcement,[19,42,81] temporal processing,[47] and other aspects of cognition.[3] While consideration of the precise functional consequences of elevated DA transmission within its various forebrain target sites is beyond the scope of the present analysis, several general inferences regarding DA function may be made. First, while DA activity plays a role in reinforcement processes,[21,23,35,81] this role is unlikely to involve either (i) a strengthening of stimulus–response connections, or (ii) a neurochemical signal of reward value. DA release increases, within forebrain target sites, in response to a large set of salient events that extend beyond that of reinforcing stimuli; it is therefore unlikely that DA elevations serve to increase the likelihood that a preceding response will reoccur under similar stimulus conditions. Similarly, DA transmission would provide an ambiguous signal of reward value.

DA neurons are activated under conditions of salient environmental change, conditions that require an organism to (i) become responsive to environmental stimuli, (ii) prepare for the possible output of high levels of behavioral activity, (iii) maintain a working memory representation of the just-encountered event (i.e. the event that caused DA neurons to release large quantities of DA into terminal regions). DA plays a role in each of these three behavioral functions. DA levels within the neostriatum, ventral striatum/accumbens, and prefrontal cortex modulate (i) motor responses to sensory inputs,[50,64,78] (ii) the response energizing or response-maintaining effects of motivationally-relevant stimuli,[24,66] and (iii) working memory processes,[30,67] respectively. While a strong case can be, and has been, made for a DA-dependent reward teaching signal,[69] the present analysis suggests an alternative view: midbrain DA neurons are driven by a large category of salient environmental events, and the consequent elevation in DA activity within its various target sites mediate the effects of arousal on a number of behavioral functions that contribute to the successful execution of goal-directed behavior. DA activity, on the other hand, is unlikely to communicate reward value.

Acknowledgements—Thanks to Jennifer Mangels, Rae Silver, and Herbert Terrace for helpful editorial comments, and to Peter Balsam for helpful conversations relevant to issues discussed here.

REFERENCES

1. Abercrombie E. D., Keefe K. A., DiFrischia D. S. and Zigmond M. J. (1989) Differential effect of stress on *in vivo* dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *J. Neurochem.* **52,** 1655–1658.
2. Amalric M. and Koob G. F. (1987) Depletion of dopamine in the caudate nucleus but not in nucleus accumbens impairs reaction-time performance in rats. *J. Neurosci.* **7,** 2129–2134.
3. Ashby F. G., Isen A. M. and Turken A. U. (1999) A neuropsychological theory of positive affect and its influence on cognition. *Psychol. Rev.* **106,** 529–550.
4. Bassareo V. and Di Chiara G. (1997) Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum. *J. Neurosci.* **17,** 851–861.
5. Bassareo V. and Di Chiara G. (1999) Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. *Neuroscience* **89,** 637–641.
6. Bassareo V., Tanda G., Petromilli P., Giua C. and Di Chiara G. (1996) Non-psychostimulant drugs of abuse and anxiogenic drugs activate with differential selectivity dopamine transmission in the nucleus accumbens and in the medial prefrontal cortex of the rat. *Psychopharmacology, Berl.* **124,** 293–299.

7. Bertolucci-D'Angio M., Serrano A. and Scatton B. (1990) Differential effects of forced locomotion, tail-pinch, immobilization, and methyl-beta-carboline carboxylate on extracellular 3,4-dihydroxyphenylacetic acid levels in the rat striatum, nucleus accumbens, and prefrontal cortex: an *in vivo* voltammetric study. *J. Neurochem.* **55,** 1208–1215.
8. Besson C. and Louilot A. (1997) Striatal dopaminergic changes depend on the attractive or aversive value of stimulus. *NeuroReport* **8,** 3523–3526.
9. Blackburn J. R., Pfaus J. G. and Phillips A. G. (1992) Dopamine functions in appetitive and defensive behaviours. *Prog. Neurobiol.* **39,** 247–279.
10. Blaszczyk J. W. (1998) Motor deficiency in Parkinson's disease. *Acta neurobiol. exp.* **58,** 79–93.
11. Bradberry C. W., Lory J. D. and Roth R. H. (1991) The anxiogenic beta-carboline FG 7142 selectively increases dopamine release in rat prefrontal cortex as measured by microdialysis. *J. Neurochem.* **56,** 748–752.
12. Carli M., Evenden J. L. and Robbins T. W. (1985) Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. *Nature* **313,** 679–682.
13. Carr G. D. and White N. M. (1986) Anatomical disassociation of amphetamine's rewarding and aversive effects: an intracranial microinjection study. *Psychopharmacology, Berl.* **89,** 340–346.
14. Cenci M. A., Kalen P., Mandel R. J. and Bjorklund A. (1992) Regional differences in the regulation of dopamine and noradrenaline release in medial frontal cortex, nucleus accumbens and caudate–putamen: a microdialysis study in the rat. *Brain Res.* **581,** 217–228.
15. Cheramy A., Romo R., Godeheu G., Baruch P. and Glowinski J. (1986) *In vivo* presynaptic control of dopamine release in the cat caudate nucleus—II. Facilitatory or inhibitory influence of L-glutamate. *Neuroscience* **19,** 1081–1090.
16. Chiodo L. A., Antelman S. M., Caggiula A. R. and Lineberry C. G. (1980) Sensory stimuli alter the discharge rate of dopamine (DA) neurons: evidence for two functional types of DA cells in the substantia nigra. *Brain Res.* **189,** 544–549.
17. Chiodo L. A., Bannon M. J., Grace A. A., Roth R. H. and Bunney B. S. (1984) Evidence for the absence of impulse-regulating somatodendritic and synthesis-modulating nerve terminal autoreceptors on subpopulations of mesocortical dopamine neurons. *Neuroscience* **12,** 1–16.
18. Damsma G., Pfaus J. G., Wenkstern D., Phillips A. G. and Fibiger H. C. (1992) Sexual behavior increases dopamine transmission in the nucleus accumbens and striatum of male rats: comparison with novelty and locomotion. *Behav. Neurosci.* **106,** 181–191.
19. Di Chiara G. (1999) Drug addiction as dopamine-dependent associative learning disorder. *Eur. J. Pharmac.* **375,** 13–30.
20. Doherty M. D. and Gratton A. (1997) NMDA receptors in nucleus accumbens modulate stress-induced dopamine release in nucleus accumbens and ventral tegmental area. *Synapse* **26,** 225–234.
21. Duvauchelle C. L. and Ettenberg A. (1991) Haloperidol attenuates conditioned place preferences produced by electrical stimulation of the medial prefrontal cortex. *Pharmac. Biochem. Behav.* **38,** 645–650.
22. Duvauchelle C. L., Levitin M., MacConell L. A., Lee L. K. and Ettenberg A. (1992) Opposite effects of prefrontal cortex and nucleus accumbens infusions of flupenthixol on stimulant-induced locomotion and brain stimulation reward. *Brain Res.* **576,** 104–110.
23. Ettenberg A. (1989) Dopamine, neuroleptics and reinforced behavior. *Neurosci. Biobehav. Rev.* **13,** 105–111.
24. Everitt B. J., Cador M. and Robbins T. W. (1989) Interactions between the amygdala and ventral striatum in stimulus–reward associations: studies using a second-order schedule of sexual reinforcement. *Neuroscience* **30,** 63–75.
25. Fallon J. H. and Moore R. Y. (1978) Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. *J. comp. Neurol.* **180,** 545–580.
26. Farnebo L. O. and Hamberger B. (1971) Drug-induced changes in the release of 3 H-monoamines from field stimulated rat brain slices. *Acta physiol. scand.* **371,** (Suppl.) 35–44.
27. Floresco S. B., Yang C. R., Phillips A. G. and Blaha C. D. (1998) Basolateral amygdala stimulation evokes glutamate receptor-dependent dopamine efflux in the nucleus accumbens of the anaesthetized rat. *Eur. J. Neurosci.* **10,** 1241–1251.
28. Freeman A. S. and Bunney B. S. (1987) Activity of A9 and A10 dopaminergic neurons in unrestrained rats: further characterization and effects of apomorphine and cholecystokinin. *Brain Res.* **405,** 46–55.
29. Galloway M. P., Wolf M. E. and Roth R. H. (1986) Regulation of dopamine synthesis in the medial prefrontal cortex is mediated by release modulating autoreceptors: studies *in vivo*. *J. Pharmac. exp. Ther.* **236,** 689–698.
30. Goldman-Rakic P. S. (1996) Regional and cellular fractionation of working memory. *Proc. natn. Acad. Sci. U.S.A.* **93,** 13473–13480.
31. Gonon F. G. (1988) Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by *in vivo* electrochemistry. *Neuroscience* **24,** 19–28.
32. Grace A. A. and Bunney B. S. (1979) Paradoxical GABA excitation of nigral dopaminergic cells: indirect mediation through reticulata neurons. *Eur. J. Pharmac.* **59,** 211–218.
33. Hernandez L. and Hoebel B. G. (1988) Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. *Life Sci.* **42,** 1705–1712.
34. Hornykiewicz O. (1979) Brain dopamine in Parkinson's disease and other neurological disturbances. In *The Neurobiology of Dopamine*, (eds Horn A. S., Korf J. and Westerning B. H. C.), pp. 633-654. Academic, London.
35. Horvitz J. C. and Ettenberg A. (1989) Haloperidol blocks the response-reinstating effects of food reward: a methodology for separating neuroleptic effects on reinforcement and motor processes. *Pharmac. Biochem. Behav.* **31,** 861–865.
36. Horvitz J. C., Stewart T. and Jacobs B. L. (1997) Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat. *Brain Res.* **759,** 251–258.
37. Imperato A., Puglisi-Allegra S., Casolini P. and Angelucci L. (1991) Changes in brain dopamine and acetylcholine release during and following stress are independent of the pituitary-adrenocortical axis. *Brain Res.* **538,** 111–117.
38. Jacobs B. L. (1986) Single unit activity of brain monoamine-containing neurons in freely moving animals. *Ann. N.Y. Acad. Sci.* **473,** 70–77.
39. Keefe K. A., Sved A. F., Zigmond M. J. and Abercrombie E. D. (1993) Stress-induced dopamine release in the neostriatum: evaluation of the role of action potentials in nigrostriatal dopamine neurons or local initiation by endogenous excitatory amino acids. *J. Neurochem.* **61,** 1943–1952.
40. Keller R. W. Jr., Stricker E. M. and Zigmond M. J. (1983) Environmental stimuli but not homeostatic challenges produce apparent increases in dopaminergic activity in the striatum: an analysis by *in vivo* voltammetry. *Brain Res.* **279,** 159–170.
41. Kiyatkin E. A. (1988) Functional properties of presumed dopamine-containing and other ventral tegmental area neurons in conscious rats. *Int. J. Neurosci.* **42,** 21–43.
42. Koob G. F. and Swerdlow N. R. (1988) The functional output of the mesolimbic dopamine system. *Ann. N.Y. Acad. Sci.* **537,** 216–227.
43. Le Moal M. and Simon H. (1991) Mesocorticolimbic dopaminergic network: functional and regulatory roles. *Physiol. Rev.* **71,** 155–234.
44. Liao R. M., Fowler S. C. and Kallman M. J. (1997) Quantifying operant behavior deficits in rats with bilateral 6-hydroxydopamine lesions of the ventrolateral striatum. *Chin. J. Physiol.* **40,** 71–78.
45. Ljungberg T., Apicella P. and Schultz W. (1992) Responses of monkey dopamine neurons during learning of behavioral reactions. *J. Neurophysiol.* **67,** 145–163.
46. Louilot A., Le Moal M. and Simon H. (1986) Differential reactivity of dopaminergic neurons in the nucleus accumbens in response to different behavioral situations. An *in vivo* voltammetric study in free moving rats. *Brain Res.* **397,** 395–400.
47. Malapani C., Rakitin B., Levy R., Meck W. H., Deweer B., Dubois B. and Gibbon J. (1998) Coupled temporal memories in Parkinson's disease. A dopamine-related dysfunction. *J. cogn. Neurosci.* **10,** 316–331.
48. Mark G. P., Rada P., Pothos E. and Hoebel B. G. (1992) Effects of feeding and drinking on acetylcholine release in the nucleus accumbens, striatum, and hippocampus of freely behaving rats. *J. Neurochem.* **58,** 2269–2274.

49. Mark G. P., Smith S. E., Rada P. V. and Hoebel B. G. (1994) An appetitively conditioned taste elicits a preferential increase in mesolimbic dopamine release. *Pharmac. Biochem. Behav.* **48,** 651–660.
50. Marshall J., Berrios N. and Sawyer S. (1980) Neostriatal dopamine and sensory inattention. *J. comp. Physiol. Psychol.* **94,** 833–846.
51. Mas M., Gonzalez-Mora J. L., Louilot A., Sole C. and Guadalupe T. (1990) Increased dopamine release in the nucleus accumbens of copulating male rats as evidenced by *in vivo* voltammetry. *Neurosci. Lett.* **110,** 303–308.
52. McCullough L. D. and Salamone J. D. (1992) Anxiogenic drugs beta-CCE and FG 7142 increase extracellular dopamine levels in nucleus accumbens. *Psychopharmacology, Berl.* **109,** 379–382.
53. McCullough L. D. and Salamone J. D. (1992) Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: a microdialysis and behavioral study. *Brain Res.* **592,** 29–36.
54. Mirenowicz J. and Schultz W. (1994) Importance of unpredictability for reward responses in primate dopamine neurons. *J. Neurophysiol.* **72,** 1024–1027.
55. Mirenowicz J. and Schultz W. (1996) Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli. *Nature* **379,** 449–451.
56. Pfaus J. G., Damsma G., Wenkstern D. and Fibiger H. C. (1995) Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats. *Brain Res.* **693,** 21–30.
57. Pleim E. T., Matochik J. A., Barfield R. J. and Auerbach S. B. (1990) Correlation of dopamine release in the nucleus accumbens with masculine sexual behavior in rats. *Brain Res.* **524,** 160–163.
58. Puglisi-Allegra S., Imperato A., Angelucci L. and Cabib S. (1991) Acute stress induces time-dependent responses in dopamine mesolimbic system. *Brain Res.* **554,** 217–222.
59. Radhakishun F. S., van Ree J. M. and Westerink B. H. (1988) Scheduled eating increases dopamine release in the nucleus accumbens of food-deprived rats as assessed with on-line brain dialysis. *Neurosci. Lett.* **85,** 351–356.
60. Rebec G. V. (1998) Real-time assessments of dopamine function during behavior: single-unit recording, iontophoresis, and fast-scan cyclic voltammetry in awake, unrestrained rats. *Alcohol clin. exp. Res.* **22,** 32–40.
61. Richardson N. R. and Gratton A. (1996) Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. *J. Neurosci.* **16,** 8160–8169.
62. Robbins T. W. and Everitt B. J. (1996) Neurobehavioural mechanisms of reward and motivation. *Curr. Opin. Neurobiol.* **6,** 228–236.
63. Romo R., Cheramy A., Godeheu G. and Glowinski J. (1986) *In vivo* presynaptic control of dopamine release in the cat caudate nucleus—III. Further evidence for the implication of corticostriatal glutamatergic neurons. *Neuroscience* **19,** 1091–1099.
64. Rothblat D. S. and Schneider J. S. (1993) Response of caudate neurons to stimulation of intrinsic and peripheral afferents in normal, symptomatic, and recovered MPTP-treated cats. *J. Neurosci.* **13,** 4372–4378.
65. Salamone J. D. (1994) The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behav. Brain Res.* **61,** 117–133.
66. Salamone J. D., Cousins M. S. and Snyder B. J. (1997) Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. *Neurosci. Biobehav. Rev.* **21,** 341–359.
67. Sawaguchi T. and Goldman-Rakic P. S. (1994) The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *J. Neurophysiol.* **71,** 515–528.
68. Schultz W. (1986) Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. *J. Neurophysiol.* **56,** 1439–1461.
69. Schultz W. (1998) Predictive reward signal of dopamine neurons. *J. Neurophysiol.* **80,** 1–27.
70. Sorg B. A. and Kalivas P. W. (1991) Effects of cocaine and footshock stress on extracellular dopamine levels in the ventral striatum. *Brain Res.* **559,** 29–36.
71. Steinfels G. F., Heym J. and Jacobs B. L. (1981) Single unit activity of dopaminergic neurons in freely moving cuts. *Life Sci.* **29,** 1435–1442.
72. Steinfels G. F., Heym J., Strecker R. E. and Jacobs B. L. (1983) Response of dopaminergic neurons in cat to auditory stimuli presented across the sleep–waking cycle. *Brain Res.* **277,** 150–154.
73. Strecker R. E. and Jacobs B. L. (1985) Substantia nigra dopaminergic unit activity in behaving cats: effect of arousal on spontaneous discharge and sensory evoked activity. *Brain Res.* **361,** 339–350.
74. Taber M. T. and Fibiger H. C. (1997) Activation of the mesocortical dopamine system by feeding: lack of a selective response to stress. *Neuroscience* **77,** 295–298.
75. Thierry A. M., Tassin J. P., Blanc G. and Glowinski J. (1976) Selective activation of mesocortical DA system by stress. *Nature* **263,** 242–244.
76. Weiss F., Imperato A., Casu M. A., Mascia M. S. and Gessa G. L. (1997) Opposite effects of stress on dopamine release in the limbic system of drug-naive and chronically amphetamine-treated rats. *Eur. J. Pharmac.* **337,** 219–222.
77. Westerink B. H., Tuntler J., Damsma G., Rollema H. and de Vries J. B. (1987) The use of tetrodotoxin for the characterization of drug-enhanced dopamine release in conscious rats studied by brain dialysis. *Naunyn-Schmiedeberg's Arch. Pharmac.* **336,** 502–507.
78. White N. M. (1986) Control of sensorimotor function by dopaminergic nigrostriatal neurons: influence on eating and drinking. *Neurosci. Biobehav. Rev.* **10,** 15–36.
79. Wilkinson L. S., Humby T., Killcross A. S., Torres E. M., Everitt B. J. and Robbins T. W. (1998) Dissociations in dopamine release in medial prefrontal cortex and ventral striatum during the acquisition and extinction of classical aversive conditioning in the rat. *Eur. J. Neurosci.* **10,** 1019–1026.
80. Wilson C., Nomikos G. G., Collu M. and Fibiger H. C. (1995) Dopaminergic correlates of motivated behavior: importance of drive. *J. Neurosci.* **15,** 5169–5178.
81. Wise R. A. and Rompre P. P. (1989) Brain dopamine and reward. *A. Rev. Psychol.* **40,** 191–225.
82. Young A. M., Joseph M. H. and Gray J. A. (1992) Increased dopamine release *in vivo* in nucleus accumbens and caudate nucleus of the rat during drinking: a microdialysis study. *Neuroscience* **48,** 871–876.
83. Young A. M., Joseph M. H. and Gray J. A. (1993) Latent inhibition of conditioned dopamine release in rat nucleus accumbens. *Neuroscience* **54,** 5–9.
84. Zetterstrom T., Sharp T. and Ungerstedt U. (1984) Effect of neuroleptic drugs on striatal dopamine release and metabolism in the awake rat studied by intracerebral dialysis. *Eur. J. Pharmac.* **106,** 27–37.
85. Zigmond M. J., Castro S. L., Keefe K. A., Abercrombie E. D. and Sved A. F. (1998) Role of excitatory amino acids in the regulation of dopamine synthesis and release in the neostriatum. *Amino Acids* **14,** 57–62.

(*Accepted* 14 *January* 2000)