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Pennartz, C.M.A.; Groenewegen, H.J.; Lopes da Silva, F.H.

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THE NUCLEUS ACCUMBENS AS A COMPLEX OF FUNCTIONALLY DISTINCT NEURONAL ENSEMBLES: AN INTEGRATION OF BEHAVIOURAL, ELECTROPHYSIOLOGICAL AND ANATOMICAL DATA

CYRIEL M. A. PENNARTZ,* HENK J. GROENEWEGEN† and
 FERNANDO H. LOPES DA SILVA*

*Graduate School Neurosciences Amsterdam, Institute of Neurobiology, Faculty of Biology,
 University of Amsterdam, Kruislaan 320, 1098 SM, Amsterdam, The Netherlands

†Graduate School Neurosciences Amsterdam, Department of Anatomy and Embryology, Faculty of
 Medicine, Free University of Amsterdam, Van der Boechorststraat 8, 1081 BT, Amsterdam, The Netherlands

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1. INTRODUCTION

Behavioural, anatomical and electrophysiological studies of the nucleus accumbens (Acb) have been rapidly growing in number over the past two decades. This growth has certainly been stimulating, but has entailed an overspecialization such that within different disciplines explanations on separate aspects of Acb function were developed, instead of an integrated theory. The lack of a multidisciplinary research framework is reflected by the fact that in 1993, two decades

after the discovery of the stimulating effects of intra-accumbens dopamine on locomotion, a comprehensive theory of how the Acb functions in regulating this and other types of behaviour still remains to be formulated.

For the past 10 years, the neuroanatomy of the basal ganglia has been dominated by the immunohistochemical and hodological analysis of the patch-matrix organization of the striatal complex, but the function of this compartmentation remains to be defined. Electrophysiological studies have advanced our understanding of the cellular mechanisms underlying excitability of single Acb neurons and of particular environmental stimuli evoking firing behaviour in the Acb of the awake animal. However, these single-cell studies do not permit to draw conclusions about the functioning

Address correspondence to: C. M. A. Pennartz, Graduate School Neurosciences Amsterdam, Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ, Amsterdam, The Netherlands.

of the Acb as an integrated network and, even more so, cannot bridge the gap between cellular firing activity and correlated behavioural acts. Behavioural neuropharmacology presents a complementary approach in that it combines micro-injections of specified neurochemicals with analysis of behavioural acts, but essentially lacks sufficient precision to allow inferences at the level of microcircuits.

In this review, an attempt is made to bring together data from various research disciplines and to formulate unifying concepts that may be valuable in explaining the functioning of Acb at an integrated level. First, evidence implicating the Acb in diverse behaviours will be summarized, with emphasis on how injection of drugs into the nucleus affects locomotion. Second, investigations on the role of Acb in several types of learning and adaptive behaviour are summarized. This brief review will lead us to a question that proves to be of central importance in developing a hypothesis: can we identify a positive or negative correlation between the average firing activity of Acb neurons and the extent to which a particular behavioural activity is manifest? This question will be pursued especially for effects of neuroactive agents on locomotion. A critical comparison of literature data indicates that a straightforward correlation between electrophysiological actions and locomotor effects of drugs is lacking.

An alternative view on Acb function is presented, based on evidence for regionally differing effects of neurochemicals injected into the Acb, for specific connectivity of compartments and for response variability in electrophysiological studies. The main postulates of this new hypothesis are: (1) the existence of functionally heterogeneous neuronal ensembles in Acb, (2) convergence of cortical, thalamic and amygdalar inputs on specific ensembles of Acb neurons, (3) recruitment of Acb ensembles by rhythmically coupled, synchronously active cortical, thalamic and amygdalar groups of neurons, and (4) subsequent inhibition or modulation of target areas mediating specific components of behavioural patterns, endocrine function and corticothalamic processing. Even though this proposal might globally explain how the Acb is functionally organized, the network functions of diverse transmitter and modulator systems remain underexposed. The computational and dynamic functions of these systems will be considered in the last section of this review.

2. BEHAVIOURAL STUDIES OF NUCLEUS ACCUMBENS FUNCTION, WITH EMPHASIS ON LOCOMOTION

Numerous studies have presented evidence that various neurochemicals injected into the Acb can affect behavioural activity. Behavioural consequences of electrolytic or neurotoxic lesions of the Acb have been evaluated in an additional number of studies. Further information on the functioning of Acb has been extracted from studies combining stimulation by chronically implanted electrodes with behavioural monitoring, although this approach has been used in Acb mainly in relation to oral behaviour (Lund and Dellow, 1971; Hockman *et al.*, 1979). Chemical,

electrical and mechanical manipulations of the Acb are able to affect specific behavioural patterns in a global way, as illustrated by the profound effect of 6-hydroxy-dopamine (6-OHDA) lesions in Acb on e.g. displacement behaviour (Robbins and Koob, 1980), but may also have distinct effects on specific behavioural components, such as chewing and swallowing (Lund and Dellow, 1971; Hockman *et al.*, 1979) and regulation of forelimb muscle tone (Ellenbroek *et al.*, 1988). The most intensively studied type of behaviour in relation to Acb function, however, is locomotor activity. Standard tests of locomotion, e.g. beam interruption methods, are commonly used and provide a convenient way to quantify this type of activity (interpreting this behaviour, however, is a different matter; see Section 5). In order to be able to compare the behavioural effects of different neurochemicals with each other and, in Section 4, with their respective electrophysiological actions on Acb neurons, we will restrict this section mainly to studies that were focussed on locomotor activity (cf. Table 1), while reviewing learning experiments in Section 3.

The Acb became a focal point of interest among behavioural neuroscientists with the discovery that dopamine injections into the Acb enhanced locomotor activity in rats (Pijnenburg and Van Rossum, 1973; Costall and Naylor, 1975; Robbins and Everitt, 1982). This stimulatory effect was mimicked by the dopamine agonist apomorphine and by amphetamine, which stimulates dopamine release (Kelly *et al.*, 1975; Swerdlow and Koob, 1987b; Kelley *et al.*, 1989). Moreover, 6-OHDA lesions in the ventral tegmental area prevented amphetamine-induced hyperactivity (Kelly *et al.*, 1975). The motor stimulant activity seems, at least in part, to be mediated by D1 receptors, as intra-accumbens injection of the D1 receptor agonists SKF 38393 and SKF 89626 also increased locomotion (Freedman *et al.*, 1979; Arnt, 1987; Andersen *et al.*, 1987; see, however, Cools *et al.*, 1988).

Contrary to these studies in intact brains, Reinstein *et al.* (1982) and Hannigan *et al.* (1984) surprisingly found a depressive effect of intra-accumbens application of the dopamine agonist 3,4-dihydroxy-phenylamino-2-imidazoline (DPI) in rats with bilateral aspiration lesions of the hippocampus. The lesioning itself caused an increase in locomotion, whereas activity returned to normal following DPI application.

Other observations suggest that the impact of intra-accumbens dopamine depends on environmental conditions: its effects were reported to be contingent upon the light/dark cycle and familiarity of the animal with its environment (Cools, 1986). Svensson and Ahlenius (1983) reported inhibitory effects of intra-accumbens application of the dopamine receptor agonist 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP) on locomotion in a presumably novel environment, instead of the more usual stimulant effects of dopamine agonists.

Studies on the behavioural function of the mesolimbic dopamine system were complemented with injection experiments using other modulators and transmitters, such as GABA. Local injection of the GABA_A antagonist picrotoxin into Acb increased locomotor activity, and thus mimicked the effect of

dopamine (Wachtel and Andén, 1978; Jones and Mogenson, 1980a, b; Mogenson *et al.*, 1980; Jones *et al.*, 1981; Morgenstern *et al.*, 1984). Conversely, injections of GABA agonists into the Acb had variable effects. At relatively high doses, application of the GABA analogue γ -hydroxybutyric acid and GABA itself produced a reduction of locomotor activity, whereas low doses led to an increase in motor activity (Wachtel and Andén, 1978; Jones *et al.*, 1981). Injection of the GABA_B agonist baclofen resulted in an initial depression followed by a stimulation of locomotor activity (Wachtel and Andén, 1978). Pycock and Horton (1979) investigated the effects of intra-accumbens GABA agonists and antagonists in relation to the hyperactivity state induced by locally injected dopamine. In their study, high concentrations of GABA agonists depressed dopamine-induced hyperactivity, whereas picrotoxin and bicuculline greatly facilitated the dopamine-induced effect, but also could give rise to generalized seizures.

Soon after the introduction of specific *glutamate* receptor agonists and antagonists, investigators initiated studies on glutamate receptor-mediated effects on behaviour. Donzanti and Uretsky (1983) reported a stimulatory action of intra-accumbens L-aspartic acid, D-glutamic acid, kainic acid, quisqualic acid and NMDA, although L-glutamic acid had, surprisingly, no effect. In addition, Shreve and Uretsky (1988) found a hypermotility response to intra-accumbens application of α -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), which could be antagonized by γ -D-glutamylaminomethylsulphonate (GAMS). In line with these results, Hamilton *et al.* (1986) reported intense locomotor activity following injection of N-methyl-aspartate (NMA) into the Acb, an effect that could be suppressed by the NMDA receptor antagonist aminophosphonopentanoic acid (DL-AP5). As for glutamate receptor antagonist effects, Mogenson and Nielsen (1984) showed that the AMPA/kainate receptor antagonist L-glutamic acid diethyl ester (GDEE) injected into Acb reduced locomotion induced by carbachol injection into the dentate gyrus. Finally, Schacter *et al.* (1989) reported that intra-accumbens administration of the broad spectrum glutamate receptor antagonist kynurenic acid reduced exploratory locomotion and increased the latency to initiate movements. Ericson *et al.* (1990), however, found more variable effects of kynurenic acid that were dependent upon the test environment used in the experiment. In an open field situation, no effect of intra-accumbens kynurenic acid on motor activity of rats could be measured, whereas an increased activity was noted when the rat was placed in a box used for conditioned avoidance testing.

A relatively large number of studies have investigated possible interactions between glutamate and dopamine receptors at the behavioural level. The hypothesis that glutamate agonists may exert behavioural effects by facilitating dopamine release has been central in these studies. Indeed, some biochemical studies have shown a stimulatory effect of glutamatergic agonists on dopamine release (Roberts and Anderson, 1979; Imperato *et al.*, 1990; Boldry *et al.*, 1991), but the results did not necessarily imply that glutamate receptors are located on dopaminergic

terminals. More specifically, these studies could not exclude indirect and aspecific effects of glutamate receptor agonists, for instance, glutamate-induced K⁺ release from postsynaptic elements followed by K⁺-stimulated dopamine release.

In behavioural experiments pertaining to this issue, Donzanti and Uretsky (1983) found that the stimulatory effects of glutamate receptor agonists on locomotion were reduced by the dopamine receptor antagonists haloperidol and fluphenazine, and therefore suggested that excitatory amino acid-induced hypermotility was mediated by activation of dopamine receptors in Acb. However, injection of haloperidol alone strongly decreased locomotion in control animals, which, in our view, precludes any firm conclusion about dopamine-excitatory amino acid interactions. In more recent work, Uretsky's group extended previous observations by showing that hyperactivity induced by intra-accumbens AMPA persisted in rats with neonatal 6-OHDA lesions, or in rats treated with sulphiride and Sch 23390 to block both D2 and D1 receptors (Boldry *et al.*, 1992). In contrast to their previous conclusion, these findings suggest glutamate receptor actions on locomotor activity that do not depend on dopamine-mediated effects. The interpretation of these results was complicated by the finding that α -methyl-p-tyrosine, a drug that inhibits tyrosine hydroxylase, almost completely prevented AMPA-induced locomotion. The effects of α -methyl-p-tyrosine were not studied on its own, and in addition, side effects on norepinephrine systems could not be excluded. Thus, it is rather difficult to evaluate the relevance of the latter finding. Pulvirenti *et al.* (1989) took a different approach by studying the effect of GDEE on hyperactivity induced by systemically administered cocaine and amphetamine. Intra-accumbens injection of GDEE reduced the stimulant effects in a dose-dependent manner, supporting the hypothesis of a glutamate receptor interaction with dopamine release. Unfortunately, their paper did not present results concerning GDEE effects on locomotion under unstimulated conditions, again precluding firm conclusions about this presumed modulation.

These behavioural studies leave us with an incomplete set of observations. In addition, a firm biochemical basis for a direct glutamatergic influence on dopamine release in Acb is still lacking. These considerations make us rather hesitant in attaching important functional consequences to the putative stimulation of dopamine release by excitatory amino acids, at least in Acb.

Two important modulatory systems in Acb remain to be discussed in relation to locomotor activity. Intra-accumbens injections of both *morphine* and *enkephalins* have been shown to enhance locomotion, and this action could be effectively antagonized by the opiate receptor antagonist naloxone but not by haloperidol (Pert and Sivit, 1977). Thus, opiate receptor activation in Acb may lead to similar, but independent stimulatory effects on behaviour as dopamine receptor activation. Recently, Cunningham and Kelley (1992) reported similar stimulatory effects of a δ receptor agonist, while mixed μ and δ agonists had both inhibitory and stimulatory effects on locomotion. In the case of *cholinergic* modulation,

intra-accumbens injection of the nicotinic and muscarinic receptor agonist carbachol was found to elicit a hypermotility response, and this effect could be reduced by haloperidol and the nicotinic receptor antagonist mecamylamine, but not by the muscarinic receptor antagonist atropine (Austin and Kalivas, 1988). The stimulatory action of ventral striatal acetylcholine on locomotion may be ascribed to an activation of nicotinic receptors that presumably facilitate dopamine release (cf. Mifsud *et al.*, 1989). However, these results do not agree with an earlier study of Jones *et al.* (1981), who reported that atropine did antagonize the enhancing effect of cholinergic agonists on dopamine-induced locomotor activity. Moreover, DeBellerroche *et al.* (1981) found an increase of dopamine-induced locomotion by the muscarinic receptor agonist oxotremorine.

A complementary approach to the intra-accumbens injection studies outlined above was to modulate activity in *afferent pathways* to Acb. The hypermotility effects of carbachol injections in the dentate gyrus (Mogenson and Nielsen, 1984) were already mentioned above. The antagonizing action of intra-accumbens GDEE suggested that excitation of Acb neurons by afferent activity from the hippocampus is associated with an enhancement of locomotion. Furthermore, excitation of ventral subicular tissue by NMDA injection also resulted in a strong increase in motility (Yang and Mogenson, 1987), and this effect

was antagonized by intra-accumbens injection of the D2 receptor agonist quinpirole. Contrary to these results, excitation of cells in the basolateral amygdala by NMDA led to a decrease in motility, and this action could be completely antagonized by intra-accumbens GDEE (Yim and Mogenson, 1989). These contrasting effects are referred to below as "amygdala-hippocampal antagonism in locomotion".

Although the limitations of electrolytic lesions are nowadays well recognized, it is worthwhile mentioning that such lesions of Acb caused an increase in locomotion (Kelly and Roberts, 1983). However, ibotenic acid or quisqualate-induced lesions of Acb did not significantly affect locomotor activity (Annett *et al.*, 1989; Everitt *et al.*, 1991; cf. Section 3). These contrasting findings may be ascribed either to the size of the lesion (cf. Annett *et al.*, 1989) or, in the electrolytic method, to damage of *en passage* fibers.

For the sake of clarity, the synopsis of behavioural studies given so far (see also Table 1) has been rather one-sided in its predominant focus on studies of locomotion. There is ample evidence underscoring a wider involvement of Acb than merely in ambulatory activity. Studies using chronically implanted electrodes reported chewing and swallowing movements following electrical stimulation of the Acb (Lund and Dellow, 1971; Hockman *et al.*, 1979). Although spread of current to adjacent areas complicates the interpretation of these experiments, they are in line

TABLE 1. SURVEY OF LOCOMOTOR EFFECTS AND ELECTROPHYSIOLOGICAL ACTIONS OF NEUROACTIVE SUBSTANCES ON SPINY PROJECTION NEURONS (SPNs) IN THE NUCLEUS ACCUMBENS

Substance	Pharmacological action	Effect on locomotion	Effect on fast synaptic transmission in SPNs	Effect on membrane properties of SPNs
Dopamine	Endogenous agonist	Mostly stimulating	Reduction of EPSPs and IPSPs	Possibly hyperpolarization (D1) and depolarization (D2)
Picrotoxin	GABA _A receptor-channel blocker	Stimulating	Block of IPSP and prolongation of EPSP	—
GABA (high dose)	Endogenous agonist	Depressing	Opening of GABA-receptor coupled Cl ⁻ channels (+ see baclofen)	Decrease of R _{input} (+ see baclofen)
GABA (low dose)	Idem	Stimulating	Idem	Idem
Baclofen	GABA _B receptor agonist	First depressing, then stimulating	Reduction of EPSP and IPSP	Hyperpolarization and decrease of R _{input}
AMPA	AMPA receptor agonist	Stimulating	Opening of AMPA receptor coupled cation channels	Depolarization and decrease of R _{input}
NMA	NMDA receptor agonist	Stimulating	Opening of NMDA receptor coupled Ca ²⁺ channels(?)	Depolarization and decrease of R _{input} (?)
Kynurenic acid	Glutamate receptor antagonist	Depressing or ineffective	Block of EPSP and (feed-forward) IPSP	—
Morphine, Enkephalin	Opiate receptor agonists	Stimulating	Reduction of EPSP and IPSP	—
Carbachol	Cholinergic receptor agonist	Stimulating	Reduction of EPSP and IPSP	Depolarization and increase of R _{input}

The effects on locomotor activity all refer to intra-accumbens application of drugs. It should be noted that the effects of GABA, AMPA and NMA (*N*-methyl-aspartate) are thought to primarily involve activation of receptor-channels functioning in fast synaptic transmission, and their effects on membrane properties must be interpreted as being a direct consequence of this action. Modulation of membrane properties by the other substances in this table is thought to be distinct from effects on fast synaptic transmission. Actions of picrotoxin, kynurenic acid and opiate receptor agonists on membrane properties of Acb neurons have not been reported in the literature. The precise electrophysiological effects of NMA, when injected *in vivo*, are difficult to estimate due to the voltage-dependence of Mg²⁺ block of the NMDA receptor-coupled channel. Literature references are mentioned in the text. R_{input}, input resistance.

with neuropharmacological studies underscoring a role for Acb in feeding behaviour (Kelley and Stinus, 1985; Evans and Vaccarino, 1986; Wise *et al.*, 1989). Other authors have investigated the involvement of the Acb in sexual behaviour. Alterations of dopaminergic transmission in Acb were shown to affect appetitive aspects of male sexual behaviour (Everitt *et al.*, 1989; Everitt, 1990) and extracellular dopamine levels were observed to increase during presentation of a receptive female and during copulatory acts (Pfaus *et al.*, 1990; Pleim *et al.*, 1990). Other studies have revealed a role for Acb and VTA in aggressive behaviour. Goldstein and Siegel (1981) reported that electrical stimulation of Acb tissue inhibited predatory attack in cats. Electrical stimulation of VTA was reported to facilitate attack behaviour in cats and to enhance prey fixation (Piazza *et al.*, 1988). A recent electrolytic lesioning study implied the medial Acb in hormone-regulated aggression (Albert *et al.*, 1989). In addition to feeding and aggressive behaviour, the mesolimbic dopamine system has been implicated in food hoarding (Kelley and Stinus, 1985), lactation and maternal behaviour (Woods *et al.*, 1969; Aulsebrook and Holland, 1969a, b; Gaffori and LeMoal, 1979; Holland and Soedjono, 1981). The role of the Acb in displacement-like behaviour (Robbins and Koob, 1980) has already been mentioned. This functional aspect of the Acb is compatible with studies suggesting a role for Acb in behavioural switching (Taghzouti *et al.*, 1985; Van den Bos and Cools, 1989; Van den Bos *et al.*, 1991; Reading *et al.*, 1991). Apart from its influences on overt behaviour, the Acb may also exert regulatory effects on hormone release (Woods *et al.*, 1969; Aulsebrook and Holland 1969a, b; Holland and Soedjono, 1981).

3. THE NUCLEUS ACCUMBENS IN LEARNING

Mogenson *et al.* (1980) recognized that the large majority of behavioural patterns affected by manipulations of the mesolimbic dopamine system represent basic biological "drives" essential for the survival and reproduction of the organism. While a large number of behavioural studies on learning processes can still be brought in line with this notion, more recent investigations have suggested a supplementary role for the Acb in behaviour that relies on "cognitive" capacities as well.

Several papers have indicated a role for the Acb in "simple" learning tasks such as *conditioned place preference*, in which the association of a primary reward with a particular environment leads to an increase in the amount of time spent in, or approach to this environment, even in further absence of the reward (Carr and White, 1983; Beninger and Hahn, 1983; Gold *et al.*, 1988; Beninger, 1991; Everitt *et al.*, 1991). Carr and White (1983) found a dissociable role of dorsal and ventral striatum when intra-striatal injections of amphetamine were consistently given in a distinct environment. Place preference was induced following injections in the nucleus accumbens, but not in the dorsolateral caudate nucleus. Beninger and Hahn (1983), using intraperitoneal injections of amphetamine, discovered a specific effect of the dopamine antagonist pimozide on the conditioning

process, while the conditioned activity itself, once established, appeared unaffected. White *et al.* (1991) found positive conditioning effects of both D1 and D2 receptor agonists when injected bilaterally into the Acb. Gold *et al.* (1988), studying conditioned locomotor responses to subcutaneous amphetamine injections, observed a decrease in conditioned locomotion after 6-OHDA lesioning of the Acb, confirming a role for dopamine in this type of adaptive behaviour. Findings of Everitt *et al.* (1991) suggested an interaction between the basolateral amygdala and Acb in conditioned place preference, since this process was disrupted by a combined unilateral lesion of the basolateral amygdala and a contralateral ventral striatal lesion. Their results are consistent with a role of the basolateral amygdala in the formation of stimulus-reward associations and a function of the Acb in linking such associations to response output systems.

In *conditioned avoidance* behaviour, the Acb may play an equally important role as in conditioned place preference. Wadenberg *et al.* (1990) reported a suppression of conditioned avoidance behaviour by local injections of (-) sulpiride into the Acb, whereas injections in the dorsolateral striatum or amygdala had only weak effects. In this study, however, motor activity was also found to decrease following intra-accumbens sulpiride injection, making it difficult to exclude the possibility that a motor-related deficit might account for the disruption in learning. McCullough *et al.* (1993) studied the involvement of the Acb in an instrumental avoidance task, in which the rat had to learn to press a lever in order to avoid electric shocks. In this study, 6-OHDA lesions of the Acb were found to cause a decrease in lever pressing, confirming a role for mesolimbic dopamine in negative reinforcement. The relative importance of D1 versus D2 receptors in conditioned avoidance learning awaits further investigation (cf. Beninger, 1991).

A third learning paradigm that has been applied in relation to Acb function is *conditioned reinforcement*. A conditioned reinforcer is defined as a stimulus that initially lacks motivational value, but acquires incentive properties by pairing it with a primary reinforcer such as food, water or a sexual partner (Robbins *et al.*, 1989). When thirsty rats were trained to associate a light flash and movement of a dipper with water, intra-accumbens d-amphetamine was found to enhance responding for the conditioned reinforcer (i.e. the light flash and movement of the dipper). Furthermore, 6-OHDA lesions of the nucleus accumbens prevented the increase in responding (Taylor and Robbins, 1986). In contrast, d-amphetamine injections in the caudate nucleus had only weak or variable effects, and 6-OHDA lesions in the caudate nucleus did not diminish the enhancement in responding induced by intra-accumbens d-amphetamine (Taylor and Robbins, 1986). Again, these results indicate a dissociation between the dorsal and ventral striatum in mediating the coupling of a stimulus-reward association to an appropriate behavioural response. In a second order schedule of sexual reinforcement, Everitt *et al.* (1989) observed an attenuation of instrumental responses in male rats after NMDA-lesions of the basolateral amygdala. As in the conditioned place preference experiments of the

same group (Everitt *et al.*, 1991), an interaction between amygdala and VTA inputs to Acb could be demonstrated. Bilateral infusion of d-amphetamine into the Acb appeared to improve the instrumental sexual responses that first had been diminished by amygdala lesions. Furthermore, these authors showed that this interaction could not be explained by effects on unconditioned sexual behaviour.

Dunnett and colleagues (Dunnett, 1990; Reading and Dunnett, 1991) studied the role of the nucleus accumbens in a reinforcement task involving temporal delays to test short-term memory in rats (*delayed matching to position*). In this task, rats were trained to remember the position of a sample lever in an operant chamber. Following a variable delay period, during which the sample lever was retracted, the subject was exposed to two levers, one of which corresponded to the sample lever and led to reward delivery when pressed down. In this paradigm, aspiration lesions of the medial prefrontal cortex, as well as quinolinic acid and ibotenic acid lesions of the Acb induced delay-dependent memory deficits, whereas lesions of the motor cortex and parietal cortex had no effect. Caudate-putamen lesions did impair performance of the task, but in a delay-independent manner (Dunnett, 1990). The performance deficit induced by Acb lesions was largely ascribed to a side-dependent response bias (Reading and Dunnett, 1991).

In related forms of reward-based learning, further evidence has been raised for a central involvement of dopamine receptors. Nakajima and coworkers (Nakajima, 1986; Kurumiya and Nakajima, 1988) found consistent effects of Sch 23390 on *operant conditioning* for rewards such as saccharin, water and intracranial brain stimulation. When Sch 23390 was injected into the Acb, brain stimulation of the ventral tegmentum was found to be reduced (Kurumiya and Nakajima, 1988). Likewise, studies using D2 receptor antagonists have shown their effectiveness in blocking reward-related learning processes (for a more extensive account, see Beninger, 1991).

Several investigators have found evidence for a role of the Acb in *spatial learning*. Rats with ibotenic acid lesions of Acb were impaired in learning a spatial discrimination task in a T-maze and in locating the hidden platform in a Morris water maze (Annett *et al.*, 1989). The impairment was especially clear during the learning phase, as the spatial task could eventually be completed with similar latencies and errors as controls. The lesioning caused only non-significant changes in unconditioned behaviours (i.e. locomotion and spontaneous alternation), suggesting a specific impairment of learning-related processes. Reversal learning in a T-maze also appeared to be impaired (Annett *et al.*, 1989; cf. Taghzouti *et al.*, 1985). In confirmation of these findings, Scheel-Krüger and coworkers found intra-accumbens injections of the NMDA antagonist AP7 in rats to decrease spatial learning performance in the Morris water maze, without causing motor disturbances (Scheel-Krüger and Willner, 1991). Similar impairments of performance were noted after injection of L-sulpiride and Sch 22390 into the Acb.

The behavioural component specifically affected by these treatments remained somewhat elusive, as both AP7 and the dopamine antagonists were found to decrease orienting and exploratory behaviours such as rearing and turning of the head and body. Whereas a specific involvement of dopamine receptors in learning processes was confirmed by the finding that L-sulpiride and Sch 23390 did not impair maze performance in well-trained rats, such a confirmative statement could not be claimed for NMDA receptors, as AP7 did apparently impair spatial navigation in fully trained subjects. In a radial arm maze test, Schacter *et al.* (1989) observed an increase in the latency to initiate movements after intra-accumbens injection of the broad spectrum glutamate receptor antagonist kynurenic acid. Even so, the number of working memory errors (i.e. visits to previously explored arms) was not changed following kynurenic acid injection, while reference memory errors (visits to unbaited arms) were increased.

Several insights can be extracted from the studies mentioned above. First, they indicate that the Acb forms part of a larger limbic cortico-striato-pallidal system mediating a variety of learning and adaptational strategies. The diversity of these behavioural repertoires forces us to widen our concept of Acb function, and emphasizes the artificiality of the distinction between "emotive", "instinct-based" or "motivational" behaviour and learning based on "cognition".

Second, the observation that manipulations of the Acb affect many types of behaviour does not exclude the possibility that this structure mediates only one functional component, or subroutine, common to all of these behaviours. Most of the studies on learning reviewed above are confirmative of, or compatible with, the notion that the Acb is crucial for *linking, or translating, a particular stimulus-reward or stimulus-punishment association to behavioural output systems* (cf. Everitt *et al.*, 1991). As will be clarified in Sections 8 and 9, such a *general* functional component can be brought in line with the concept of Acb as a collection of heterogeneous ensembles that each influence different behavioural actions, such as feeding, locomotion and sexual behaviour. In fact, a hypothesis as to how stimulus-reward related information may gain facilitated access to response output systems is proposed in Section 9 (cf. Fig. 11).

At this point, however, the question as to whether firing activity of Acb neurons may be correlated with a *specific* behavioural parameter has not yet been explored to a satisfying extent. At present, the only parameter suitable for a direct comparison with electrophysiological effects of neurochemicals would be locomotor activity. It is clear that neurochemical injections alter levels of motor activity in some learning experiments, but not in others. However, the conditions for eliciting locomotion by chemical injections may not have been optimal in some of these studies. It would therefore be instructive to return to the locomotion results of the previous section and draw comparisons to electrophysiological data.

4. CAN THE OVERALL ACTIVITY OF SPINY PROJECTION NEURONS BE CORRELATED TO LEVELS OF LOCOMOTOR ACTIVITY?

Many behavioural studies have been, understandably, focussed on whether the behavioural effects of diverse neuroactive substances can be explained by interactions with dopamine release. However, the question as to what occurs *after* dopamine is released in Acb should be addressed as well. In order to affect behaviour, intra-accumbens drugs should directly or indirectly influence the activity of the medium spiny neurons, for these elements are most likely to constitute the *exclusive output route* of Acb and thus will eventually affect fore- and midbrain centers for motor control (Chang and Kitai, 1985; Pennartz *et al.*, 1991a; Pennartz and Kitai, 1991; Arts and Groenewegen, 1992). Therefore, the analysis given below will be primarily focussed on how neuroactive substances may be expected to regulate firing activity of the spiny projection neuron of Acb. Of course, slow metabolic and genome-mediated effects of dopamine and other neuromodulators are likely to be present in Acb and may possibly influence behaviour, but the onset of behavioural effects of e.g. dopamine is usually fast (within several minutes; Costall and Naylor, 1975; Kelly *et al.*, 1975). Therefore one should, in the first instance, attempt to explain these effects on the basis of electrophysiological actions known to be effective in a similar time range.

As a starting point, we will reconsider the hypothesis proposed by Mogenson and others that a *strong firing activity of Acb neurons projecting to the ventral pallidum eventually results in inhibition of motor circuits* (Mogenson *et al.*, 1980; Jones and Mogenson, 1980a, b; Kelly and Roberts, 1983; Swerdlow and Koob, 1987b; Yang and Mogenson, 1989). Mogenson and colleagues specifically pointed to the ventral pallidal area as the main target area for regulation of locomotion since this area receives a strong, presumably GABAergic input from Acb (Heimer and Wilson, 1975; Pycock and Horton, 1976; Jones and Mogenson, 1980a; Mogenson *et al.*, 1983; Heimer *et al.*, 1985). Furthermore, GABA injection into the ventral pallidum attenuated locomotor activity induced by intra-accumbens dopamine (Jones and Mogenson, 1980a) or by carbachol injected into the dentate gyrus (Mogenson and Nielsen, 1984). Koob and Swerdlow (1988) further confirmed these observations by showing that injections of the GABA_A receptor agonist muscimol into the ventral pallidal-lateral preoptic area antagonized locomotion induced by systemically applied apomorphine in 6-OHDA lesioned rats. As pointed out by Chang and Kitai (1985) and Pennartz *et al.* (1991a, 1992a; Pennartz and Kitai, 1991), medium spiny neurons are the output cells of the Acb and it is these cells that are mostly impaired in intracellular recordings. Thus, a comparison between the cellular effects of neurochemicals on spiny projection neurons and their effects on behaviour should help to evaluate this hypothesis.

The following findings can be put forward in favor of Mogenson's hypothesis: (1) iontophoretically applied dopamine, or electrical stimulation of the VTA, attenuates unit activity and EPSPs in the Acb studied

in vivo (Yang and Mogenson, 1986; Yim and Mogenson, 1988), while behaviourally, intra-accumbens dopamine usually stimulates ambulatory activity (cf. Table 1). Although the types of recorded neurons were not identified in these *in vivo* studies, it is reasonable to assume that the majority of cells were spiny projection neurons. (2) Stimulation of the basolateral amygdala primarily excites Acb neurons (Yim and Mogenson, 1988) and, in behaviour, suppresses locomotion by way of Acb (Yim and Mogenson, 1989). (3) As shown by Yuan *et al.* (1992), opiate receptor agonists reduce EPSPs in Acb neurons studied *in vitro*. The behavioural study by Pert and Sivit (1977) demonstrated a clear dopamine-independent stimulation of locomotion by intra-accumbens morphine and enkephalin. (4) Muscarinic attenuation of EPSPs is one of the most powerful actions of cholinergic agonists in slices of Acb (Sugita *et al.*, 1991; Pennartz and Lopes da Silva, 1994). De Belleruche *et al.* (1981) and Jones *et al.* (1981) ascribed the stimulatory effects of intra-accumbens carbachol on locomotion to muscarinic receptor activation.

As was already recognized by Yim and Mogenson (1989), some findings could not be explained by the proposed hypothesis. Synaptic responses of spiny projection neurons in Acb to stimulation of hippocampal afferents are similar to amygdalar responses, since they both consist of a fast EPSP-IPSP sequence (Yim and Mogenson, 1988; Pennartz and Kitai, 1991), but in contrast to amygdala stimulation, hippocampal activation by e.g. novelty enhances locomotor activity (Mogenson, 1984). Furthermore, the locomotor stimulation induced by carbachol injections into the dentate gyrus is probably mediated by excitatory effects in Acb (Mogenson and Nielsen, 1984). The results of Hannigan *et al.* (1984), Svensson and Ahlenius (1983) and Cools (1986) indicated that the behavioural effect of dopamine is not unidirectional (i.e. does not always stimulate or inhibit locomotion), but depends on the presence of hippocampal input and on multiple environmental factors. This suggests a more complicated function of mesolimbic dopamine than originally thought. The hypothesis faces a further problem in that it primarily relies on neuroactive substances exerting multiple actions on spiny projection neurons—actions that may affect excitability in opposite ways. Dopamine, carbachol and opiate receptor agonists are all able to depress IPSPs in addition to EPSPs (Table 1) and it is unknown which of these effects (i.e. the disinhibitory or inhibitory action) prevails in behaviourally meaningful states of the striatal network. With the introduction of the *in situ* patch-clamp technique, it has become clear that spontaneous IPSCs occur in many brain regions including Acb (Dubinsky, 1989; Edwards *et al.*, 1990; Ropert *et al.*, 1990; Pennartz and Schneggenburger, unpublished observations). Moreover, dopamine and muscarinic agonists may modulate membrane properties in addition to synaptic responses (Table 1; Uchimura *et al.*, 1986; Uchimura and North, 1990; see, however, Pennartz *et al.*, 1992a).

With hindsight to the survey given in Section 2, there appears to be as much ground for proposing exactly the opposite of Mogenson's original hypothesis, viz. that a *strong firing activity of Acb neurons*

projecting to the ventral pallidum eventually stimulates locomotion (cf. Pennartz *et al.*, 1991b). Evidence supporting this proposition comprises the following findings: (1) The GABA_A antagonists picrotoxin and bicuculline enhance and prolong EPSPs in spiny projection neurons recorded in slices (Pennartz *et al.*, 1990, 1991a; Pennartz and Kitai, 1991) and stimulate locomotion in behavioural experiments (Wachtel and Andén, 1978; Jones *et al.*, 1981; Morgenstern *et al.*, 1984). (2) Glutamate receptor antagonists strongly depress EPSPs in slices (Pennartz *et al.*, 1990, 1991a; Horne *et al.*, 1990; Pennartz and Kitai, 1991) and reduce locomotor activity (Mogenson and Nielsen, 1984; Schacter *et al.*, 1989; Pulvirenti *et al.*, 1989). The observation that glutamate receptor agonists such as AMPA and *N*-methyl-aspartate stimulate ambulatory activity (Donzanti and Uretsky, 1983; Hamilton *et al.*, 1986; Shreve and Uretsky, 1988; Boldry *et al.*, 1992) is also in line with this hypothesis, since these substances excite spiny projection neurons in Acb (Pennartz *et al.*, 1992a; Pennartz and Lopes da Silva, 1994 and unpublished observations). However, in view of the possibility that concentrated solutions of glutamate receptor agonists may easily elicit depolarization block, the latter findings may, in our view, only serve as circumstantial evidence.

The particular strength of the first two arguments is that the action of both GABA_A antagonists and glutamate receptor antagonists is almost *unambiguous* with respect to how they affect the excitability of Acb projection neurons ("almost", since AMPA/kainate receptor antagonists not only block EPSPs but also feed-forward IPSPs. However, it is extremely unlikely that firing of spiny projection neurons would be promoted by glutamate receptor block; cf. Section 8 and Pennartz *et al.*, 1991a; Pennartz and Kitai, 1991). As shown by Chang and Kitai (1986), Uchimura *et al.* (1989b), Horne *et al.* (1990) and Pennartz *et al.* (1990, 1991a; Pennartz and Kitai, 1991), glutamatergic excitation and GABAergic inhibition are the principal determinants of the synaptic excitability of spiny projection neurons. Although additional effects of glutamate and GABA antagonists, such as an alteration of dopamine release, cannot be excluded, these are likely to be relatively subtle in comparison to their direct and dramatic actions on Acb projection neurons.

Nevertheless, there are other reasons for rejecting the second hypothesis. Firstly, it does not solve the problem of amygdalar-hippocampal antagonism in locomotion. Secondly, it fails to explain why dopamine receptor activation in Acb leads to decreased locomotion in hippocampus-lesioned animals, whilst stimulating motility in normal rats (Reinstein *et al.*, 1982; Hannigan *et al.*, 1984). Thirdly, the hypothesis predicts that destruction of Acb projection neurons will be associated with decreased locomotion, but this was not observed in animals with ibotenic and quisqualic acid lesions of Acb (Annett *et al.*, 1989; Everitt *et al.*, 1991). Finally, micro-injection of GABA agonists into Acb may be expected to inhibit firing activity of spiny projection neurons across a wide dose range, since GABA_A receptor activation depresses synaptic excitability (Pennartz *et al.*, 1990, 1991a; Pennartz and Kitai, 1991) and GABA_B recep-

tors attenuate EPSPs and, in addition, hyperpolarize Acb neurons (Uchimura and North, 1991; Table 1). Behaviourally, however, a dose-dependent dissociation was found, with high doses of GABA agonist inhibiting locomotion and low doses being stimulant (Wachtel and Andén, 1978; Jones *et al.*, 1981). In conjunction with further considerations, these anomalous findings prompted us to propose a third hypothesis which is delineated below.

5. AN ALTERNATIVE HYPOTHESIS OF NUCLEUS ACCUMBENS FUNCTION

The main purpose of the preceding section was to illustrate that it is not feasible to associate a particular behavioural state (locomotion) with the *overall* activity of Acb projection neurons. Instead of attempting to re-shape the old paradigm, we hypothesize that *behaviourally meaningful information in the nucleus accumbens is represented by fine-grained spatiotemporal firing patterns in spiny projection neurons* rather than by massive waves of activity uniformly sweeping from Acb to the ventral pallidum and related terminal fields.

In connection schemes of the basal ganglia, it has become common practice to use "+" and "-" signs to describe how a projection may globally affect its target structure (see, for instance, Bergman *et al.*, 1990; Alexander *et al.*, 1990; Chevalier and Deniau, 1990). Such an approach can be often validated on account of pharmacological studies characterizing some projections as GABAergic ("−") or glutamatergic ("+"). The use of this approach has proven to be heuristically valuable in developing therapeutic strategies alleviating extrapyramidal motor disorders (Bergman *et al.*, 1990). Despite the fact that this "+/− paradigm" may help in understanding the gross impact of a particular projection on a target structure, it is conceptually related to the view that the brain may actually use massive excitatory or inhibitory waves as *modes of operation*. Indeed, the first and second hypothesis stated in Section 4 reflect this way of thinking.

The alternative view presented here holds that the Acb is a collection of neuronal ensembles, or groups, with different functional and behavioural connotations. This concept implies that the Acb, in its entirety, does not send a monolithic output to its target structures, which would then effectuate a unidirectional change in some behavioural parameter. It is proposed that each distinct ensemble is capable of generating an output which is then transferred to a specific set of target structures characteristic for this ensemble, and hence may induce behavioural effects that are specifically linked to this ensemble. Literature data do not yet permit us to specify what the nature or encoding mechanism of an ensemble output might be (i.e. uniform inhibitory, or again spatiotemporally differentiated). However, by analogy to encoding mechanisms found in both motor and sensory areas of the monkey neocortex (Georgopoulos *et al.*, 1989; Young and Yamane, 1992), we would tend to favour spatiotemporal encoding within each ensemble. The arguments given below and worked out in more detail in Sections 6, 7 and 8 mainly elaborate

FIG. 1. Brightfield photomicrographs showing a few aspects of the compartmental structure of the nucleus accumbens in rats. (A) Low-power micrograph of a transverse section stained for Nissl substance. (B) Autoradiographic image of the same section shown in A, revealing the inhomogeneous distribution of naloxone-binding sites. As shown by Herkenham *et al.* (1984), the nucleus accumbens exhibits numerous patches of dense naloxone binding which, at least in part, coincide with clusters of cells (arrows). (C, D) Low-power micrographs of transverse sections stained for enkephalin-immunoreactivity. The section through the rostral part of the Acb (C) reveals compartments of strong enkephalin immunoreactivity (open arrows) surrounded by a moderately stained "matrix". The shell region in a more caudal section (D) exhibits extensive areas of moderate enkephalin staining interspersed with areas of very low enkephalin-immunoreactivity. In the border region between the dorsal Acb and the ventromedial part of the caudate-putamen complex relatively small patches of strong enkephalin immunoreactivity are present (arrows). For a more complete description, cf. Voorn *et al.* (1989). ac, anterior commissure; AcbC, core of the nucleus accumbens; AcbSh, shell of the nucleus accumbens; CP, caudate-putamen complex; LV, lateral ventricle; OT, olfactory tubercle. Bar in (B) is 500 μ m and also applies to (A). Bar in D is 400 μ m and also applies to (C).

FIG. 2. Photomicrographs showing the relationships between immunohistochemically defined compartments in the Acb and fibers originating in midline thalamic nuclei (for full details, cf. Berendse and Groenewegen, 1990). (A) Labeling of fibers and terminals in the rostral part of the Acb following an injection of the anterograde tracer *Phaseolus vulgaris*-leucoagglutinin (PHA-L) in the anterior portion of the paraventricular thalamic nucleus. In (B) the adjacent section stained for enkephalin-immunoreactivity is shown. In both pictures, corresponding blood vessels (starlets) and tissue locations (arrows and arrowheads) are indicated with the same symbols. Note the dense terminal labeling in the medial part of the shell and the patchy labeling in the core of the Acb. To a great extent, the patches of terminal labeling in the core coincide with compartments of strong enkephalin-immunoreactivity (open and filled arrows). It must be emphasized that the configuration of the compartments changes rather rapidly from one section to the next such that there is no perfect match; even the blood vessels are not exactly in the same position in these two adjacent sections. ac, anterior commissure; AcbC, core of the nucleus accumbens; AcbSh, shell of the nucleus accumbens. Bar is 250 μ m.

the concept of the Acb as a set of ensembles, avoiding further speculations about within-ensemble encoding.

(1) Amygdalar-hippocampal antagonism in locomotion is difficult to reconcile with the existence of a tight coupling between a particular behavioural state (viz. locomotion) and the overall level of firing activity of Acb neurons (Sections 2 and 4). It will be pointed out in Section 7 that there may well be a difference in connectivity of the amygdala and hippocampus to the ventral pallidum. However, if one takes into account Yim and Mogenson's finding (1989) that suppression of locomotor activity induced by intra-amygdala NMDA injections was *completely* antagonized by intra-accumbens GDEE application, the possibility that the substrate for the amygdalar-hippocampal antagonism is located in the Acb should be considered rather likely. It should be mentioned that the literature offers some further indications for amygdalar-hippocampal antagonism in locomotion, which go beyond the scope of this review. While several authors interpret some of the experimental findings differently, they usually agree that the influence of amygdala and hippocampal outputs on locomotion, as far as mediated by Acb, is dissimilar, if not opposite. Cools *et al.* (1991), for instance, have interpreted this problem in terms of a dual gate-model.

(2) Recent behavioural evidence, not reviewed in Sections 2 and 3, indicates regionally specific effects of neuroactive substances injected into the Acb. Dauré *et al.* (1989) reported a decrease of exploratory behaviour after cholecystokinin (CCK) injection into the caudomedial Acb, whereas no effect was found in the rostral part. Vaccarino and Rankin (1989) found opposing effects of intra-accumbens CCK-injections on amphetamine-induced locomotion, with rostral sites having attenuating effects and caudal injections stimulating locomotion. Similar antagonistic effects of rostrally and caudally placed injections of the CCK receptor antagonist proglumide were reported for intracranial self-stimulation in the VTA (Vaccarino and Vaccarino, 1989). Deutch and Cameron (1992) found that short-lasting immobilization stress increased dopamine utilization in the shell but not in the core of Acb and reported further shell-core differences in dopamine and serotonin metabolism in rats. Other biochemical studies, directed e.g. at D2 receptor-mediated modulation of acetylcholine release (Henselmans and Stoof, 1991) are beginning to reveal regional differences as well. Although these studies describe fairly macroscopic effects, they do suggest a functional partitioning of Acb.

(3) The method of measuring locomotion by beam interruptions is, of course, laudable for its objectiveness, but provides no information about the *significance* of locomotor behaviour in the context of its adaptive value for an animal coping with environmental changes. The possibility that strongly enhanced locomotion reflects a state of panic and/or disorder rather than a "motivational state" can often hardly be excluded. This consideration reminds us of the fact that locomotion should not be regarded as a behavioural entity in itself, but rather as a component process of more complex behavioural patterns, e.g. attack, feeding and exploration (cf. Mogenson *et al.*, 1980; Mogenson, 1984). Evidence underscoring a

much wider involvement of Acb in behaviour than just in locomotion has been presented in Sections 2 and 3. Clearly, it would be very difficult to maintain the proposition that the function of Acb is just to regulate the overall level of motor activity, studied on its own, or within a particular learning task. Many papers have shown that, following severe manipulations of Acb, the motor component is not specifically affected (e.g. Kelley and Stinus, 1985; Annett *et al.*, 1989; Everitt *et al.*, 1991). In contrast, the functionally heterogeneous role of Acb in behaviour matches the concept of the Acb being a complex of functionally distinct neuronal ensembles.

(4) Electrophysiological studies in awake animals, although limited in number, have underscored the diversity of response types displayed by Acb units following sensory and motivation-related stimuli. As pointed out in Section 6, the response of many units to sensory- or movement-related stimuli depends on different aspects of the stimulus context (Rolls and Williams, 1988; Williams, 1989), indicating the lack of a one-to-one correlation between stimulus, unit firing, and subsequent motor activity. Recent work by the group of Henriksen (Callaway and Henriksen, 1992; Henriksen *et al.*, 1992) has confirmed the absence of such a correlation and produced further evidence for context-dependent discharges of Acb units. Schultz *et al.* (1992) identified neuronal responses in the Acb that may be specifically linked to the signalling of rewards, and produced further evidence for the functional diversity of ventral striatal neurons. Altogether, these unit recording studies in awake animals contradict a monolithic functional organization of the Acb and support the physiological heterogeneity of its neuronal populations.

(5) Anatomical evidence to be outlined in Sections 7 and 8 has revealed the existence of multiple compartments and subterritories in Acb, which are characterized by specific afferent-efferent relationships and patterns of neurochemical staining. The existence of "bypass" routes to several target structures, and the diversity of response types found in these target structures after stimulation of Acb or ventral pallidum indicate that the entire output of Acb sent to target centers mediating motor output should not be read as a uniform plus or minus-sign. On the contrary, the richness of differential output projections of multiple subterritories in Acb is in line with the assumption that different types of behaviour can be sustained by spatially differentiated firing patterns of Acb projection neurons.

6. FUNCTIONAL HETEROGENEITY OF NUCLEUS ACCUMBENS NEURONS AS INDICATED BY UNIT RECORDINGS IN AWAKE ANIMALS

Considerations on the functional connotations of neural activity in Acb can be derived from two types of *in vivo* electrophysiological studies: unit recordings made in relation to sensory stimuli or in relation to overt activities of the animal. Rolls and Williams (1988; see also Williams, 1989) were the first to correlate unit responses of primate Acb to a test set of sensory stimuli, some of which were associated

with reinforcement. A relatively large number of cells (32% out of 1013) responded to visual stimuli, with unit-specific discrimination between novel-familiar, foveal-peripheral, non-specific vs. specific (e.g. faces) and aversive-rewarding features of the stimulus. Interestingly, reward-related neurons did not *unconditionally* generate responses to sensory stimuli, but usually responded in a context-dependent manner. In addition to generating visual responses, some neurons fired after presentation of auditory, gustatory and somatosensory cues. Typically, the response to sensory stimuli was dependent on context, memory, reward and behavioural task in a majority of neurons. Cells characterized by multimodal responses often showed preferential firing to the reward- or aversion-signalling property of the cue (Williams, 1989). As yet, the neural mechanism underlying the conditional nature of most unit responses is unknown, but it may be useful to mention in advance an important concept that will be elaborated in Section 8. This concept holds that firing activity in Acb neurons arises due to near-simultaneous activity along cortical, thalamic and amygdalar fibers that converge onto single cells. A biologically plausible mechanism that may account for the conditional nature of unit responses is that spikes can only be generated if the Acb neuron receives many coincident inputs from two or more active source areas, engaged in representing different aspects of the perceived stimulus.

Apicella *et al.* (1991) confirmed the occurrence of responses to reward and noted that the responding neurons were encountered twice as frequently in the ventral as compared to the dorsal striatum of the monkey. Whereas ventral striatal neurons were reported to respond *after* reward delivery in the paper of Apicella *et al.* (1991), a related study also revealed responses *preceding* the reward (Schultz *et al.*, 1992). In the delayed go-no go task used in the latter investigations, 43 out of 420 ventral striatal neurons showed an increase in firing activity that was tightly linked in time to subsequent reward delivery. Additional tests revealed that these responses were not correlated to the planning or execution of arm or mouth movements. Furthermore, the unit responses

disappeared following omission of the reward in only a few trials.

West and Michael (1990) and West *et al.* (1992) recorded unit responses in the rat Acb and olfactory tubercle in response to somatosensory and olfactory stimuli. They found that Acb units can be both excited and inhibited in response to these stimuli, disproving the notion that large numbers of neurons would generate unidirectional responses during processing of inputs and/or preparation of subsequent actions. On the contrary, their findings match well with the concept of spatiotemporally differentiated patterns of activity.

Only few studies published to date have attempted to correlate unit firing in Acb to motor activity in the freely moving rat. Callaway and Henriksen (1992) reported both positive and negative correlations between firing and locomotion in a sample of six neurons. It was further noted that the discharge rate was unrelated to rearing and nose-poking activity of the animal. Lavoie and Mizumori (1992) also recorded mixed unit responses in Acb, some being related to changes in motor behaviour such as turning, others varying according to the location of the animal in an eight-arm maze. A relatively small proportion of the cells (14%) fired upon encountering rewards. Woodward *et al.* (1992) trained rats to self-administer cocaine by bar pressing on a modified fixed-ratio schedule. They recorded increases in unit firing of Acb neurons before bar pressing, and interpreted these responses as being anticipatory. The magnitude of these responses was not related to the delivery of cocaine, and the responses were unchanged during the extinction phase. These three recent studies tentatively support three conclusions: (1) a one-to-one relationship between the overall firing activity in Acb and the level of locomotor activity, or another specific behavioural type of activity, seems to be lacking; (2) Acb neurons are heterogeneous with respect to how their firing behaviour correlates to distinct components of behavioural sequences; and (3) most unit responses do not seem to be specifically evoked by reward, but may be more generally related to appetitive and goal-directed behaviour. With respect to the third con-

FIG 3. Brightfield photomicrographs showing a number of aspects of the relationships between the immunohistochemically defined compartments in the Acb and the afferent fibers from the amygdala (A, B) and the prelimbic area (C, D). (A, B) Photomicrographs of a section through the rostral part of the core of the Acb, double immunostained for enkephalin and the anterograde tracer *Phaseolus vulgaris*-leucoagglutinin (PHA-L). PHA-L was injected in the anterior part of the basolateral amygdaloid nucleus and immunohistochemically visualized through a DAB-Ni staining procedure, resulting in a crisp reaction product. Enkephalin-immunoreactivity was visualized through a DAB staining procedure, resulting in a more diffuse reaction product. The arrowheads in (A) and (B) demarcate a slender compartment of strong enkephalin-immunoreactivity just dorsal to the anterior limb of the anterior commissure (rostrocaudal level is comparable with that of Fig. 1C). Another enkephalin-positive compartment is indicated by the starlet in (A). The micrograph in (B) is a higher magnification of the boxed area in (A). Note the sparsity of labeling in this enkephalin-positive compartment as compared to the dense termination of fibers in the "matrix" surrounding this compartment. (C, D) Double immunostained sections showing the relationships of PHA-L labeled fibers and terminals from the deep layers of the prelimbic area and the enkephalin-positive compartments in the Acb (for details, cf. Berendse *et al.*, 1992a). (C) In the rostral part of the core of the Acb clusters of PHA-L labeled fibers are found (indicated by arrowheads) outside the enkephalin-positive compartments (starlets). (D) In the border region between the dorsal part of the core of the Acb and the ventromedial part of the caudate-putamen, PHA-L labeled fibers are preferentially present in the enkephalin-positive patches. Bar in (A) is 250 μ m, bar in B is 100 μ m and also applies to C and D. ac, anterior commissure.

FIG. 3.

clusion, however, it should be kept in mind that Schultz *et al.* (1992) did find a relatively small fraction of ventral striatal neurons (about 10%) exhibiting increases in firing specifically preceding rewards.

A general notion that can be extracted from virtually all of the above mentioned unit studies in awake animals, is that they present a wealth of evidence for functional heterogeneity of ventral striatal neurons. Considering the anatomical evidence presented in the following sections, it is highly unlikely that this diversity results from a randomized connectional organization. Neurons with common sensory- or motor-related responses are probably organized in groups that each process information connotated with different sensory modalities and different aspects of the spatiotemporal context framing a particular stimulus. Until now, however, the spatial distribution of neurons belonging to one group, or ensemble, has not been treated. In the next section, possible anatomical substrates for the proposed ensembles are highlighted.

7. ANATOMICAL EVIDENCE FOR FUNCTIONALLY DISTINCT ENSEMBLES, WITH EMPHASIS ON THEIR EFFERENT RELATIONSHIPS

7.1. COMPARTMENTAL ORGANIZATION

The Acb can be divided into a core and shell region. This major subdivision has been validated by immunohistochemical and axonal tracer studies, as well as by electrophysiological, biochemical, electronmicroscopical and behavioural approaches (Zaborszky *et al.*, 1985; Groenewegen *et al.*, 1989; Zahm and Heimer, 1990; Heimer *et al.*, 1991; Zahm and Brog, 1992; Deutch and Cameron, 1992; Meredith *et al.*, 1992, 1993; Pennartz *et al.*, 1992b). The postulate of functionally distinct ensembles in the present hypothesis goes a little further and, in an anatomical sense, primarily relies on the available evidence for the existence of neurochemical compartments throughout the ventral striatum, which are characterized by rather specific afferent/efferent relationships. The results of the first systematic studies of the heterogeneous structure of the Acb by Herkenham *et al.* (1984) indicated the existence of distinct cell clusters, characterized by dense naloxone-binding sites (Fig. 1A, B) and avoided by thalamostriatal fibers. Subsequent immunohistochemical and neuroanatomical tracing studies confirmed the compartmental structure of the nucleus accumbens (Voorn *et al.*, 1989; for reviews, see Groenewegen *et al.*, 1989; Zahm and Brog, 1992). For instance, in the rostral Acb compartments can be distinguished by dense enkephalin (Fig. 1C) and calcium-binding protein immunoreactivity (IR) and by low levels of substance P, dopamine and cholineacetyltransferase (ChAT) IR (Herkenham *et al.*, 1984; Voorn *et al.*, 1989; Meredith *et al.*, 1989; Groenewegen *et al.*, 1989). These compartments receive inputs from the paraventricular nucleus of the thalamus (Fig. 2) and from the lateral prefrontal cortex, and send outputs to the substantia nigra pars reticulata (Berendse and Groenewegen, 1990; Berendse *et al.*, 1992a, b). In contrast, the "matrix" compartment surrounding these rostral compartments is innervated by the central

medial and paracentral thalamic nuclei, the rostral part of the basolateral amygdaloid nucleus (Fig. 3A, B) and the deep layers of the prelimbic area (Fig. 3C; Berendse *et al.*, 1992a). Neurons in this compartment project to the substantia nigra pars compacta, VTA and retrorubral area (Fig. 4A, B; Berendse *et al.*, 1988; Groenewegen *et al.*, 1989; Berendse and Groenewegen, 1990; Berendse *et al.*, 1992b).

At more caudal levels, in the border region between the core of Acb and the ventromedial caudate-putamen complex, smaller patches of high enkephalin-IR, surrounded by a matrix of weaker enkephalin-IR, are present. These patches, largely comparable with those in the dorsal striatum, exhibit high levels of substance P-IR and low levels of calcium-binding protein and ChAT-IR (Voorn *et al.*, 1989; Meredith *et al.*, 1989). They receive inputs from the deep layers of the prelimbic area (Fig. 3D), the basolateral amygdaloid nucleus, and the paraventricular thalamic nucleus and project to the pars compacta of the substantia nigra (Berendse and Groenewegen, 1990; Kita and Kitai, 1990; Berendse *et al.*, 1992a, b; Gerfen, 1992). The "matrix" surrounding the enkephalin-positive patches, high in calcium-binding protein and ChAT-IR, receives input from the superficial layers of the prelimbic area and from the central and precentral thalamic nucleus and projects to the ventral pallidum and the reticular part of the substantia nigra (Berendse and Groenewegen, 1990; Berendse *et al.*, 1992a, b; Gerfen, 1992). It has not yet been established whether the patches in this border region between the nucleus accumbens and the ventromedial caudate-putamen project to the ventral pallidum.

Recently, Arts and Groenewegen (1992) found dendritic arborizations of core neurons that project to the ventral mesencephalon to be largely segregated by compartmental boundaries as identified by enkephalin staining (Fig. 4C, D), reinforcing the notion of a functional separation between ensembles of spiny projection neurons.

In the shell, cell clusters with low enkephalin, substance P, dopamine and ChAT immunostaining surround a larger cone-shaped area that is distinguished by dense substance P, dopamine, ChAT staining and moderate enkephalin-IR (Fig. 1D). These small compartments receive dense inputs from the amygdala and the ventral prelimbic area, whereas the cone-shaped area is strongly innervated by the ventral subiculum, the infralimbic area, the amygdala and the paraventricular thalamic nucleus (Berendse *et al.*, 1988, 1992a; Groenewegen *et al.*, 1989; Berendse and Groenewegen, 1990). This intricate organization of the ventral striatum, which may be more complex than the patch-matrix dichotomy proposed for the dorsal striatum, seems to comprise *at least* five different compartments.

Can these compartments be identified as the *functionally distinct* neuronal ensembles proposed in the present hypothesis? What is actually meant by the concept of "neuronal ensembles"? In the present context, the term "ensemble" refers to a group of neurons characterized by similar afferent/efferent relationships as well as closely related functions in overt behaviour, neuroendocrine regulation and sensorimotor gating. As yet, our anatomical and behavioural knowledge does not permit to give an exact answer to the question

of how large the hypothesized ensembles in Acb are, since many connectional and behaviour-related differences have not yet been worked out at the detailed level of compartments. Furthermore, the impression should not arise that the ensembles have a fixed size; rather, the number of neurons, afferent and efferent connections and brain volume occupied by an ensemble may change as a consequence of experience.

Apart from the compartments referred to above, another candidate substrate for these ensembles should not be omitted. Paskevich *et al.* (1991) described clusters of closely apposed cells in the Acb, which may or may not be electrotonically coupled. Zoli *et al.* (1990) found similar aggregates or "islands" of glucocorticoid receptor-immunoreactive neurons in the Acb and caudate-putamen with a small (10 μ m) average distance between the cells. These aggregates are reminiscent of the cell clusters first described by Herkenham *et al.* (1984). Although the afferent/efferent relationships of these clusters are unknown, they may fulfill distinct functions in Acb.

Despite the fact that the question as to the *exact size* of the region occupied by a single ensemble is left unanswered, there is at least some good evidence for functional and hodological distinctions at the level of Acb subterritories (i.e. caudomedial, rostromedial area; see Section 5 and below). Future research may be able to reveal more fine-grained subdivisions corresponding to functionally distinct areas. For now, we will attempt to strengthen the concept of neuronal ensembles as spatially confined subterritories by a more detailed consideration of the efferent (Section 7.2) and afferent relationships (Section 8) of different subregions of Acb.

7.2. EFFERENT RELATIONSHIPS

A central notion in this section is that the output pathways of Acb reflect a *functional multi-partitioning* of the nucleus. The anatomical evidence reviewed here indicates that different regions of Acb project to at least four target areas that can be associated with relatively distinct behavioural and sensorimotor functions (Fig. 5). None of these target areas is thought to

be exclusively linked to a specific and complete behavioural pattern or internal sensorimotor operation, but rather to one or more *component processes* of such patterns or operations. In Section 8, anatomical literature will be reviewed in order to validate the assumption that functionally distinct ensembles of Acb neurons receive specific afferent information. Subsequently, the coordinated recruitment of multiple ensembles (or more precisely, their projection neurons) is proposed to mediate the integration of component processes as observed in natural behaviour.

Outputs from the Acb can be globally divided in those directed towards "limbic" structures and those towards other components of the basal ganglia and related areas. We will first describe the rather massive projections from Acb to the ventral pallidum, substantia nigra and ventral tegmental area and continue with the small but probably significant connections to the pedunculopontine/mesencephalic locomotor region. The subsequently reviewed "limbic" targets can be subdivided into mediodorsal thalamus-limbic cortex circuitry and the preoptic-hypothalamic areas of the basal forebrain.

(1) *First output pathway: accumbens-ventral pallidum-substantia nigra/ventral tegmental area.* The core and shell of the Acb have been shown to project to different targets in the mesencephalic area. Whereas the shell primarily innervates the ventral tegmental area and medial substantia nigra pars compacta, the core projects most strongly to the substantia nigra pars reticulata. In addition, the ventrolateral extension of the shell and several subterritories of the core project to the pars compacta and retrorubral area (Fig. 5A; Nauta *et al.*, 1978; Groenewegen and Russchen, 1984; Heimer *et al.*, 1985; Haber *et al.*, 1990; Heimer *et al.*, 1991; Arts and Groenewegen, 1992; Berendse *et al.*, 1992b; Zahm and Brog, 1992). In more detail, the medial pars compacta is predominantly innervated by the enkephalin-poor compartments of the rostral Acb and several subterritories of the shell, whereas the pars reticulata is preferentially innervated by the enkephalin-dense compartments in the rostral Acb (Berendse

FIG. 4. Brightfield photomicrographs showing a number of aspects of the relationships between the output neurons and compartmental structure of the Acb as revealed by enkephalin-immunohistochemistry. (A) Inhomogeneous distribution of retrogradely labeled cells in the rostral part of the Acb following an injection of cholera toxin subunit B (CTb) in the medial part of the substantia nigra pars compacta and the adjacent lateral part of the ventral tegmental area. (B) Section adjacent to the one in (A), stained for enkephalin-immunoreactivity to reveal the compartmental structure of the Acb. In (A) and (B), corresponding blood vessels (starlets) and tissue locations (arrows) are indicated with the same symbols. Note that most of the CTb labeled cells are present in the enkephalin-poor areas; an exception is formed by a cluster of labeled cells dorsal to the anterior commissure, which is situated in an enkephalin-positive patch (arrows). (C, D) Photomicrographs to show the relationships of the dendrites of medium-sized neurons with the enkephalin compartments in the Acb. (C) Clusters of neurons labeled in the periphery of an injection site of the tracer biotinylated dextranamide (BDA) in the Acb in a section double immunostained for BDA and enkephalin. Note that the dendrites of these labeled neurons are largely restricted to the compartment in which the cell body resides. Enkephalin-positive compartments are indicated by white stars. (D) Photomicrograph showing the relationship between the geometry of the dendritic arborizations and the boundaries of an enkephalin-positive compartment in the Acb. This neuron was injected with Lucifer yellow following its identification as a striatomesencephalic projection neuron (for details of the technical procedure, cf. Arts and Groenewegen, 1992). The dendritic arbors of this neuron are completely restricted to the enkephalin compartment; two of the dendrites recurve into the compartment at its boundaries (filled arrows). Open arrow indicates the axon. ac, anterior commissure. Bar in (B) is 400 μ m and also applies to (A). Bar in (C) is 250 μ m and bar in (D) is 100 μ m. ac, anterior commissure.

FIG. 4

FIG. 5. Efferent pathways of the nucleus accumbens. Major efferent projections are shown as thick solid lines, minor ones are drawn thinner. The ventral pallidal back-projection to Acb is represented by a thick broken line. (A) Connections of the shell and core of accumbens (Acb) with the dorsolateral (VPdl) and ventromedial (VPvm) part of the ventral pallidum, ventral tegmental area (VTA), dopaminergic cell group A10/substantia nigra pars compacta, substantia nigra pars reticulata (SNR) and dopaminergic cell group A8/reticulobulbar area. (B) Connections of the nucleus accumbens with the mesencephalic locomotor region (MLR-grey shaded area, also referred to as pedunculopontine area in the text). The indirect connection of Acb, through the ventral pallidum, with the MLR is considered more important than the putative direct projection. (C) Projections of the nucleus accumbens and ventral pallidum to the mediodorsal thalamus (MD). The existence and extent of a direct accumbens-mediodorsal thalamic projection, drawn here as a thin broken line, is still debatable. (D) Projections of the shell of accumbens to the preoptic area and to the medial and lateral hypothalamus. An additional projection from the ventromedial part of the ventral pallidum to the same target areas is included in this diagram.

et al., 1992b). As in the accumbens-ventral pallidum pathway, the ventral striato-mesencephalic projection fibers probably carry GABA as their main transmitter (Walaas and Fonnum, 1980).

In addition to this direct mesencephalic projection, the Acb is also able to influence nigral and ventral tegmental activity by way of the ventral pallidum. The medial part of the shell projects to the ventral and medial parts of the ventral pallidum (Zahm and Heimer, 1988, 1990) and this region, in turn, sends outputs to the ventral tegmental area and medial pars compacta (Groenewegen *et al.*, 1993). The ventrolateral extension of the shell projects to the ventrolateral

part of the ventral pallidum, which directly innervates the pars compacta and retrorubral area (Zahm and Heimer, 1990; Heimer *et al.*, 1991; Groenewegen *et al.*, 1993). The Acb core projects to the dorsolateral part of the ventral pallidum (Groenewegen *et al.*, 1993) which subsequently innervates the pars reticulata (Haber *et al.*, 1985; Zahm, 1989; Zahm and Heimer, 1990; Groenewegen *et al.*, 1993). Both the ventral striatopallidal and striatomesencephalic projections are considered extensive in comparison to the below mentioned pedunculopontine, mediodorsal and hypothalamic-preoptic links of the Acb. This observation underscores, first, the tight relationship

between the ventral striatal system and the mesencephalic dopaminergic cell groups, which in turn influence the dorsal striatopallidal system and the prefrontal cortex, and, second, the importance of presumably GABAergic feedback regulation of the ventral tegmental area.

(2) *Second output pathway: accumbens-ventral pallidum-pedunculopontine area.* Mogenson and colleagues were the first to obtain both anatomical and electrophysiological indications for the existence of this route. The most important component of this pathway is the disynaptic Acb-ventral pallidum-pedunculopontine projection (Fig. 5B), whereas a direct Acb-pedunculopontine projection may make a smaller contribution. The existence of a ventral pallidum-pedunculopontine projection has been confirmed both electrophysiologically and anatomically (Mogenson *et al.*, 1985; Yang and Mogenson, 1987), although most tracer studies suggested a rather sparse projection (Nauta *et al.*, 1978; Haber *et al.*, 1985; Mogenson *et al.*, 1985; Haber *et al.*, 1990; Berendse *et al.*, 1992b; Groenewegen *et al.*, 1993). The small, direct projection to the pedunculopontine area may arise in the medial Acb (Fig. 5B), as reported in the rat (Nauta *et al.*, 1978; Berendse *et al.*, 1992b), the cat (Groenewegen and Russchen, 1984) and in the rhesus monkey (Haber *et al.*, 1990), suggesting an alternative route bypassing the ventral pallidum. The relationship between ventral striatal compartments and direct or ventral pallidum-mediated influences on the pedunculopontine area has not yet been examined.

Ventral pallidal neurons were reported to fire antidromically following electrical stimulation in the pedunculopontine area, suggesting a monosynaptic projection from the ventral pallidum to this area (Yang and Mogenson, 1987; Tsai *et al.*, 1989). Furthermore, Tsai *et al.* (1989) showed an intriguing differential effect of amygdala and hippocampus inputs to subpallidal-pedunculopontine projection neurons, viz. that they were primarily excited by amygdala stimulation and mainly inhibited by stimulation of the ventral subiculum. This finding does not fit easily into the scheme supposing a disynaptic amygdala/subiculum-accumbens-pallidal projection, which would, in the first instance, predict uniform inhibition of pallidal neurons in response to both amygdala and subiculum stimulation. Indeed, there is anatomical evidence for a direct projection from the amygdala to the ventral pallidal area (Krettek and Price, 1978) in addition to the disynaptic pathway through Acb. In contrast, no such projection has been reported for the hippocampus in tracer studies (Groenewegen *et al.*, 1987; Witter and Groenewegen, 1990). The presumably excitatory projection from amygdala to ventral pallidum bypassing Acb may help to explain amygdalar-hippocampal antagonism observed in locomotion studies (cf. Tsai *et al.*, 1989; Section 2 but see also Section 5).

The pedunculopontine area has been shown to be involved in the generation of motor activity and is thought to be a major component of the mesencephalic locomotor region. Chemical and electrical manipulations of this area elicit rhythmic limb movements in rats and cats (Garcia-Rill, 1986, 1991; Milner and Mogenson, 1988). Tracer studies indicate major projections of the pedunculopontine area to several parts

of the basal ganglia, such as the substantia nigra and subthalamic nucleus (Garcia-Rill, 1986, 1991), and to the deep cerebellar nuclei and the ponto-medullary and magnocellular tegmental region, while a direct pathway to the spinal cord, if existing at all, is considered to be of minor importance (Mogenson, 1984; Garcia-Rill, 1986, 1991; Rye *et al.*, 1988). Thus, the pedunculopontine area is in a position to exert an influence on the extrapyramidal system by its ascending efferents as well as an influence on central pattern generators in the spinal cord by way of multisynaptic circuits in the brain stem.

(3) *Third output pathway: accumbens-ventral pallidum-mediadorsal thalamic nucleus.* The ventral striatum may exert a dual influence on the mediadorsal nucleus of the thalamus, viz. by way of ventral pallidum-thalamic projection neurons (Fig. 5C; Heimer *et al.*, 1982; Tsai *et al.*, 1989; Zahm and Brog, 1992) as well as by a small, direct projection (Fig. 5C; Nauta *et al.*, 1978; Haber *et al.*, 1985; Groenewegen, 1988; Alheid *et al.*, 1989; Haber *et al.*, 1990; see, however, Groenewegen and Russchen, 1984). The putative accumbens-thalamic projection has been reported to originate in the medial portion of the nucleus (Haber *et al.*, 1990). Electrophysiologically, relatively little is known about the ventral striatopallido-thalamic connections. Tsai *et al.* (1989) recorded unit activity in the ventral pallidum and found antidromic responses to stimulation of the mediadorsal thalamic nucleus, confirming the existence of a direct pallidothalamic projection. The putative direct accumbens-thalamic route, however, still awaits confirmation by *in vivo* recording studies.

The mediadorsal thalamus is generally considered a "limbic" nucleus in view of its tight associations with many prefrontal areas and the anterior cingulate cortex (Leonard, 1969; Krettek and Price, 1977a; Groenewegen, 1988). Due to its reciprocal connections with various areas of the prefrontal cortex, the mediadorsal nucleus is part of a prefrontal-striatopallido-thalamic loop (Heimer *et al.*, 1982; Room *et al.*, 1985; Sesack *et al.*, 1989; Groenewegen *et al.*, 1990; Alexander *et al.*, 1990). Its exact functions in sensori-limbic processing and behavioural control are largely unknown. In 1982, Heimer *et al.* emphasized the motor-related functions of the mediadorsal nucleus in view of the fact that one of its target areas, the anterior cingulate, is connected to the supplementary motor area. Recently, Hutchins *et al.* (1988) described a projection from the cingulate cortex to the primary motor cortex and spinal cord. In support of motor-related functions of the mediadorsal nucleus, Swerdlow and Koob (1987b; Koob and Swerdlow, 1988) reported that ibotenic acid lesions of this nucleus reduce the hyperactive locomotor response induced by apomorphine injected in the 6-OHDA lesioned Acb. Interestingly, Swerdlow and Koob (1987b) found no attenuation of hyperactivity by lesioning the pedunculopontine area and thus, the ventral striatopallido-thalamic projection may serve as an alternative route for influencing locomotor behaviour next to its link to the pedunculopontine area.

However, other views on mediadorsal thalamic functions are equally tenable. The cingulate cortex, for instance, has been strongly implicated in the perception of pain, visual and somatosensory attention and associative conditioning (Teuber *et al.*, 1977; Vogt

1985; Gabriel *et al.*, 1987; Lopes da Silva *et al.*, 1990). The prefrontal cortex is generally recognized to comprise a conglomerate of areas involved in diverse functions that certainly go beyond a simple classification as motor-related circuits. The dorsal agranular area, which receives mediodorsal thalamic afferents and has limbic-striatal projections (Groenewegen *et al.*, 1990), is thought to receive gustatory information and may play a role in oral behaviour (Kosar *et al.*, 1986; Scheel-Krüger and Willner, 1991). The prelimbic area has been assigned a dual function, viz. regulation of visceral motor activity (Hurley-Gius and Neafsey, 1986) and spatial orientation (Kolb, 1984). The infralimbic cortex is likely to subserve visceral-motor and related autonomous functions as well (Hurley-Gius and Neafsey, 1986).

These prefrontal areas, all being connected to the mediodorsal thalamus as well as to the ventral striatum (Groenewegen *et al.*, 1990), show that multisynaptic influences of Acb on neocortical function are not to be understood solely in terms of voluntary movement and behavioural planning; they probably extend to representation of emotion- and motivation-related sensory percepts as well. In support of this conclusion, Swerdlow *et al.* (1990, 1992) found an involvement of the ventral striatopallidal system in prepulse inhibition of the acoustic startle response. In this behavioural model of sensorimotor gating, where a lead stimulus precedes an intense sensory stimulus evoking a startle response, micro-infusion of dopamine into the Acb disrupted pre-pulse inhibition. McAlonan *et al.* (1993) recently found a strong involvement of the mediodorsal thalamic nucleus in the acquisition of conditioned place preference, an adaptive process that was also shown to depend on the amygdala and the Acb (see Section 3; Everitt *et al.*, 1991).

(4) *Fourth output pathway: accumbens-lateral hypothalamic and preoptic area.* Ventral striatal projections to the preoptic and medial as well as lateral hypothalamic areas are thought to originate mainly in the shell of the Acb (Fig. 5D; Groenewegen and Russchen, 1984; Heimer *et al.*, 1991). The ventromedial region of Acb also projects to the sublentiform part of the so-called "extended amygdala" (Heimer *et al.*, 1991; Zahm and Brog, 1992). The prominent role of the lateral hypothalamus and preoptic area in aggressive, feeding, drinking and sexual behaviour has been recognized since the electrical stimulation experiments of Hess (1957; Glickman and Schiff, 1967) and need not be extensively reviewed here. Approaches using chemical intervention techniques showed, for instance, that testosterone injection into the hypothalamus elicited copulatory movements (Fisher, 1956). Lesions of the medial preoptic area and anterior hypothalamus disrupt consummatory and performance measures of male sexual behaviour, while apparently leaving instrumental/appetitive behaviour relatively intact (Hansen *et al.*, 1982; Everitt and Stacey, 1987; Everitt, 1990). The preoptic area has also been implicated in drinking behaviour, as shown by local angiotensin II injections (Epstein *et al.*, 1970), regulation of sleep-wakefulness (Serman and Shouse, 1985) and body temperature (Boulant, 1991). The preoptic and hypothalamic target areas of Acb show perhaps the clearest and most straightforward link of

this nucleus to elementary goal-directed behaviour. The likely involvement of the Acb in appetitive aspects of sexual behaviour has already been mentioned in Sections 2 and 3.

(5) *Other output pathways of the nucleus accumbens.*

The existence of multiple target zones of the Acb provides strong anatomical evidence for the proposition that distinct subterritories of Acb are likely to have different functions in sensorimotor gating, motor control and neuroendocrine regulation. However, a number of other projections should be added to this overview. Relatively modest projections from the Acb shell to the lateral septum, amygdala, bed nucleus of the stria terminalis, lateral habenula and central grey have been reported (Nauta *et al.*, 1978; Groenewegen and Russchen, 1984; Haber *et al.*, 1985; Haber *et al.*, 1990; Heimer *et al.*, 1991). Furthermore, the core of Acb is likely to exert influences on the medial subthalamic nucleus directly and, more importantly, by way of the dorsolateral part of the ventral pallidum (Haber *et al.*, 1985; Heimer *et al.*, 1985; Zahm, 1989; Berendse and Groenewegen, 1991). In addition, the core sparsely projects to the medial part of the entopeduncular nucleus (internal pallidal segment; Nauta *et al.*, 1978; Groenewegen and Russchen, 1984; Heimer *et al.*, 1991; Zahm and Brog, 1992). Finally, Grove *et al.* (1986) and Haber *et al.* (1990) obtained evidence for an Acb projection to the nucleus basalis of Meynert, a structure implicated in neocortical memory systems and Alzheimer's disease (Whitehouse *et al.*, 1982; Candy *et al.*, 1983; Price, 1986; Smith, 1988; see, however, Dunnett, 1990; Dunnett *et al.*, 1991). Zaborszky and Cullinan (1992) recently presented evidence that projection fibers from Acb reach the ventral pallidal/nucleus basalis area of the rat and form synaptic contacts with cholinergic neurons, which project to diverse neocortical areas.

As pointed out by Haber *et al.* (1985), these additional projections further underscore a global dichotomy in the ventral striatopallidal system, viz. that the ventromedial striatopallidal axis directs its outflow mainly to "limbic" structures (i.e. lateral septum, bed nucleus of stria terminalis, ventral tegmental area, lateral hypothalamus, preoptic area, etc.) whereas its ventrolateral counterparts are heavily interconnected with extrapyramidal circuits (i.e. subthalamic nucleus, substantia nigra, entopeduncular nucleus, pedunculopontine area, etc.).

7.3. IMPLICATIONS OF EFFERENT CONNECTIVITY

Our overview of anatomical and physiological findings on Acb output pathways brings several general remarks to mind. First, the great diversity of primary and secondary target areas of Acb should refrain us from placing undue emphasis on one particular output pathway, e.g. the ventral striatopallidal projections to the pedunculopontine region. Rather than assigning a functional prevalence to one of the target areas above others, we adhere to the concept that the Acb may be able to modulate activity of multiple target areas in a parallel manner and possibly within one behavioural sequence, and may influence neural activities in a multitude of even lower, distributed brain centres closely linked to neuroendocrine and motor effector systems. While

for many Acb projections the areas of origin are only globally known (i.e. shell-core, medial-lateral levels of distinction), the neurochemical compartments, with their specific afferent/efferent relationships, clearly form a putative substrate of the functionally distinct ensembles, and lend further credibility to our hypothesis.

Second, the limitations of regarding the Acb purely as a limbic-motor interface were illustrated by the functional considerations on the "mediodorsal thalamic connection" of the Acb and ventral pallidum. Even the heavy link to the substantia nigra and ventral tegmental area does not firmly place the Acb in the realm of higher brain centers for motor command, since the nigral-dorsal striatal axis probably also functions in cognitive and sensory processing in addition to movement-related tasks (Cools *et al.*, 1977; Lidsky *et al.*, 1985; Brown and Marsden, 1987). The ventral pallidal projection to the pedunculopontine area may provide an anatomical link between the Acb and motor activity, but as mentioned, the importance of this pathway can be debated on anatomical grounds. With hindsight to the behavioural studies on Acb, it can be noted that the numerous reported locomotor effects (Section 2) do, by themselves, not demonstrate the Acb to be a motor command center. This point can be illustrated by an analogy to other brain areas. For instance, there is no reason to argue that the dentate gyrus would be a motor command center just because of the stimulant effects of intra-dentate injections of carbachol on locomotion.

Third, the anatomical findings summarized above should make one more cautious in designing unidirectional, monopolar flow charts of basal forebrain connectivity. This was illustrated above by the amygdalar "bypass" projection to ventral pallidum and by the dual striatopallido-mesencephalic subsystem. A further complication is the ventral pallidal back-projection to Acb (Fig. 5; Beckstead, 1983; Haber *et al.*, 1985; Austin and Kalivas, 1991; Kuo and Chang, 1992; Groenewegen *et al.*, 1993). Electrophysiological evidence for this projection was obtained by Hakan *et al.* (1992). It may provide a negative feedback control of the activity of spiny projection neurons.

Appreciation of the functional diversity of the output pathways in relation to subterritories in Acb makes it unavoidable to discuss yet another problem: what principles govern the selection of neuronal ensembles in Acb and subsequent target structures in order to achieve a coordinated integration of the multiple components constituting a particular behavioural pattern? In other words, how is the activity of each ensemble initiated and regulated in relation to the activities of neighbouring ensembles? This question will be discussed in the next section.

8. RECRUITMENT OF NEURONAL ENSEMBLES IN THE INTEGRATION OF MULTIPLE FUNCTIONS OF THE NUCLEUS ACCUMBENS

The main thrust of the previous section was to underscore the wide variety of Acb functions as

shown by tract-tracing and physiological studies. The divergence of Acb outputs is proposed to be the main substrate for its involvement in a wide range of behavioural, neuroendocrine and sensorimotor functions, reviewed in Sections 2 and 3. The next issue to be considered is how afferent activity from cortical, thalamic and amygdalar sources may be able to achieve a coordinated activation of neuronal ensembles in Acb, in a way that is compatible with the paradigm of spatiotemporally organized output activity put forward in Section 5. First, however, we will reconsider the elementary electrophysiological features of spiny projection cells, and work out a hypothesis of ensemble recruitment from that point.

In vivo recordings in awake rats and monkeys have shown that ventral striatal neurons have low to moderate spontaneous firing rates in resting conditions (0.1–18 Hz according to Callaway and Henriksen, 1992; cf. Williams, 1989; West and Michael, 1990). This spontaneous activity occurs in spite of the presence of a strong inward-rectifying K⁺ conductance in spiny projection neurons which is active at rest (Uchimura *et al.* 1989a; Pennartz *et al.*, 1991a). In slices, this current tends to keep neurons in a strongly polarized state, at least under unstimulated conditions. Indeed, the resting membrane potential of spiny projection neurons varies between –70 and –85 mV, which is unusually negative as compared to most brain areas. Furthermore, electrophysiological *in vitro* recordings have yielded no evidence for periodicity in firing behaviour or resting membrane potential, such as encountered in thalamic neurons and dopaminergic cells in the mesencephalic tegmentum. In sensory-stimulation paradigms, strong discharge activity of Acb neurons recorded *in vivo* seems to require presentation of visual, auditory, olfactory or somatosensory stimuli, which may or may not be associated with reward (Rolls and Williams, 1988; Williams, 1989; West and Michael, 1990). Furthermore, intracellular recordings in the Acb *in vitro* show that stimulus-evoked EPSPs capable of eliciting spikes are generally 25–35 mV in peak amplitude (Uchimura *et al.*, 1989b; Pennartz *et al.*, 1991a; Pennartz and Kitai, 1991), which is larger than usually found in cortical structures *in vitro*.

These observations indicate that Acb neurons (1) may show moderate firing rates *in vivo*, even under unstimulated conditions; (2) have a relatively negative resting membrane potential and do not possess intrinsic membrane properties that may, by themselves, lead to spontaneous patterns of firing; (3) and thus need strong afferent activity, probably generated by cortical, thalamic and amygdalar areas (see below), to overcome inward rectification and to reach spike threshold. Figure 6D represents an activation scheme starting with glutamatergic excitation of a silent neuron (Fig. 6A, B; Uchimura *et al.*, 1989b; Pennartz *et al.*, 1990, 1991a; Pennartz and Kitai, 1991; Horne *et al.*, 1990), proceeding to de-activation of the inward rectifier as a consequence of cell depolarization (Fig. 6C; Uchimura *et al.*, 1989a), spike generation, GABAergic inhibition by feed-forward circuits (Fig. 6A, B; Pennartz and Kitai, 1991) and finally, re-activation of the inward rectifier

leading to reinstatement of the silent resting mode. This concatenation of events makes the activation function (i.e. relationship between input and output activity) of spiny projection neurons highly non-linear.

Consequently, the Acb is unlikely to serve as an "initiator" or "behavioural switching device" solely by virtue of the membrane properties of its principal cells. Regardless of whether such terms are appropri-

FIG. 6. (A) Representative intracellular EPSP-IPSP sequence elicited by electrical stimulation of the fornix in slices. Similar responses are observed following local stimulation or stimulation of prefrontal afferents, albeit that the amplitude of the IPSP can vary. This fornix response was recorded at various levels of membrane potential, indicated on the left-hand side. At membrane potentials more negative than -45 mV, a depolarizing response was recorded. At membrane potentials depolarized to -45 mV, a biphasic response emerged, consisting of an early depolarizing and a slightly delayed, hyperpolarizing component. Further pharmacological experiments identified the early component as a glutamatergic EPSP and the delayed component as a GABA_A-receptor mediated feed-forward IPSP. The onset latency of the IPSP component, recorded at about -2 mV, was slightly longer than the onset latency of the EPSP, recorded at resting membrane potential (-71 mV). The IPSP onset typically coincided with the mid-rising phase of the EPSP, in agreement with the feed-forward circuitry proposed for this type of inhibition. (A) was recorded from a medium spiny neuron identified with biocytin-avidin staining. Intracellular spikes were blocked by intracellular application of the lidocaine derivative QX-314. Calibration (for A and B): 20 mV, 10 msec. Reproduced, with permission, from Pennartz and Kitai (1991). (B) I/V curve illustrating the voltage-dependence and barium-sensitivity of the inward-rectifying potassium conductance in nucleus accumbens neurons. Microelectrode recordings in slices were used for voltage-clamp with 2.5–3.5 kHz switching frequency. Voltage steps lasted 3 sec and plotted values reflect steady-state currents. Holding potential in this experiment was -85 mV. Increasing extracellular barium concentrations (1–100 μ M) were observed to gradually block the inward rectification. Reproduced, with permission, from Uchimura *et al.* (1989a). (C) Diagram illustrating the main factors that regulate transitions between "silent" and "firing" states of spiny projection neurons in the nucleus accumbens. Glutamatergic excitation depolarizes the cell and thereby reduces the inward-rectifying K⁺ conductance. The neuron is briefly allowed to fire until the GABA_A-receptor coupled Cl[−] conductance gains sufficient shunting strength to restrain the excitatory depolarization and to prevent further firing. The decay of glutamatergic excitation, in conjunction with the GABAergic IPSP, results in a repolarization and re-activation of the inward rectifier.

ate to describe Acb function at all, experimental evidence implies that *spiny projection neurons require a relatively large amount of excitatory afferents to be approximately simultaneously active in order to reach spike threshold*. In situ patch clamp recordings provide as yet the most reliable data for estimating how many glutamatergic afferents would be required. The mean input resistance of Acb neurons under tight-seal whole-cell voltage clamp conditions was estimated at $217 \pm 33 \text{ M}\Omega$ (Pennartz and Lopes da Silva, 1994). Our own unpublished observations, generally agreeing with measurements in hippocampal slices (Malinow and Tsien, 1990) indicate that EPSCs evoked by minimal afferent stimulation are 3–10 pA in magnitude, although determination of the lower limit is confounded by noise. If it is assumed that these minimal stimulus-evoked EPSCs reflect glutamate release from only one afferent fiber (Malinow and Tsien, 1990), it follows from Ohm's law that about 14–46 glutamatergic terminals should be near-simultaneously active to produce EPSPs 30 mV in amplitude and thus giving rise to spikes. These numbers probably are an underestimation because (1) the inward rectification is active at rest (Uchimura *et al.*, 1989a) and needs to be overcome by synaptic depolarization; (2) GABAergic shunting inhibition becomes rapidly active (Fig. 6A, B; cf. Pennartz *et al.*, 1991a; Pennartz and Kitai, 1991), and (3) many co-occurring individual EPSPs may summate non-linearly. Branching of afferents and cable attenuation along dendrites may also be of significance in determining how many input fibers should be active to make the postsynaptic neuron fire, but the precise influence of these parameters is difficult to estimate at this time.

Thus, the collective firing activity of spiny projection neurons can be inferred not to arise from intrinsic membrane properties, but is probably contingent upon near-simultaneous co-activation of relatively large numbers of cortical, thalamic and amygdalar afferents. Reasoning along the same line, but now from the perspective of the cortical projection fields, it can be hypothesized that *spatially distributed, but nearly synchronized groups of cortical, thalamic and amygdalar neurons, by virtue of their specific convergent characteristics, temporarily recruit particular ensembles of accumbens neurons*. Our hypothesis assumes a tight coordination amongst the neuronal populations projecting to Acb, in order to assure close temporal correlations in distributed firing activities. In turn, these correlations may result in sufficient excitation of Acb neurons and hence may explain the vigorous discharges seen under stimulated conditions in awake animals. Synchronous activity in ensembles of the Acb may be a consequence of these temporally correlated cortical, thalamic and amygdalar inputs, and can be further strengthened by lateral inhibition between spiny projection neurons (see Section 9.2). Synchronization of spiny projection neuron ensemble activity, however, is not a prerequisite for our hypothesis, since the effector areas receiving Acb outputs may independently effectuate components of behavioural acts, sensory gating and neuroendocrine regulation. Admittedly, this basic concept of Acb function is rather broad and certainly permits to be extended to parallel sensori-

motor information flows through the dorsal striatum and olfactory tubercle.

How can a synchronization of cortical, thalamic and amygdalar populations of neurons projecting to Acb be established? First, functionally related fields of the limbic cortex usually appear to be reciprocally connected (see below and Fig. 7) and second, synchronous activity may be reinforced by mutual entrainment at the pace of a particular periodic activity, e.g. rhythmic slow activity (in rats: 4–12 Hz; cf. Bland, 1985; Lopes da Silva *et al.*, 1990; Lopes da Silva, 1991). Rhythmic slow activity prominently occurs during rapid-eye-movement sleep and in the awake state, while the animal performs voluntary movements (e.g. walking, rearing and swimming; Vanderwolf, 1969; Kramis *et al.*, 1975; Leung *et al.*, 1982). Strikingly, spontaneous firing of Acb units *in vivo* is strongest during wakefulness and rapid eye movement sleep (Callaway and Henriksen, 1992).

In a behavioural context, the direct consequence of this collective recruitment in Acb would be that subsets of activated projection axons to pallidal, mesencephalic and hypothalamic targets bring about a cascade of activity changes in even further removed brain centers, collectively constituting an altered state of brain activity that realizes new behavioural acts as well as changes in neuroendocrine regulation and cortical sensory processing. Behavioural switching, then, may be accomplished when higher processing of multimodal sets of external and internal sensations results in the activation of different groups of cortical, thalamic and amygdalar projection neurons, hence recruiting completely or partially differing sets of striatal projection neurons which, due to their specific links to other target areas, contribute to changes in behaviour.

Substantial anatomical evidence indicates a *parallel* organization of cortico-striatopallido-thalamic projections (Alexander *et al.*, 1990; Groenewegen *et al.*, 1990, 1993). Physiological findings suggest that these parallel loops reflect a functional segregation of corticostriatal circuits (DeLong *et al.*, 1984; Alexander *et al.*, 1990). It should be emphasized that this parallel organization is compatible with the present hypothesis, despite the fact that it ascribes a major role to cortical, thalamic and amygdalar convergence at the level of ensembles and of single spiny neurons. To clarify the latter point, we will briefly review the anatomical relationships between cortical, thalamic and amygdalar areas projecting to Acb (Fig. 7).

(1) *Hippocampal formation, prelimbic cortex and basolateral amygdala*. The ventral subiculum projects to the caudomedial part of Acb as well as to the posterior and ventral prelimbic area (Groenewegen *et al.*, 1990; Jay and Witter, 1991). The projection of this prelimbic sector to Acb, in turn, overlaps with the ventral subicular termination pattern in the caudomedial Acb (Fig. 7A; Sesack *et al.*, 1989). Strikingly, both the posterior prelimbic area and ventral subiculum are implicated in visceral-autonomous functions (Hurley-Gius and Neafsey, 1986; Scheel-Krüger and Willner, 1991). The dorsal CA1-subiculum complex primarily projects to the rostromedial Acb and also projects to the prelimbic cortex (Groenewegen *et al.*, 1987, 1990; Jay and Witter, 1991). Sesack *et al.* (1989) showed that the anterior prelimbic area sends fibers

FIG. 7. Examples of coupled cortico-thalamic-amygdalar circuits having convergent projections to specific subterritories of the nucleus accumbens. (A) The posterior prelimbic cortex (Prelimbic Cx posterior) and ventral subiculum both project to the caudomedial accumbens and are reciprocally interconnected. The posterior part of the basolateral amygdala (amygdala BL posterior) also projects to the caudomedial Acb and is mutually interconnected with the posterior prelimbic cortex. A parallel circuit can be drawn for the anterior prelimbic cortex and dorsal subiculum. (B) The lateral entorhinal cortex (EC lat) is connected to multiple regions of the hippocampus proper and reciprocates the dorsal subiculum (Sub dors) and CA1 area (the weaker back-projections from these hippocampal areas to the entorhinal cortex are drawn as thin broken lines). The dorsal subiculum and lateral entorhinal cortex have convergent projections to lateral parts of the accumbens. A parallel circuit can be drawn for the medial entorhinal cortex, ventral subiculum and medial accumbens. (C) Main afferent and efferent connections of the midline and intralaminar thalamic nuclei. Afferent pathways originating in the reticular formation (Brain stem Ret Form) and prefrontal cortex (Pref Cx) are shown, as well as thalamic projections to the nucleus accumbens, basolateral amygdala (Amygd BL), prefrontal cortex, subiculum (Sub) and entorhinal cortex (Ent Cx). This figure also illustrates the diverging connections of the amygdala to the nucleus accumbens, prefrontal cortex, subiculum and entorhinal cortex. This is a general scheme which does not show the specific projections of particular thalamic nuclei and functionally related cortical areas to neurochemical compartments in the nucleus accumbens.

to the rostralateral Acb, again overlapping subicular termination patterns. The latter cortico-striatal triple alliance is likely to be strongly engaged in spatial orientation and multimodal sensory information processing (O'Keefe and Nadel, 1978; Kolb, 1984; Kùbie *et al.*, 1985; Ranck, 1985). Communication between the medial prefrontal cortex and hippocampal formation may be mediated by reciprocal connections (Fig. 7A; White *et al.*, 1990; Jay and Witter, 1991).

The basolateral amygdala may further contribute to enhance the synaptic excitability of prelimbic and subiculum-driven Acb neurons, since the caudomedial Acb is part of its projection field (Fig. 7A; Krettek and Price, 1978; Groenewegen *et al.*, 1990;

Kita and Kitai, 1990). However, at this point it should be recalled that the amygdala and hippocampus may also differentially innervate distinct neurochemical compartments in this part of the shell (Section 7). Importantly, both the amygdala-prefrontal and amygdala-subicular interconnections are probably reciprocal (Krettek and Price, 1977b; Kolb, 1984; Sarter and Markowitsch, 1985; McDonald, 1987; Kita and Kitai, 1990; Canteras and Swanson, 1992; Mello *et al.*, 1992).

(2) *Hippocampal formation and entorhinal cortex.* The entorhinal cortex is intricately connected to the trisynaptic circuits of the hippocampus (Lopes da Silva *et al.*, 1990) and again, both entorhinal cortex

and CA1-subiculum project to the Acb (Fig. 7B; Sørensen and Witter, 1983; Witter and Groenewegen, 1986; Witter *et al.*, 1989). The functional distinction between the septal and temporal pole of the hippocampus, referred to above, is reflected in the organization of the entorhinal cortex, with its lateral portion receiving mainly multimodal information from the external environment and its medial portion processing olfactory and autonomous inputs. The most medial part of the entorhinal cortex predominantly projects to the medial Acb, whereas the lateral entorhinal cortex directs its fibers mainly to the rostrolateral parts of Acb (Fig. 7B; Witter and Groenewegen, 1986; Witter *et al.*, 1989), thus complying with the subicular-Acb topography.

(3) *Hippocampal formation and infralimbic cortex.* The hippocampus and infralimbic cortex are likely to converge upon single Acb neurons (Pennartz *et al.*, 1992a). As in the previous circuits, the ventral portion of the CA1-subiculum and the infralimbic cortex are probably reciprocally connected (Swanson, 1981; Room *et al.*, 1985; Lopes da Silva *et al.*, 1990; Jay and Witter, 1991). In general, this circuit is thought to process information from the autonomous nervous system; one of its specific functions is to control visceromotor functions (Groenewegen *et al.*, 1990).

(4) *Prefrontal cortex and midline/intralaminar thalamic nuclei.* The prefrontal cortex, the midline and intralaminar thalamic nuclei and the ventral striatum maintain a "triangular" relationship such that a particular thalamic nucleus projects to a specific area of the cortex and to a subregion in the striatum which also receives input from the same cortical area (Fig. 7C; Berendse and Groenewegen, 1990, 1991; Berendse *et al.*, 1992a). For instance, the intermediodorsal thalamic nucleus and dorsal agranular insular area both project to the caudal part of the Acb core. This thalamic nucleus also projects to the dorsal agranular cortex (Krettek and Price, 1977a; Berendse and Groenewegen, 1991); their functions probably include the processing of visceral sensory information and regulation of orofacial behaviour (Van der Kooy *et al.*, 1982; Kosar *et al.*, 1986; Hurley-Gius and Neafsey, 1986; Scheel-Krüger and Willner, 1991). The midline and intralaminar nuclei receive a significant input from the reticular formation and thus may also play an important role in arousal (Berendse and Groenewegen, 1990). Furthermore, these nuclei project to the subiculum, entorhinal cortex and amygdala, which in turn innervate the Acb (Fig. 7C; Groenewegen *et al.*, 1990; Berendse and Groenewegen, 1990; Berendse *et al.*, 1992a).

Having considered the macroscopic indications for convergence between functionally related areas projecting to Acb, we should admit that there is as yet no electron-microscopic evidence for convergence of subicular, prefrontal, thalamic and/or amygdalar afferents onto spiny projection neurons. In an intracellular slice study, however, we recorded convergent monosynaptic EPSPs elicited by prefrontal and subicular afferent stimulation in single spiny projection neurons of the shell (Pennartz *et al.*, 1992a). DeFrance *et al.* (1980) and, more recently, Callaway *et al.* (1991) found single units in the caudomedial Acb responding to both amygdala and fornix-fimbria stimulation. According to the study of Callaway

et al., amygdalar-subicular convergence extends even into the anterior part of Acb.

Thus, anatomical and electrophysiological evidence suggests the existence of convergence of prefrontal, hippocampal, amygdalar and/or thalamic fibers into specific subareas of Acb, and also onto single cells within distinct subareas (Fig. 8). Referring to Section 7, it should be emphasized that the specific subterritories of Acb receiving information from converging sources also have specific output connections. Hence, distinct subterritories or neuronal ensembles are likely to influence sets of target structures and regulate behaviour, neuroendocrine function as well as cortico-thalamic processing in a specific manner.

9. WHAT TYPE OF OPERATIONS MAY BE CONDUCTED BY THE AFFERENT FIBERS AND INTRINSIC CIRCUITS OF THE NUCLEUS ACCUMBENS?

9.1. INTRODUCTORY REMARKS

Thus far, we have been focussing on the afferent and efferent relationships of spiny projection neurons. Despite the large number of functional behavioural and electrophysiological studies, it remains difficult to bring ventral striatal information flows under one common denominator. Behavioural evidence for Acb involvement in elementary behavioural patterns such as drinking and food hoarding has been reviewed (Section 2), but none of this evidence implies that the Acb would *encode 'instructions' or 'motor commands' for effectuating these behaviours*. In a similar vein, unit recordings in awake monkeys have revealed the impact of (motivation and non-motivation related) sensory stimuli on Acb (Section 6). Yet none of these studies permits one to state that ensembles of Acb neurons would *encode sensory representations*. The basic problem is that these studies allow to *correlate* neuronal activities in Acb to sensory stimuli and/or motor output, but do not permit interpretations in terms of *information content*. Indeed, the Acb is embedded deeply enough in the basal forebrain to allow for numerous transformation and re-encoding operations in brain areas preceding and succeeding this structure in global serial-parallel sensorimotor networks.

Despite the fact that this conceptual restriction forces us to stick to necessarily vague terms as "limbic", "sensorimotor", "motivational" and "multimodal sensory" information, it is certainly worthwhile to investigate how intrinsic circuits, in relation to spiny projection neurons, operate on these information flows. We will especially emphasize the putative network functions of five striatal neurochemical systems, i.e. the transmitters glutamate and GABA and the modulators dopamine, acetylcholine and the enkephalins. Finally, dopamine and opiate receptor-mediated mechanisms of reward-dependent learning will be briefly considered.

9.2. SHORT- AND LONG-RANGE LATERAL INHIBITION

Previous reviews of basal ganglia function have highlighted the role of intrastriatal lateral (recurrent)

inhibition by GABAergic axon collaterals of spiny projection neurons (Groves, 1983; Penney and Young, 1983; Swerdlow and Koob, 1987a; Smith and Bolam, 1990; cf. Park *et al.*, 1980 and Somogyi *et al.*, 1981). These axon collaterals would, amongst others, contact other spiny projection neurons. In the medial Acb, Pickel *et al.* (1988) reported glutamic acid decarboxylase (GAD)-positive terminals on primarily unlabelled perikarya, dendrites and spines, but they also noted a relatively small number of presumably GABAergic terminals on GAD-positive dendrites. The latter observation does provide some ultrastructural evidence for lateral inhibition between spiny projection neurons in the Acb, although the extent to which it occurs may be limited.

According to Chang and Kitai (1985; see also

Pennartz *et al.*, 1991a; Pennartz and Kitai, 1991), most axon collaterals of spiny projection neurons branch within the dendritic domain of the parent cell. Some axon collaterals, however, have a considerably wider spatial extension; these have also been reported in the dorsal striatum (DiFiglia *et al.*, 1976; Kawaguchi *et al.*, 1989). Suggestions in support of a relatively "long-range" complex of axonal ramifications in Acb have also been advanced by Heimer *et al.* (1991). These pieces of anatomical evidence, although somewhat preliminary, suggest the existence of both a "short-range" and "long-range" system of axon collateralization (Fig. 8). Since the dendrites of a spiny projection neuron are usually confined to the neurochemical compartment in which the neuron is found (Arts and Groenewegen, 1992), its short-range

FIG. 8. Two types of convergence and two putative types of lateral inhibition in the nucleus accumbens. (A) Inputs from the hippocampal formation (HPF), the amygdala (Amy) and prefrontal cortex (PFCx) converge onto single spiny projection neurons, represented here by circles. Electrophysiological evidence is available for amygdala-hippocampal convergence and for prefrontal-hippocampal convergence onto single neurons, whereas amygdalar-prefrontal convergence is still hypothetical. Lateral inhibition within one neuronal ensemble may be mediated by the short-range collaterals of spiny projection neurons. Excitatory projections are represented by arrows; inhibitory connections are drawn as flat endings. Neurons belonging to one ensemble are hypothesized to project to common target areas (see Fig. 5). (B) Convergence may also take place at the level of entire neuronal ensembles, represented here by a group of small circles. As an example, convergent projections from the ventral posterior prelimbic cortex (vpPrelimbic), ventral subiculum (vSub) and basolateral amygdala (BL amy) are drawn towards the left-hand ensemble. The dorsal anterior prelimbic cortex (daPrelimbic) and dorsal subiculum (dSub) are postulated to converge onto a different ensemble. The lateral inhibition between the two ensembles may be established by long-range axon collaterals of spiny projection neurons, but is otherwise hypothetical. Different neuronal ensembles are considered to influence different sets of target areas, although there may be some overlap as suggested here.

axon collaterals may be confined to this compartment as well. Therefore, the putative "short-range" inhibition is proposed to have a function primarily within the spatial domain of a compartment or functionally distinct ensemble, whereas the "long-range" inhibition may subserve interactions *among* compartments/ensembles. First we will consider possible functions of the "short-range", or within-domain collateral inhibition as revealed by intracellular injection studies (Chang and Kitai, 1985; Pennartz *et al.*, 1991a; Pennartz and Kitai, 1991).

Lateral inhibition by axon collaterals, according to Groves (1983), "may provide a means for sharpening the diffuse pattern of input from cerebral cortex and brainstem into neostriatal target systems". This idea originally dates back to the early studies on the retina (Kuffler, 1953; Hartline and Ratliff, 1972) and also has become an important feature of several neural network architectures (Kohonen, 1989; Hopfield and Tank, 1989). Although we subscribe to the concept of lateral inhibition as a means for "focussing" or "sharpening" corticostriatal information flows, it is worthwhile to draw attention to some other putative functions of this type of inhibition. Firstly, model studies have shown that lateral inhibition significantly affects synchronization and propagation of rhythmic activity through neural networks (Lopes da Silva *et al.*, 1974; Traub and Miles, 1991; see also Hartline and Ratliff, 1972). Indeed, inhibitory connections between spiny projection neurons may enhance temporal coherence within neuronal ensembles. Since cortical projection fields converging on ensembles in Acb may already be rhythmically active to begin with (see Section 8), lateral inhibition in Acb would be in an excellent position to modulate the transmission of rhythmic activity to lower basal forebrain areas. Secondly, the constellation of spiny projection neurons receiving converging, modifiable glutamatergic inputs is, in principle, able to store representations in an associative manner (see Section 9.4). According to Kohonen (1989), lateral inhibition may serve to enhance the separability (mutual orthogonality) of stored input patterns.

Studies of retinal information processing have yielded additional insights that may be applicable to other areas of the central nervous system. In addition to serving contrast enhancement, lateral inhibition has been proposed to remove spatial redundancy and to remove tonic components of input signals (Barlow, 1961; Marr and Hildreth, 1980; Srinivasan *et al.*, 1982). A striatal neuron embedded in a three-dimensional lateral-inhibitory array receives a certain amount of monosynaptic excitatory cortical input and a disynaptic inhibitory load from adjacent neurons in the network. If the central excitatory input and the surrounding excitatory inputs driving the lateral-inhibiting units are statistically correlated, the lateral-inhibitory load on the central neuron may partially cancel out the excitatory input in a way that depends on the distance to the focus of activity—thereby reducing spatial redundancy in the input pattern. The inhibition effectively limits the output range of the central neuron, but at the same time renders the neuron more sensitive to subtle spatially distributed differences in cortical input patterns. Subsequent stations of sensorimotor processing (pallidum, thalamus)

would benefit from this operation, because the output range of the central striatal neuron can be fully utilized for representing subtle local details that remain discernible despite addition of noise in later stages (cf. Srinivasan *et al.*, 1982).

Whereas the function of short-range inhibition is hypothesized to affect information transfer within a neuronal ensemble occupying a given spatial domain, long-range intrastriatal inhibition (Fig. 8B) may mediate *competitive phenomena* between different ensembles. If, at a certain point in a behavioural sequence, a particular sensory input (e.g. visceral) is prominently represented in a given cortico-thalamic-amygdalar circuit, the convergent excitatory activity onto the corresponding ensemble in the Acb (e.g. caudomedial area) would, next to directing outputs to the appropriate target areas, lead to inhibition of adjacent ensembles.

9.3. FEED-FORWARD INHIBITION

Functions of feed-forward inhibition, probably mediated by GABAergic interneurons in Acb (Pennartz and Kitai, 1991) are as yet difficult to evaluate in the spatial domain. In the dorsal striatum, Kita *et al.* (1990) showed that GABAergic, parvalbumin-positive interneurons have extensive axon collaterals onto a multitude of spiny cellular elements, suggesting that firing activity of a single interneuron will inhibit many spiny projection neurons at approximately the same time. However, the spatial extent of collateralization has not yet been elucidated. In principle, feed-forward inhibition (Fig. 9) may support the computational operations of both short- and long-range lateral inhibition. Depending on its spatial working range, feed-forward inhibition may mediate interactions between neurons within an ensemble, or on a larger scale, may enhance competitive interactions between ensembles (Fig. 9B). In the temporal domain, the rapid onset of feed-forward inhibition is particularly striking (Pennartz and Kitai, 1991). This fast activation of feed-forward circuits shortens the excitatory response, limits postsynaptic Ca^{2+} influx through NMDA-receptor coupled channels (Pennartz *et al.*, 1990, 1991a) and hence restrains induction of long-lasting synaptic modifications (Pennartz *et al.*, 1993). The tendency to produce "transient" firing behaviour may be important for the coordinated timing of on- and offset of ensemble activities in the ventral striatal complex. Furthermore, feed-forward inhibition may remove temporal redundancy from bouts of cortical input and will bring peaks and dips in the input stream into greater prominence at the cost of tonic levels of activity. Finally, in correlation matrices and related models of associative memory, feed-forward inhibition has been proposed to mediate a division operation in the recall of stored patterns (Marr, 1971; McNaughton and Nadel, 1990).

9.4. GLUTAMATERGIC INPUTS

Glutamatergic synapses are indispensable for ventral striatal functioning since they mediate cortical, thalamic and amygdalar excitation of spiny projection neurons, as well as of GABAergic (Pennartz and

FIG. 9. Schematic illustration of two putative types of feed-forward inhibition in the nucleus accumbens. (A) The hippocampal formation (HPF) monosynaptically excites the spiny projection neuron (large white circle) and a GABAergic interneuron (small grey circle). The interneuron is likely to have axon collaterals synapsing on multiple spiny projection neurons. The basolateral amygdala (BL Amy) monosynaptically excites spiny projection neurons, but may also activate GABAergic interneurons (thin arrow). The feed-forward inhibitory circuit as represented here raises the possibility that the basolateral amygdala exerts an inhibitory influence on some hippocampus-driven neurons and vice versa. (B) The spatial extent of the collaterals of GABAergic interneurons is unknown; here it is hypothesized that feed-forward inhibition (driven by e.g. the hippocampal formation) may also occur between different ensembles.

Kitai, 1991) and cholinergic interneurons (Henselmans and Stoof, 1991; Stoof *et al.*, 1992). Here we will focus on three functional properties of glutamatergic synapses: paired-pulse facilitation, frequency depression and long-term plasticity.

In vitro, glutamate receptor-mediated EPSPs elicited by stimulation of hippocampal or prefrontal inputs to the Acb display a paired-pulse facilitation in the interval range of 10–120 msec (Fig. 10B; Pennartz *et al.*, 1990, 1991a; Pennartz and Kitai, 1991; Pennartz *et al.*, 1992a). *In vivo*, fimbria-fornix stimulation evokes two distinct positive components (termed P10 and P25) in a field potential profile through Acb, with peak latencies of about 10 and 25 msec, respectively. Conspicuously, these two components have different paired-pulse characteristics, with the P10 showing facilitation at intervals similar to those found *in vitro* and the P25 showing facilitation at intervals between 100 and 500 msec (Boeijinga *et al.*, 1990). In unit recordings, spike activity is usually found in the latency range corresponding to the P10 or P25 peak, and indeed the time range of facilitation in fornix-evoked unit activity matches the time range of facilitation of the field potential component accompanying the evoked spikes. Figure 10A shows an example of fornix-evoked spike activity

approximately corresponding to the P25 peak. Clearly, a large amount of paired-pulse facilitation is present at an interval of 100 msec. The late P25-component and its remarkably long facilitation have not been found *in vitro* and probably result from fornix-evoked spike propagation in fibers ascending to the hippocampus. Following transmission through a polysynaptic hippocampal loop, a spike volley was inferred to exit the hippocampus through the fornix and to subsequently enter the Acb (Boeijinga *et al.*, 1993).

When in slices prolonged trains of stimuli spaced by 80–500 msec are applied instead of just two, the initially facilitated EPSP is depressed and stabilizes at a lower amplitude after about 10 stimuli ("frequency depression"; Fig. 10C; Pennartz and Lopes da Silva, 1994). Both paired-pulse facilitation and frequency depression may significantly affect synaptic transmission of cortical, thalamic and amygdalar inputs in different modes of rhythmic activity. Short-lasting clusters of excitatory rhythmic slow activity (RSA; 4–12 Hz) input, for example, may be amplified by mechanisms underlying paired-pulse facilitation. However, more long-lasting bouts of input activity in the same frequency range may be prone to frequency depression. Interestingly, this "time-domain filtering" appears to be modulated by dopamine and acetylcholine (Pennartz *et al.*, 1992a; Pennartz and Lopes da Silva, 1994).

A recently discovered feature of glutamatergic synapses in Acb, which is the main topic of this subsection, is NMDA receptor-dependent plasticity (Fig. 10D–E; Pennartz *et al.*, 1993; Boeijinga *et al.*, 1993). The associative properties of long-term potentiation (LTP) induced by activation of NMDA receptors are now well recognized and have been found in neocortical as well as hippocampal areas (Teyler and DiScenna, 1987; Bliss and Collingridge, 1993). Relying on our finding that LTP-induction in Acb can be largely blocked by NMDA receptor antagonists, we propose that glutamatergic inputs converging on nearby parts of a postsynaptic spiny dendrite of an Acb neuron can become associatively strengthened if the local calcium influx is sufficiently intense (Müller and Connor, 1991). This process may lead to the strengthening of synapses originating within a single source area (e.g. ventral subiculum; cf. Boeijinga *et al.*, 1993), or to the *associative storage* of input patterns carried by fibers from different, but interconnected source areas. The plastic properties of these glutamatergic afferents offer a possible mechanism underlying associative learning processes in cortico-, thalamic- and amygdalar-ventral striatal circuits.

This proposition will be illustrated by an example taken from the work of Everitt *et al.* (1991). In excitotoxin-induced disconnection lesions of the amygdala and ventral striatum in rats, they demonstrated a serial involvement of these structures in conditioned place preference (Section 3). Whereas the basolateral amygdala has been strongly implicated in the association of initially neutral environmental stimuli with rewards (secondary reinforcement; Sarter and Markowitsch, 1985; Gaffan and Harrison, 1987; Robbins *et al.*, 1989), the Acb was hypothesized to mediate approach responses of the rat towards rewarding stimuli or their environments (Everitt

et al., 1991). These and other examples of adaptive behavioural changes (see Section 3) may be realized by an associative strengthening of sets of prefrontal, amygdalar, thalamic and subicular inputs onto shared dendritic elements of spiny projection neurons. According to our hypothesis, the co-occurrence of particular environmental cues and primary reinforcers or punishers would lead to the collective activation of interconnected cortical, amygdalar and thalamic subregions. Before consummatory acts have taken place, the corresponding outputs are assumed to reach sufficient strength to recruit a neuronal ensemble in Acb which subsequently activates a corresponding set of target areas participating in a particular appetitive behavioural act. *At this point, however, the outputs are still insufficient for triggering synaptic weight changes, or effectuate only decremental changes.* When the behavioural act is appropriate, e.g. leads to consummation of the reward, additional limbic-cortical circuits are activated as a direct consequence of reward consumption (e.g. prelimbic cortical subregions in response to gastrointestinal sensations). When this co-activation occurs within a restricted time-window, the subsequent associative outputs to the same neuronal ensemble in Acb may now become sufficiently strong to induce LTP, thus leading to the *facilitated* generation of the same cascade of neural activity in lower target areas. A crucial assumption of this concept, which has been proposed by Crow (1968) in a different and more general form, is that the neuronal ensemble was already recruited before *consummatory* behaviour and synaptic reinforcement occurred. If this assumption would be omitted, synaptic reinforcement could also take place following reward consumption, but now it would be uncertain whether or not the appropriate neuronal ensemble and corresponding target areas would have been recruited. Schemati-

cally, this hypothetical link between appetitive behaviour and reward can be envisaged as depicted in Fig. 11.

9.5. DOPAMINERGIC INPUTS

Before addressing the issue of the functions of dopamine in the circuits of the ventral striatum, we will briefly touch upon a related theme, viz. what type of information is correlated to dopamine release in Acb, or correspondingly, to activation of dopaminergic neurons in the ventral tegmental area. There are many experimental data contradicting the concept that unit firing in VTA would signal or encode the presence of a reward itself (cf. Scheel-Krüger and Willner, 1991). When rats were trained to press a lever for a light that was coupled to a primary reinforcer (i.e. water), amphetamine was observed to enhance responding. If, however, VTA activity would signify the presence or oncoming delivery of reward, 6-OHDA lesions of Acb would affect the choice of the lever, but this was not observed experimentally (Robbins *et al.*, 1989). Evenden and Robbins (1983) already noted that dopamine antagonists slow response speed in reinforcements tasks, but leave the organization of the response basically intact. This *facilitating or amplifying action* of dopamine in behaviour is further underlined by experiments of Salamone (1988) and Cador *et al.* (1991). With respect to the functional distinction between dorsal and ventral striatum, it has been noted that dorsal striatal dopamine may primarily function in organizing consummatory behaviour and skilled responses, whereas mesolimbic dopamine would influence the coupling of reward-related or salient stimuli to appetitive and instrumental behaviour (Robbins and Everitt, 1992). In a spatial discrimination task including a reversal test, dopamine-lesions hampered spontaneous alternation behaviour and induced failures to

FIG. 10. Overview of use-dependent changes in glutamatergic neurotransmission in the nucleus accumbens. (A) In the anaesthetized rat, a paired-pulse facilitation of field potentials as well as unit activity evoked by fornix stimulation can be observed at intervals of 100–500 msec. This peristimulus time histogram (courtesy of A. B. Mulder) shows the accumulated unit activity evoked by 16 paired fornix stimulations. The unit response is much larger for the second as compared to the first stimulus. Interstimulus interval was 100 msec, bin width 1 msec. Stimuli are indicated by downward arrows. This long-lasting form of paired-pulse facilitation appears to depend in part on fornix stimulation-induced activation of a hippocampal-subicular loop, followed by secondary activation of subicular input fibers to the nucleus accumbens (cf. Boeijinga *et al.*, 1993). (B) Paired-pulse facilitation of monosynaptic EPSPs recorded intracellularly in accumbens slices usually lasts up to 150 msec, similar to the facilitation effects found in e.g. hippocampal or neocortical slices. Here, responses to stimulation of prefrontal afferents are shown with an interval of 30 msec. (C) When stimulus trains of frequencies above 2 Hz are applied, the synaptic response gradually subsides until reaching a steady-state value. This frequency depression is accompanied by a slowly developing depolarization of the postsynaptic cell (usually 4–8 mV in amplitude for 12 Hz trains), which is, however, not causally related to the depression phenomenon itself (Pennartz and Lopes da Silva, 1994). Here, steady-state EPSPs are shown during stimulus trains at 1, 4 and 12 Hz (baseline was corrected for slow depolarization). No long-lasting effects were induced by these trains. (D) Tetanization of subicular (Boeijinga *et al.*, 1993) or prefrontal (Pennartz *et al.*, 1993) inputs to the nucleus accumbens may induce short- and/or long-term potentiation. This example shows induction of short-term potentiation, lasting up to 20 min, of an EPSP evoked by stimulation of mainly prefrontal afferents in a slice preparation. The tetanic stimulation consisted of a train of 100 pulses at 50 Hz; the perfusion medium contained the GABA_A antagonist picrotoxin (10 μ M) for pharmacological disinhibition. The time course of the EPSP is shown on the left-hand side, with the tetanus being indicated by an arrow. Overlaid control and potentiated (10 min after tetanus) traces are shown on the right. (E) In a different cell, the same stimulus protocol resulted in induction of LTP of the EPSP evoked by prefrontal fiber stimulation. Overlaid potentiated trace in the right-hand panel was taken 100 min after tetanization. A small proportion of the neurons showed long-term depression in response to 2 sec 50 Hz tetani (not shown here). (D) and (E) were reproduced, with permission, from Pennartz *et al.* (1993). Calibration: (B) 36 mV, 15 msec; (C) 13 mV, 28 msec; (D and E) 24 mV, 23 msec.

FIG. 10.

adapt properly to an altered location of the reward (Taghzouti *et al.*, 1985). In a conditional visual discrimination task, rats with ibotenic acid lesions of Acb showed a marked impairment in extinction learning, whereas caudate-putamen lesions had no significant effect on extinction (Reading *et al.*, 1991). Furthermore, intra-accumbens injection of d-amphetamine in the Acb was shown to enhance switching between cue-directed behaviours in a swimming test (Van den Bos and Cools, 1989; Van den Bos *et al.*, 1991). This ability to allow switching may constitute another basic functional feature of the mesolimbic dopamine system.

Activation of units in the VTA of awake monkeys

consistently occurs when salient or arousing stimuli are accompanied by appetitive behavioural responses (Ljungberg *et al.*, 1991, 1992). However, these recordings also show that dopaminergic neurons respond to stimuli that elicit behavioural reactions more in general, not specifically to rewarding stimuli. A further indication that the activity of dopaminergic neurons is not *specifically* related to reward, is that in over-trained animals unit responses sometimes decreased while the incentive or rewarding properties of stimuli did not change and consummatory behaviour remained constant (Ljungberg *et al.*, 1991). These findings are in accordance with an arousing or amplifying function of dopamine in behaviour, and are

consistent with a role in behavioural switching as well.

A previously proposed hypothesis (Penney and Young, 1983; see also Swerdlow and Koob, 1987a;

FIG. 11 Hypothesis on the role of ventral striatal neuronal ensembles in reward-dependent learning. In the left-hand column, behavioural actions are represented; the right-hand column presents events within the central nervous system. While this scheme explicitly focusses on the nucleus accumbens, it should be noted that it can be extended to other brain areas implicated in reward-dependent learning. Initially, exploratory behaviour and detection of a primary reward in the animal's environment leads to activation of a particular set of cortical, thalamic and amygdalar areas. These areas are hypothesized to be engaged in general sensory representations, spatial navigation and planning of behavioural strategies. Their outputs are directed to neuronal ensembles in the nucleus accumbens which in turn modulate target areas in lower brain centers for e.g. motor control. The modulation of these target areas of the nucleus accumbens may generate two types of output: an "inappropriate" output that leads to "punishment" (pain, stress, etc.) or fails to lead to a reward (food, juice, etc.). Following the inappropriate output, avoidance behaviour may occur and exploratory behaviour is reinstated. Following the "appropriate behavioural output" route, goal-directed approach behaviour leads to a consummatory act, as a consequence of which different cortical, thalamic and amygdalar circuits become active. In contrast to the cortical, thalamic and amygdalar areas that were initially active, these circuits are hypothesized to be mainly engaged in sensory processing triggered by e.g. food or liquid ingestion, and in evaluation of the rewarding properties of the consumed substance. A crucial assumption of the hypothesis is that these circuits are co-activated with the cortical, thalamic and amygdalar areas that were already active following detection of cues and primary reward. This co-activation may lead to associative strengthening of convergent glutamatergic inputs to the activated ensemble(s) in the nucleus accumbens. Enhancement of synaptic efficacy of inputs to the nucleus accumbens will subsequently lead to facilitated modulation of the same target areas as those being active before the consummatory act occurred. The modulatory role of dopamine in this sequence is discussed in the text.

Percheron and Filion, 1991) of striatal dopamine function is that dopaminergic synapses reduce the strength of lateral inhibition between spiny projection neurons, thus opposing the narrowing or spatial filtering of afferent cortical activity. In addition, dopamine would suppress striatal outputs to the ventral pallidum, thus maintaining a state of tonic activity in pallidal neurons and, in the next stage, pallidal inhibition of thalamocortical processing (Swerdlow and Koob, 1987a). Another influential theory is that catecholamines mediate an increase in a neuron's signal-to-noise ratio (Rolls *et al.*, 1984; Oades, 1985; Chiodo and Berger, 1986; Foote and Morrison, 1987; Mamelak and Hobson, 1989). Such an action was proposed to account for catecholamine-induced improvement in signal detection performance in behavioural experiments. Mamelak and Hobson (1989) and Servan-Schreiber *et al.* (1990) worked out these ideas in a neural network model, assuming that catecholamines would increase the steepness of neuronal activation functions. Indeed, such a change in cellular response properties was shown to enhance global neural network performance defined in terms of signal detection in noisy transmission lines.

Let us re-examine the available physiological evidence on dopamine function in the Acb in the light of these theories. In Acb slices, dopamine appears capable of attenuating both EPSPs and IPSPs in the shell region by way of D1 receptors (Fig. 12; Hara *et al.*, 1989; Pennartz *et al.*, 1992a, b). Dopamine effects on postsynaptic membrane potential and input resistance, presumably recorded in spiny neurons (Uchimura *et al.*, 1986), could not be reproduced in our experiments (Pennartz *et al.*, 1992a). Furthermore, the spike threshold current was not significantly affected (Pennartz *et al.*, 1992a). *In vivo* studies have raised additional evidence for D2 receptor-mediated suppression of excitatory limbic inputs (Yang and Mogenson, 1986, 1987, 1989). In addition, data obtained by White and Wang (1986) indicate D1 and D2 receptor-mediated depression of spontaneous firing activity, which may or may not depend on afferent input. With reference to the "focussing" theory of dopamine action, electrophysiological and anatomical studies in the dorsal and ventral striatum have produced no direct evidence for dopaminergic modulation of lateral inhibition. As long as dopamine tests in dual recording studies of interconnected pairs of striatal neurons are lacking, there is no convincing reason to adhere to this theory.

As shown by Pennartz *et al.* (1992a, their Fig. 2), dopamine attenuates synaptic responses over the entire range of the input-output curve. When this finding is interpreted in terms of a neuronal activation function, its rising slope can be inferred to become less steep and the output threshold will shift to the right. These changes are clearly different from the increase of slope steepness previously proposed (Mamelak and Hobson, 1989; Servan-Schreiber, 1990). The consequence of the dopamine-induced changes in activation function will be a decreased efficiency of both "signal" and "noise". However, the sigmoid shape of the activation curve also implies that the output resulting from "noise" may be suppressed more strongly than output resulting from

FIG. 12. Reduction of excitatory and inhibitory synaptic responses by bath-applied dopamine in slices. (A) Locally-evoked EPSPs were reduced by 100 μ M dopamine in a potential range from -22 to -55 mV. Using a microelectrode filling solution containing 3 M CsCl in order to block rectifying currents in the depolarized range, DC currents were injected into the cell to adjust the membrane potential to the values given on the right. The modulatory effect was reversible. Bicuculline (25 μ M) was present to block the GABA_A-receptor mediated IPSP. Pharmacological experiments revealed that the modulation shown here is largely mediated by D1 receptors. (B) In a different slice, fornix stimulation elicited a predominant IPSP, which reversed at about -73 mV in this neuron, and a small EPSP, which is manifested by the positive deflection recorded at -73 mV. Dopamine (100 μ M) attenuated the IPSP over a test range from -43 to -98 mV. Reproduced, with permission, from Pennartz *et al.* (1992a). Calibration: (A) 15 mV, 30 msec; (B) 25 mV, 30 msec.

strong input activity. Thus, our findings can still be brought in line with the signal-to-noise concept of catecholamine function. In addition, it should be noted that in a paired-pulse stimulation paradigm applied in slices, dopamine depresses a first synaptic response more strongly than a second one, when using intervals of 20–120 msec. Thus, dopamine enhances paired-pulse facilitation in the Acb *in vitro* (Pennartz *et al.*, 1992a). By the operation of this mechanism, short-lasting bouts of input activity may be transmitted more strongly than singular, loosely spaced inputs during periods of strong VTA activity, and more strongly than long-lasting bouts, which are subjected to frequency depression (Pennartz and Lopes da Silva, 1994).

However, these considerations apply to single neurons and do not take into account the within- and between-ensemble interactions postulated above. What, then, could be the specific functions of dopamine in regulating ensemble activity in the ventral

striatum, and how may these implement the “amplifying” and “behavioural switching” functions of dopamine?

Dopaminergic attenuation of feed-forward inhibition (Pennartz *et al.*, 1992a) can be inferred to disinhibit spiny projection neurons innervated by GABAergic interneurons. In the adult hippocampal formation *in vitro*, spontaneous IPSCs or IPSPs, ascribed to spontaneous activity of interneurons, are commonly encountered (Ropert *et al.*, 1990; Edwards *et al.*, 1990). Spontaneous IPSCs were also observed in cultured postnatal neurons of the caudate-putamen complex (Dubinsky, 1989) and in slices of Acb (Schneggenburger and Pennartz, unpublished observations). In the absence of strong excitatory inputs to spiny projection neurons, dopaminergic attenuation of IPSCs will disinhibit these neurons and thus enhance their firing probability during subsequent bouts of excitation. These excitatory inputs, in turn, are also attenuated by

dopamine and this action *decreases* the probability of firing. The net result of this dual action depends on both the inhibitory and excitatory load onto a particular ensemble (Pennartz *et al.*, 1992a) and may differ in various behavioural situations. Interestingly, West and Michael (1990) indeed found that the effect of VTA stimulation on unit responses evoked by olfactory or somatosensory stimuli was not unidirectional, but could promote or depress sensory-evoked responses. Although the spatial extent of interneuronal collateralization is unknown, the dopaminergic modulation of feed-forward inhibition permits to speculate that dopamine may weaken competitive interactions between neuronal ensembles (see Section 9.3 and Fig. 9B). As mentioned, dopamine is also capable of presynaptically attenuating excitatory inputs to recruited neuronal ensembles (Pennartz *et al.*, 1992a). As such, dopamine may facilitate transitions of ensemble activities in Acb and in corresponding target systems and thus allow for behavioural switching (cf. Oades, 1985; Taghzouti *et al.*, 1985; Van den Bos and Cools, 1989; Van den Bos *et al.*, 1991). The "amplifying" effects of dopamine in behaviour can also be brought in line with this notion if it is assumed that dopamine is able to attenuate excitatory inputs to some ensembles, while leaving others unaffected. Such a mechanism of selective synaptic modulation (in agreement with a presynaptic site of action, cf. Pennartz *et al.*, 1992a) may allow the activity of a particular ensemble, and thus a particular behavioural tendency, to prevail above others.

Recent electrophysiological *in vivo* experiments have revealed further aspects of dopamine function in Acb. In 6-OHDA-lesioned rats, fornix-evoked field potentials appeared to be strongly enhanced with respect to controls. Furthermore, the maximal firing rate attained by neurons exposed to iontophoretically applied L-glutamate was found to be considerably higher in 6-OHDA lesioned animals than in controls (Mulder and Lopes da Silva, unpublished observations). Although the mechanisms of field potential enhancement and changes in glutamate-induced firing patterns have not yet been elucidated, these findings suggest an additional function of dopamine in Acb. Dopamine may act as a "limiter" for transmission of information through ventral striatopallidal channels, first by placing constraints on the maximal firing rate of spiny projection neurons, and second by restraining the magnitude of excitatory responses to afferent stimulation. The possible role of dopamine in reward-mediated learning is discussed below.

9.6. ACETYLCHOLINE, ENKEPHALINS AND THE SIGNIFICANCE OF NEUROCHEMICAL COMPARTIMENTATION

As discussed by Meredith *et al.* (1993), both muscarinic and opiate receptors exert a similar synaptic modulation in the Acb as dopamine does. Cholinergic agonists were shown to attenuate EPSPs by way of muscarinic receptors (probably of the M3 subtype; Sugita *et al.*, 1991) located on glutamatergic terminals (Pennartz and Lopes da Silva, 1994). Notably, EPSP attenuation was alleviated when using stimulus rates

of 4–12 Hz, demonstrating frequency-dependent neuromodulation (Pennartz and Lopes da Silva, 1994). IPSPs were also reduced by muscarinic receptor agonists, but through a different receptor (M1; Sugita *et al.*, 1991). Acetylcholine is presumably released from large aspiny interneurons in Acb, which may have an extended spatial working range that does not obey compartmental boundaries as revealed by enkephalin staining (Meredith *et al.*, 1989). As such, cholinergic interneurons may mediate interactions between neuronal ensembles. Through activation of μ and δ receptors, enkephalins depress EPSPs and IPSPs as well (Yuan *et al.*, 1992). Thus, cholinergic, enkephalinergic and dopaminergic synapses share at least some synaptic modulatory actions in Acb that are relevant to understanding its network functions.

At this point it is interesting to reconsider the heterogeneous distribution of dopamine-, ChAT and enkephalin-immunoreactivity across the shell and core of Acb. The neurochemical compartments referred to in Section 7 are generally in register with specific afferent/efferent relationships. If one accepts the assumption that the intensity of immunoreactive staining is directly or indirectly linked to the modulation strength exerted by a particular neuromodulator, neurochemical compartmentation implies a *differential modulation* of inputs and intrinsic processing across different ensembles. For instance, ensembles in the caudomedial Acb, specialized in processing autonomous information, may have different requirements as to the intensity, or strength, of dopaminergic modulation than the rostromedial compartments. An important indication in favour of this concept is that D1 receptor-mediated, presynaptic modulation of limbic inputs to Acb in slices was found in the shell but not in the core (Pennartz *et al.*, 1992b). These main subregions of Acb are also characterized by a differential dopaminergic innervation, as manifested by a higher mean dopamine-IR in the shell versus core (Voorn *et al.*, 1986).

9.7. DOPAMINE AND ENKEPHALINS IN REWARD-DEPENDENT LEARNING

According to the hypothesis explained in Section 9.4, plasticity of cortical, thalamic and amygdalar synapses onto Acb neurons is proposed to mediate an enhanced coupling of a particular behavioural output to primary or secondary reinforcers. The profound impact of dopaminergic as well as opioid receptors on reward-dependent learning has been extensively reviewed elsewhere (Koob and Bloom, 1988; Wickens, 1990; Beninger, 1991; Le Moal and Simon, 1991; Wise and Hoffman, 1992; Koob, 1992; Di Chiara and North, 1992). As pointed out by Le Moal and Simon (1991), the role of the mesoaccumbens dopamine system in reward-dependent learning presently risks to be over-emphasized in comparison to other brain areas. Nevertheless, electrical self-stimulation along the VTA-accumbens pathway is recognized to be particularly reproducible and effective, and the evidence implicating dopamine in paradigms using intracranial self-administration of psychostimulants is strong (Koob and Bloom, 1988; Stellar and Corbett, 1989; Wise and Hoffman, 1992; Koob, 1992). Thus,

within the framework of the present hypothesis, we should at least attempt to explain how dopamine and enkephalins may contribute to the many varieties of reward-dependent learning.

Findings presented by Pennartz *et al.* (1993) indicate a lack of specific dopaminergic modulation of LTP/LTD induction in prefrontal-accumbens synapses, although effects on a very extended time-scale (≥ 1 hr) could not be excluded. Basically, there seem to be two ways for reconciling such a lack of specific effect with dopamine's role in behavioural reinforcement. A first consideration is that dopamine may influence synaptic plasticity through its "regular" modulatory actions. By altering the balance between the excitatory and inhibitory load on spiny projection neurons in particular ensemble states (Pennartz *et al.*, 1992a), dopamine may shift the probability of inducing LTP or LTD. In a combined electrophysiological-network modelling study, Hasselmo *et al.* (1992; Hasselmo and Bower, 1992) showed that cholinergic attenuation of intrinsic synaptic transmission in the piriform cortex during learning increased associative (i.e. Hebb-based) memory performance of the neural network. Of course, cortical and striatal intrinsic connectivity are very different, but the principle illustrated by this study is that ordinary, "reversible" neuromodulation may strongly affect long-term adaptations of neuronal ensembles. This principle is likely to apply to many ~~brain areas characterized by different connectivities~~ and forms of plasticity, but admittedly, detailed network simulations of ensembles in Acb would be necessary for proposing a more precisely defined function of dopamine in reward-dependent learning.

A second consideration is that dopamine may affect learning in Acb by influencing forms of synaptic plasticity other than LTP or LTD in afferent glutamatergic synapses, or even by modulating *non-synaptic* plasticity. In support of the latter possibility, midbrain 6-OHDA lesions generally increase levels of preprotachykinin and preproenkephalin A mRNA in the Acb and caudate-putamen complex, while decreasing substance P-IR (Young *et al.*, 1986; Gerfen *et al.*, 1991; Gerfen, 1992; Voorn and Docter, 1992). Subsequent alterations in enkephalin release are likely to have repercussions on collateral network function, output efficacy in the ventral pallidum and on learning and information storage in the striatum. As yet, it proves difficult to estimate what the exact time span of these effects on peptide synthesis is, but the possibility of postsynaptic, genome-mediated changes in reward-dependent learning is clearly present.

Similar to dopamine agonists, the opioid receptor agonists heroin, morphine and enkephalins have a strong potential to be self-administered in rats. This phenomenon forms the basis for animal models of opiate drug abuse (Olds and Williams, 1980; Goeders *et al.*, 1984; Koob and Bloom, 1988; Koob, 1992; Di Chiara and North, 1992). The rewarding action of opiates is likely to depend, at least partially, on the integrity of the ventral tegmental area and Acb. Administration of the opiate antagonist methylnaloxonium in rat Acb increased an animal's efforts to self-administer heroin (Koob and Bloom, 1988; Koob, 1992). Moreover, opioid antagonists have

been observed to block self-stimulation in Acb (Trujillo *et al.*, 1989).

Heroin self-administration largely continues after disruption of the dopaminergic innervation of Acb (Pettit *et al.*, 1984; Koob and Bloom, 1988; Koob, 1992; see, however, Di Chiara and North, 1992), suggesting that the rewarding effects of opiates are only partially contingent upon mesolimbic dopamine release. Importantly, both cocaine and heroin self-administration are disrupted after cell body lesions in the Acb (Zito *et al.*, 1985), indicating a *common target site* of both opiates and psychostimulants in Acb. In this context it is striking to note that both dopamine and μ and δ opiate receptors agonists depress EPSPs as well as IPSPs in the shell of Acb by a presynaptic mechanism (Pennartz *et al.*, 1992a; Yuan *et al.*, 1992). Although the precise consequences of this dual action in terms of network functions remain to be defined (Section 9.5), the great similarities in electrophysiological action suggest a common physiological substrate that may contribute to opiate as well as to psychostimulant (i.e. cocaine, amphetamine) addiction.

However, the similarity in the synaptic modulatory actions of dopamine and opioid receptor agonists is unlikely to be *sufficient* to account for their addictive properties. Muscarinic agonists exert similar EPSP- and IPSP-attenuating effects as dopamine and opioid receptor agonists (Sugita *et al.*, 1991; Pennartz and Lopes da Silva, 1994), ~~but do not have similar~~ addictive properties. Indeed, chronic administration of cocaine and opiates in the Acb has been reported to induce various additional and often long-lasting changes in second messenger cascades (i.e. G-protein subunits, adenylate cyclase and cyclic AMP dependent protein kinase, phosphorylation of tyrosine hydroxylase; Nestler, 1992). Furthermore, long term effects of cocaine in the Acb include activation of immediate early genes such as *c-fos*, *c-jun* and *zif/268* (Graybiel *et al.*, 1990; Nestler, 1992) and an altered control of gene transcription, as reflected by a long-term increase in AP1-binding activity in Acb (Hope *et al.*, 1992). In conclusion, a common basis of psychostimulant and opiate addiction may be constituted by a combination of similar electrophysiological actions and similar influences on intracellular signal transduction pathways and regulation of gene expression.

10. CONCLUDING REMARKS

The necessity to include assumptions in many aspects of the present hypothesis underlines its heuristic character. Clearly, more experiments and theoretical refinements are required to lend our hypothesis the status of a complete theory. Evidence supporting the existence of distinct neuronal ensembles has been raised in Sections 4–8, but an important approach for further testing this assumption is the combination of electrophysiology and behavioural observation, investigating unit recordings in freely moving animals in relation to detailed analysis of behavioural acts. New insights from this type of study are beginning to emerge (Henriksen *et al.*, 1992; Callaway and Henriksen, 1992; Lavoie and Mizumori, 1992; Woodward *et al.*, 1992; Schultz *et al.*,

1992). Particularly in the monkey putamen, unit recordings have been correlated to components of behavioural patterns, such as limb movements, with success (Alexander *et al.*, 1990; Alexander and Crutcher, 1990). Albeit that these recordings have not yet identified unit activity as encoding a particular type of sensorimotor information with certainty, they have at least provided evidence for the existence of spatially and functionally segregated clusters of neurons (DeLong *et al.*, 1984; Alexander *et al.*, 1990; Alexander and Crutcher, 1990). This approach may be complemented with pharmacological studies using micro-injection of drugs in small sectors of striatal tissue. The behavioural effects of such microinjections may then be correlated to particular anatomical subterritories on the basis of histological examination and immunohistochemical counterstaining.

Our considerations on the functions of intrinsic striatal circuits were accompanied by repeated cautionary remarks, but hopefully some of these can be removed over the next decade. In cellular electrophysiology, an important point for future investigation would be to examine the hypothesized dopaminergic modulation of lateral inhibition in dual intracellular or patch-clamp recordings. Furthermore, the physiological mechanism underlying dopamine- and opiate receptor involvement in reward-dependent learning remains enigmatic and calls for intensified efforts at the research front of synaptic plasticity, including genome-mediated changes in neurotransmission.

In neuroanatomy, parallel organization has been recognized to be a cardinal feature of corticostriatal processing. Specific testing of the present hypothesis, however, will depend especially on ultrastructural and electrophysiological studies examining to what extent functionally coupled cortical, thalamic and amygdalar areas converge onto common ensembles of neurons in Acb, or even onto single neurons. Equally important is a combined anatomical-behavioural approach to the unsolved problem of amygdalar-hippocampal antagonism in locomotion. In the field of local striatal circuitry, much remains to be learned from anatomy about the putative distinction between short- and long-range inhibition. Ongoing efforts in pharmacological research are likely to supplement the existing set of neurotoxins such as 6-OHDA with specific probes for investigating the physiological and behavioural role of e.g. GABAergic and cholinergic interneurons in the striatum. Hopefully, this integrated and multidisciplinary approach will make large-scale computer simulations of striatal functioning feasible before the turn of the century.

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