Functions of the dopaminergic innervation of the nucleus accumbens

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Two different current views hold that the mesolimbic dopaminergic projection to the nucleus accumbens mediates (1) the behavioral effects of reward or positive incentive motivation and (2) the cognitive functions that go awry in acute schizophrenia. These two views are difficult to integrate with each other. The former view fits better with the established role that the nucleus accumbens plays in the motor programming circuitry of the basal ganglia; but it fits poorly with evidence that dopamine release is provoked in the nucleus accumbens not only by rewarding, but also by aversive, stimuli. We review evidence, especially from experiments using the prepulse and latent inhibition paradigms, consistent with a role for the mesolimbic dopaminergic pathway in the cognitive dysfunctions of schizophrenia. We also propose a new model for the functions of this pathway which draws on recent evidence that the nucleus accumbens has outputs to perceptual as well as motor systems. The model is able in principle to account for the data sets that support both major current views of the functions of the mesolimbic dopaminergic system. It has not yet received support, however, from direct experimental tests.

Current Views of

Mesolimbic Dopaminergic Function

The literature on the behavioral functions of the nucleus accumbens is so intimately intertwined with that on the functions of the ascending (mesolimbic) dopaminergic projection to the nucleus accumbens, originating in nucleus A10 in the ventral tegmental area, that it is difficult to discuss the one without the other. Our own work in this field has focused largely on the role played by dopamine release in the nucleus accumbens. We shall therefore structure this review around that theme.

There are two widely received views about the mesolimbic dopaminergic projection—the one, that it mediates the behavioral effects of reward or positive incentive motivation (Depue & Collins, 1999; Schultz, Dayan, & Montague, 1997); and the other, that it is in some way involved in the cognitive functions that go awry in acute schizophrenia (J. A. Gray, Feldon, Rawlins, Hemsley, & Smith, 1991; Weiner, 1990). Unfortunately, although each of these hypotheses has substantial evidence in its support,

they are not easily compatible with one another. This incompatibility can be stated simply as follows: (1) the “schizophrenia” hypothesis postulates excessive dopaminergic transmission in the nucleus accumbens in acutely psychotic patients; (2) on the “reward” hypothesis, such heightened transmission should give rise to excessive sensitivity to reward; (3) excessive sensitivity to reward is not part of the spectrum of schizophrenic symptoms; (4) the nature of these symptoms suggests, rather, dysfunction in processes such as stimulus selection or cognitive inhibition (Hemsley, 1987); (5) there is no apparent close relation of these processes to the actions of reward. Thus, without radical revision of at least one of these two views of the functions of the mesolimbic dopaminergic projection, both cannot be right.

Of the two views, the one with the broadest acceptance is the reward hypothesis. A virtue of this hypothesis is that it fits well with the central role that the nucleus accumbens plays in the motor systems of the basal ganglia (of which, of course, it constitutes one of the key nuclei; Swerdlow & Koob, 1987). The concept that best provides this fit is that of incentive motivation (Depue & Collins, 1999; J. A. Gray, 1975). Within this framework, activation of the mesolimbic dopaminergic system forms part of the chain of neural events that underlies the running-off of an action plan directed to the attainment of a positively reinforcing goal (J. A. Gray, 1994). Phenomena consistent with this view include, for example, the close association between activation of accumbens dopaminergic transmission, on the one hand, and, on the other, forward

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locomotion accompanied by exploratory behavior such as sniffing (Kelly, Seviour, & Iverson, 1975) or behavioral responses to conditioned positive incentive stimuli (Le Moal & Simon, 1991; Robbins, Cador, Taylor, & Everitt, 1989).

The reward hypothesis of mesolimbic dopamine function is currently receiving particularly strong attention in the context of studies of drug addiction. The major plank linking the mesolimbic dopaminergic projection to drugs of abuse is that these all appear to cause release of dopamine in the nucleus accumbens. This generalization holds for heroin, cocaine, amphetamine, ethanol, nicotine, and cannabis (see, e.g., Di Chiara, Acquas, & Carboni, 1992; Di Chiara & Imperato, 1988; Pontieri, Tanda, & Di Chiara, 1995). Coupled with evidence that more conventional rewarded behavior, such as the seeking of food or water, is also associated with dopamine release in the nucleus accumbens and with the firing of dopaminergic neurons in the ventral tegmental area (Le Moal & Simon, 1991; Schultz et al., 1997), these data have given rise to a wide-spread belief that the addictive properties of drugs of abuse arise because, as it were, they hijack the normal neural route by which rewards exert their behaviorally reinforcing effects (Wise, 1996). This view is now so entrenched that the capacity to release dopamine in the nucleus accumbens has come to be taken as virtual proof that a compound *is* indeed addictive (see, e.g., Pontieri, Tanda, Orzi, & Di Chiara, 1996).

However, despite the wide acceptance of the reward hypothesis of mesolimbic dopamine function, and despite its substantial evidential base (of which we have indicated here only a few salient features), it has been clear for many years that this hypothesis cannot be correct. There is a simple but strong reason for this assertion. It is true that dopamine release in the nucleus accumbens is elicited by biologically clear-cut rewards such as food or water, as well as by stimuli that have become associated, through Pavlovian conditioning, with such rewards (for a review, see Salamone, Cousins, & Snyder, 1997). However, accumbens dopamine release is *also* elicited by stimuli that can by no stretch of the imagination be regarded as rewarding, including a variety of forms of stress, that universally used experimental *punishment*, electric footshock, and stimuli associated by Pavlovian conditioning with footshock (Besson & Louillot, 1995; Salamone et al., 1997; Saulskaya & Marsden, 1995; Young, Joseph, & J. A. Gray, 1993). The reward hypothesis has survived these clearly contrary data only because those who espouse it usually ignore them.

The hypothesis that links mesolimbic dopaminergic function with the cognitive processes that are dysfunctional in schizophrenia, however, also suffers major problems. First, as already indicated, it fits badly with the data that support a role for this system in reward processes. Second, it also apparently fits badly with the role that the nucleus accumbens has been shown to play in motor behavior. Although disordered motor function figures to some degree in the symptomatology of schizophrenia, it

is not a prominent feature. Furthermore, this motor dysfunction tends to take the form of repetitive stereotyped movements, suggestive of excessive dopaminergic transmission in the dorsal rather than the ventral (accumbal) striatum (Kelly et al., 1975). Thus, if the major role of the mesolimbic dopaminergic projection is concerned with positively reinforced forward locomotion, it is difficult to see how dysfunction in this projection could readily give rise to the cognitive aberrations characteristic of schizophrenia. This difficulty may, however, be more apparent than real. As pointed out by an anonymous referee, "locomotor activity in rats involves very complex strategies that can be shown to mimic aspects of human cognitive structure using mathematical models." It may be the case, therefore, that the effects of dopaminergic manipulation of rodent locomotor behavior are homologous to changes in human cognitive function of the kind observed in acute schizophrenia. This possibility warrants explicit experimental attention.

In recent years, however, a different line of research has come to offer strong support for the schizophrenia hypothesis. This research has taken as its starting point theory and data about schizophrenia, in order to devise experimental paradigms in which, it is predicted, the mesolimbic dopaminergic system will play a specified role. There are, in fact, two such lines of research: the one, concerned with prepulse inhibition; the other, with latent inhibition.

Prepulse Inhibition

Prepulse inhibition of the startle reflex, a cross-species phenomenon, refers to a reduction in the response to an intense, startling stimulus (pulse) if this is preceded shortly (30–100 msec) by a nonstartling stimulus of subthreshold intensity (prepulse) (Graham, 1975). The paradigms most commonly used to demonstrate this phenomenon use a strong noise burst as the pulse and a weak noise as the prepulse, both over a continuous background noise. The startle response is usually indexed in the rat as the displacement of a stabilimeter in response to the acoustic stimuli; in human beings, it is easily and reliably measured electromyographically as the eyeblink response. Prepulse inhibition is expressed as the reduction in response amplitude on prepulse+pulse trials as compared with the amplitude over pulse-alone trials. Despite different methods of measurement, prepulse inhibition shows similar sensitivity to stimulus parameters in rats and human beings (Swerdlow, Braff, Taaid, & Geyer, 1994). Both animal and human subjects display a threshold range for acoustic startle gating at a prepulse intensity approximately 4 dB above background noise. Prepulse inhibition is a similar positive function of prepulse intensity across species and over a wide range of prepulse intensities (2–17 dB). However, sex effects are observed in human but not animal subjects, with women showing less prepulse inhibition than men (Swerdlow, Auerbach, et al., 1993).

Prepulse inhibition is usually thought to reflect a process, that of the filtering or gating of sensory information,

which is protective of early processing of the prepulse (Geyer, Swerdlow, Mansbach, & Braff, 1990). However, the precise relationship between prepulse inhibition and sensory gating has not yet been established, although there is evidence to suggest that the effect, at least in part, is mediated by automatic as distinct from controlled processing (Schneider & Shiffrin, 1977). For example, prepulse inhibition occurs in sleeping human adults (Silverstein, Graham, & Calloway, 1980). This is an important issue, since the mechanism by which a weak prepulse attenuates the response to the strong pulse may be the same mechanism as that which underlies the gating of sensory input in general, given that subnormal prepulse inhibition is observed in a number of neuropsychiatric disorders, including schizophrenia (Braff, Grillon, & Geyer, 1992; Braff et al., 1978; Grillon, Ameli, Charney, Krystal, & Braff, 1992; for a review, see Swerdlow, Caine, Braff, & Geyer, 1992), Huntington's disease (Swerdlow et al., 1995), obsessive compulsive disorder (Swerdlow, Benbow, Zisook, Geyer, & Braff, 1993), and Tourette's syndrome (Castellanos et al., 1996), all of which are characterized by an inability to suppress intrusive sensory, motor, or cognitive information.

The possible relevance of prepulse inhibition to schizophrenia was first tested by Braff et al. (1978). These authors reasoned that deficiencies in the early stages of information processing in schizophrenia should give rise to information overload and thus should cause subnormal prepulse inhibition in this population. In support of this hypothesis, they observed reduced prepulse inhibition in schizophrenic patients, as compared with normal controls, and interpreted this effect as reflecting impaired inhibitory processes that predispose schizophrenic patients to sensory overload, cognitive fragmentation, and thought disorder. Consistent with this interpretation, a number of subsequent studies (Bolino et al., 1994; Braff et al., 1992; Grillon et al., 1992; for a review, see Swerdlow et al., 1992) have not only replicated the initial finding of reduced prepulse inhibition in schizophrenia, but also shown that impaired prepulse inhibition is associated with thought disorder (Perry & Braff, 1994), poor performance on the Wisconsin Card Sorting Test (Butler, Jenkins, Geyer, & Braff, 1991), and increased distractibility (Karper et al., 1996). Moreover, subnormal prepulse inhibition has been observed in individuals who are supposed to be at the "boundaries of schizophrenia," such as those with schizotypal personality disorder (Cadenhead, Geyer, & Braff, 1993) or those scoring high on psychometric measures of psychosis-proneness (Kumari, Toone, & Gray, 1997; Simons & Giardina, 1992). The control of prepulse inhibition in the rat is thought to be discharged by widespread, interacting limbic and mesolimbic-cortico-striato-pallido-thalamic circuits (Swerdlow et al., 1992); and disturbances in this circuitry have been implicated in the pathophysiology of schizophrenia (for a review, see Swerdlow et al., 1994).

The findings of reduced prepulse inhibition in schizophrenic patients and related disorders have prompted

various independent research groups to examine the effects of dopaminergic manipulations on prepulse inhibition of the acoustic startle in experimental animals, yielding data consistent both with the general hypothesis (Carlsson, 1988) that postulates dopaminergic hyperactivity as underlying the positive (Crow, 1980) symptoms of schizophrenia and with the criticality of the nucleus accumbens as the site of this hyperactivity. Major findings that have emerged from this line of research are as follows:

1. Systemic administration of either the indirect dopamine agonist amphetamine (Mansbach, Brooks, Sanner, & Stevin, 1998; Mansbach, Geyer, & Braff, 1988; Ott & Mandel, 1995; Zhang, Engel, Soderpalm, & Svensson, 1998) or the direct agonist apomorphine (Campeau & Davis, 1995; Depoortere, Perrault, & Sanger, 1997; Mansbach et al., 1998; Mansbach et al., 1988; Swerdlow & Geyer, 1993; Varty & Higgins, 1995) disrupts prepulse inhibition. These observations are consistent with both the general dopamine hypothesis of schizophrenia and the evidence of a psychotomimetic action of amphetamine in human beings (Meltzer & Stahl, 1976).

2. Disruption of prepulse inhibition by apomorphine is reversed by antipsychotic drugs, such as haloperidol, raclopride, risperidone (Varty & Higgins, 1995), or clozapine (Swerdlow & Geyer, 1993).

3. In addition to reversing the disruption of prepulse inhibition by apomorphine, haloperidol enhances prepulse inhibition when administered on its own (Swerdlow & Geyer, 1993) with weak prepulses (1–5 dB above the background).

4. Apomorphine, at low doses that have no effects in control animals, disrupts prepulse inhibition in rats with supersensitive nucleus accumbens dopamine receptors following intra-accumbal infusion of 6-hydroxydopamine (Swerdlow, Braff, Geyer, & Koob, 1986). This effect is strongest on prepulses delivered with a 60-msec prepulse-to-pulse interval, though it is also evident with prepulses delivered at 120-msec and 480-msec intervals. A similar effect of apomorphine on prepulse inhibition is seen in rats with 6-hydroxydopamine lesions in the substantia nigra, though it is most evident in this case on prepulses delivered at a 120-msec prepulse-to-pulse interval (Swerdlow et al., 1986).

5. 6-Hydroxydopamine lesions of the nucleus accumbens reverse the loss of prepulse inhibition caused by systemic amphetamine (Swerdlow et al., 1986; Swerdlow, Mansbach, et al., 1990).

6. Electrolytic lesions of the central nucleus accumbens, as well as lesions that predominantly damage either the nucleus accumbens shell or core, disrupt prepulse inhibition (Kodsi & Swerdlow, 1997).

7. Prepulse inhibition is decreased in a dose-dependent manner by direct infusion of dopamine into the nucleus accumbens (Leon, Reijmers, Vanderheyden, & Peeters, 1995; Swerdlow, Braff, Masten, & Geyer, 1990; Wan & Swerdlow, 1996), and this effect is prevented by pretreatment with haloperidol (Swerdlow et al., 1994).

8. Measurement of extracellular dopamine in the nucleus accumbens by intracerebral microdialysis has shown a decrease in dopamine levels in response to an intense noise (pulse); this decrease was prevented if the pulse was preceded by a noise (prepulse) of lower intensity (Humby, Wilkinson, Robbins, & Geyer, 1996). This result is consistent with the effects on prepulse inhibition of intracerebral dopamine infusion as indicated above (7).

9. 6-Hydroxydopamine lesions of the medial prefrontal cortex, which sends efferents to the nucleus accumbens and the anteromedial striatum, *disrupt* prepulse inhibition (Bubser & Koch, 1994), acting therefore like systemic treatments that increase dopaminergic activity. This effect is viewed as reflecting increased dopamine activity in the nucleus accumbens and anteromedial striatum secondary to the loss of dopaminergic terminals in the medial prefrontal cortex.

These findings offer strong support for the hypothesis that the loss of prepulse inhibition observed in schizophrenia can be accounted for by excessive dopaminergic activity specifically in the nucleus accumbens.

Latent Inhibition

Latent inhibition (Lubow, 1973, 1989) consists in a retardation of learning about the significance of a stimulus that has previously been repeatedly presented without other consequence (*preexposure*). The phenomenon has been demonstrated in many different species, including human beings. Most commonly the paradigms used to demonstrate latent inhibition utilize Pavlovian conditioning. In the first, or preexposure, stage of the experiment, the to-be-conditioned stimulus (CS) is presented to the subject a number of times (30 or 40 in most of the experiments described below); in the second stage, it is paired in a standard Pavlovian manner with an unconditioned stimulus (UCS). Learning is measured as the strength of the conditioned response (CR) elicited by the CS during Stage 2 and/or in a third stage when the CS is presented on its own. Latent inhibition is usually measured in a between-subjects design, in which a nonpreexposed group does not receive presentations of the CS in Stage 1 but is treated identically to the preexposed group in Stages 2 and 3. It is also possible, however, to demonstrate latent inhibition in a within-subjects design comparing two CSs, both paired with the same UCS, of which only one is preexposed. In both cases, latent inhibition is demonstrated as a stronger CR in the nonpreexposed than in the preexposed condition.

The possible relevance of latent inhibition to schizophrenia was first pointed out by groups in Massachusetts (Solomon et al., 1981) and Tel Aviv (Weiner, Lubow, & Feldon, 1981). These groups both showed that latent inhibition is disrupted in the rat by systemic administration of amphetamine, the strength of conditioning in the drugged preexposed condition reaching the same level as that of both the drugged and the placebo nonpreexposed conditions. Like the similar observations with prepulse inhibition, this drug effect was seen as consistent

with both the general dopamine hypothesis of schizophrenia (Carlsson, 1988) and the evidence for a psychotomimetic action of amphetamine in human beings (Meltzer & Stahl, 1976). It was further interpreted as showing that heightened dopaminergic transmission disrupts selective attention, thus causing behavior similar to the inability to focus or sustain attention observed in the acute phase of schizophrenia (see Hemsley, 1987, for a review). The locus at which amphetamine-induced dopamine release might cause these effects was at that time uncertain, although the Massachusetts group proposed the nucleus accumbens as the critical site and advanced some evidence (since criticized; see Killcross & Robbins, 1993) in favor of this hypothesis (Solomon et al., 1981; Solomon & Staton, 1982).

Subsequent studies have strongly supported and refined these initial conclusions. The salient findings are as follows (for reviews and detailed references, see J. A. Gray, Feldon, et al., 1991; J. A. Gray, Hemsley, Feldon, N. S. Gray, & Rawlins, 1991; J. A. Gray et al., 1995; J. A. Gray, Moran, et al., 1997; Weiner, 1990; Weiner & Feldon, 1997):

1. Disruption of latent inhibition in the rat by systemic administration of indirect dopamine agonists has been repeatedly confirmed. In addition, oral amphetamine disrupts latent inhibition in human subjects.

2. The blockade of latent inhibition by indirect dopamine agonists is reversed by dopamine receptor antagonists with antipsychotic properties.

3. Under conditions in which too few CS preexposures are given for latent inhibition to occur in controls, systemic administration of dopamine receptor antagonists with antipsychotic properties potentiates latent inhibition.

4. Both the blockade of latent inhibition by indirect dopamine agonists and its potentiation by dopamine receptor antagonists are seen when drug treatment is confined to the conditioning stage (but not the preexposure stage) of the experiment. These results imply that the critical process engaged by these manipulations of dopaminergic transmission is not selective (in)attention to the CS, but the integration of previous information ("the CS is associated with no significant consequence") with new information ("the CS is associated with the UCS") current at the time of conditioning. This interpretation is consistent with Hemsley's (1987) hypothesis that the positive symptoms of schizophrenia arise from a failure to utilize past experience of environmental regularities in the control and interpretation of current information processing.

5. The majority of reported findings confirm, in agreement with predictions derived from the views initially advanced by the Massachusetts (Solomon et al., 1981) and Tel Aviv (Weiner et al., 1981) groups, that latent inhibition is disrupted in the acute stage of a schizophrenic episode in early medicated or nonmedicated schizophrenics (Baruch, Hemsley, & J. A. Gray, 1988; N. S. Gray, Hemsley, & J. A. Gray, 1992; N. S. Gray, Pilowsky, J. A. Gray, & Kerwin, 1995; Vaitl & Lipp, 1997), with, however, some contrary data (Swerdlow, Braff, Hartston, Perry, & Geyer, 1996; Williams et al., 1998). Normalization of latent in-

hibition takes place over a period of approximately 6 weeks of antipsychotic medication (Baruch et al., 1988) or 1 year without medication (N. S. Gray et al., 1995).

6. Both the blockade of latent inhibition in the rat by amphetamine and its potentiation by haloperidol have been shown to reflect actions specifically in the nucleus accumbens (J. A. Gray et al., 1995; J. A. Gray, Moran, et al., 1997).

7. Much evidence indicates a role for the hippocampal formation and entorhinal cortex in latent inhibition (J. A. Gray, Feldon, et al., 1991; J. A. Gray, Hemsley, et al., 1991; Sotty, Sandner, & Gosselin, 1996; Weiner & Feldon, 1997; Yee, Feldon, & Rawlins, 1995). This role appears to be exercised in close association with the nucleus accumbens. In this connection, recent work from Weiner's laboratory suggests differentiated roles for the core and shell subterritories of the nucleus accumbens. Specifically, Weiner and Feldon (1997) propose that (1) the mechanism responsible for switching to a newly appropriate CR resides in the accumbens core; (2) release of dopamine in the core activates this mechanism; (3) latent inhibition is mediated by signals from the hippocampal formation and entorhinal cortex to the accumbens shell, which indirectly inhibit the core switching mechanism (by activating the shell GABAergic output to nucleus A10 in the ventral tegmental area, inhibiting dopamine release in the core); and (4) disruption of latent inhibition (e.g., by amphetamine) is due to increased dopamine release in the accumbens shell, since this inhibits the shell output to A10, thus interrupting Step 3.

Taken together with the evidence from studies of prepulse inhibition, reviewed in the previous section, these data offer strong support for the schizophrenia hypothesis of mesolimbic dopamine function. Increased dopaminergic transmission in the nucleus accumbens appears to alter information processing in a manner that, in these two well-specified behavioral paradigms, closely parallels what happens in acute schizophrenia.

Importantly, the experiments on both prepulse and latent inhibition suggest that the information processing that is altered by increased accumbens dopaminergic transmission relates to the integration of *perceptual* input rather than motor output or signals of reinforcement. Prepulse inhibition appears normally to serve a sensory gating function, allowing time for the prepulse to be processed rather than its being blotted out by the following pulse. Latent inhibition similarly appears normally to serve a perceptual selection function, weakening processing of stimuli that, in the past, have been uninformative. These experiments, therefore, lead us to question the completeness of the usual view that the nucleus accumbens forms part exclusively of a motor programming system (a view that we have previously endorsed ourselves; see J. A. Gray, Feldon, et al., 1991).

Sensory Preconditioning

We are further impelled to question the completeness of the motor programming perspective on accumbens

function by results recently obtained in our laboratory when we used *in vivo* intracerebral microdialysis to measure changes in extracellular levels of dopamine in the nucleus accumbens of rats participating in a sensory preconditioning experiment.

The subject in a sensory preconditioning paradigm is exposed, in the first stage of the experiment, to a Pavlovian pairing between two stimuli (e.g., in our case, a light and a tone), neither of which has any major biologically reinforcing properties, whether rewarding or aversive. Let these stimuli be termed CS1 and CS2, with CS1 occurring in each pairing prior to CS2 (i.e., CS2 occupies the temporal locus of a UCS in the basic Pavlovian paradigm). In the second stage of the experiment, CS2 is paired in the normal Pavlovian manner with a biologically reinforcing UCS, which in our case was footshock. In the third and final stage of the experiment, each CS is presented on its own, so that its capacity to elicit a CR (which, in our case, was suppression of licking for water) can be measured. The occurrence of sensory preconditioning is demonstrated by the fact that not only CS2 (directly paired with the UCS), but also CS1 (paired directly only with CS2), comes to elicit the CR. The usual interpretation of this phenomenon is that in Stage 1, the subject forms an association between CS1 and CS2, and in Stage 2, one between CS2 and the UCS. Presentation of CS1 then elicits a representation of CS2, which in turn elicits a representation of the UCS, giving rise to the observed CR.

We had previously (Young et al., 1993) demonstrated that prior to conditioning, neither the light nor the tone used in these experiments was capable of eliciting measurable change in accumbens dopamine levels. The footshock UCS, in contrast, does elicit a marked rise in accumbens dopamine levels, confirming many previous similar reports (Salamone et al., 1997). When we paired either the light or the tone with the footshock (two pairings over a 5-min period), we observed two effects. First, during a dialysis sampling period covering the two CS-shock pairings, the increase in extracellular dopamine levels was approximately doubled over the increase observed in response to footshock alone. Second, when the conditioned CS (light or tone) was presented on its own, subsequent to the conditioning phase, it now elicited a substantial increase in accumbens dopamine levels, while no change was seen in response to the other, nonconditioned stimulus. This experiment, therefore, demonstrated stimulus-specific conditioned dopamine release in the nucleus accumbens, both during conditioning and, subsequently, in response to the CS. Furthermore, preexposure of the CS a sufficient number of times to give rise to behavioral latent inhibition also robbed it of its capacity to elicit an increase in accumbens dopamine release either during the CS-shock pairings or when the CS was subsequently presented on its own. Thus, latent inhibition of accumbens dopamine release faithfully mirrored latent inhibition at the behavioral level.

In our more recent experiment (Young, Ahier, Upton, Joseph, & J. A. Gray, 1998), we used the sensory pre-

conditioning paradigm to ask whether, in order to observe conditioned dopamine release in the nucleus accumbens, it is essential to pair a CS with a biological reinforcer. Our results show this not to be the case. In a control group in which, in Stage 1, presentations of the light and the tone were intermixed randomly, but with the same total number of presentations as were given to the sensory preconditioning group, we saw no change in accumbens dopamine levels while these presentations occurred. When the light and tone were presented in Pavlovian pairings, light predicting tone, in contrast, there was a significant increase in accumbens dopamine levels. Furthermore, subsequent presentations of the light (never directly paired with shock) gave rise to conditioned dopamine release in the group that went through the sensory preconditioning paradigm, but not in the controls given random presentations of light and tone. These results indicate, therefore, that accumbens dopamine release is sensitive to the associations between stimuli irrespective of whether the stimuli used initially elicit dopamine release (since neither the light nor the tone did this) and irrespective of whether they have biologically reinforcing properties (either rewarding or punishing).

Taken together, these results from experiments applying dialysis to the latent inhibition and sensory preconditioning paradigms suggest that the common denominator underlying the capacity of a stimulus to elicit dopamine release in the nucleus accumbens is neither its appetitive nor its aversive quality per se, but rather its *salience*, whether this derives from its innate biologically reinforcing properties (footshock, food), from its capacity to predict other biological reinforcers (either rewarding or aversive), or from its capacity simply to predict other environmental events of any kind (Joseph, Young,

& J. A. Gray, 1996; Robinson & Berridge, 1993; Young, 1993). Schmajuk, Lam, and J. A. Gray (1996) have previously developed a neural network model able to simulate a large body of data gathered in behavioral experiments on latent inhibition, which has been summarized in Lubow's (1989) book-length treatment of this topic. Within that model, the variable here called "salience" is well defined, but termed *novelty*. Elsewhere (Schmajuk, Buhusi, & J. A. Gray, 1998), we show that, by equating pharmacologically induced changes in accumbens dopamine release to changes in the value of novelty, we are able to use the model to simulate the reported effects of both dopamine agonists and antagonists on latent inhibition, as well as the interaction of these treatments with variations in either CS or UCS intensity. Applied to schizophrenia, this line of argument leads to the inference that patients suffering from this condition should experience unduly high levels of stimulus salience. This indeed is a plausible summary of much schizophrenic symptomatology (Anscombe, 1987; Hemsley, 1987).

Output From the Nucleus Accumbens to Perceptual Systems

The data and arguments adduced in the last two sections fit badly with an exclusively motor programming perspective on accumbens function. To be sure, the major connections of the nucleus accumbens do indeed appear to form part of basal ganglia motor programming circuitry (for reviews, see J. A. Gray, Feldon, et al., 1991; Swerdlow & Koob, 1987). However, there is one connection, recently described by Grace and his colleagues (Lavin & Grace, 1994; O'Donnell & Grace, 1998), which seems able to provide the output to perceptual systems that has been missing till now. This is the projection, via the ven-

Figure 1. Connections from the subiculum (Sub) and entorhinal cortex (ERC) to the nucleus accumbens (NAC) component of the basal ganglia, and from that system to the nucleus reticularis thalami (NRT) and thalamocortical sensory pathways. PFC, prefrontal cortex; DM, dorsomedial thalamic nucleus; VP, ventral pallidum; A10, dopaminergic nucleus A10 in the ventral tegmental area; GLU, GABA, DA, the neurotransmitters glutamate, gamma-aminobutyric acid, and dopamine; +, excitation; -, inhibition; I, II, III, feedback loops, the first two positive, the third negative.

tral pallidum and the nucleus reticularis thalami, to the thalamocortical sensory relay nuclei (Figure 1). Indeed, this projection appears to be exceptionally well placed to influence virtually all the ascending sensory systems destined for the neocortex. Inspection of Figure 1 reveals certain very interesting properties in the relevant circuitry. The release of dopamine in the nucleus accumbens acts via receptors belonging to the D2 receptor family to inhibit the accumbens GABAergic (inhibitory) cells that project to the ventral pallidum. Inhibition of this projection would be expected to disinhibit the further GABAergic outputs from the ventral pallidum to (1) the thalamic dorsomedial nucleus and (2) the nucleus reticularis thalami. The next stages in these two cascades are interestingly different.

As Swerdlow and Koob (1987) have emphasized, one may conceptualize much of the circuitry depicted in Figure 1 as being made up of three interconnected loops. Loop I consists of reciprocal glutamatergic excitatory connections between (1) the prefrontal plus cingulate (motor) cortices and (2) the dorsomedial thalamic nucleus. Once initiated, therefore, this loop is able to continue reverberating, thus sustaining the running of a "step" in a motor program (J. A. Gray, Feldon, et al., 1991). Loop II consists of (1) an excitatory projection from the motor cortices to the nucleus accumbens, which activates (2) the inhibitory GABAergic projection from there to the ventral pallidum, thus inhibiting (3) the further inhibitory GABAergic projection from the pallidum to the dorsomedial nucleus of the thalamus. The effect of activation of Loop II, therefore, is to protect continued activation of Loop I, thus further maintaining the running of the current step in the motor program. Finally, Loop III responds to (1) the excitatory projection from the motor cortices to the nucleus accumbens by (2) again sending an inhibitory output to the ventral pallidum which inhibits (3) the further inhibitory GABAergic projection from the pallidum to the dopaminergic cells of nucleus A10, thus disinhibiting (4) the dopaminergic projection to the nucleus accumbens, which finally brings activity in all three loops to a halt by (5) inhibiting the accumbens output to the pallidum, followed by (6) disinhibition of the pallidal inhibitory projection to the dorsomedial nucleus of the thalamus. Note that, according to Swerdlow and Koob's model therefore, the action of dopamine in the nucleus accumbens is not to excite motor activity, but to bring the current step in the motor program to an end, thus allowing passage to the next step (J. A. Gray, Feldon, et al., 1991). Weiner (1991) added to this model the proposal that the passage to the next step in the motor program is accomplished also by the output from the nucleus accumbens to the dopaminergic cells of the substantia nigra, but we shall not follow this part of the circuitry further here.

The pathway that connects these three loops to thalamic sensory processing systems differs from the pathway via the dorsomedial thalamic nucleus in one intriguing

respect: There is an extra synapse within the thalamus. The ventral pallidal GABAergic projection goes in one step to the dorsomedial nucleus before this projects to frontal motor systems in the neocortex, but there is an additional step via the nucleus reticularis thalami before the pallidal output reaches the thalamic nuclei that project to posterior sensory cortical regions. Furthermore, since the projection from the nucleus reticularis is itself GABAergic (E. G. Jones, 1975), this extra step implies that when thalamic excitatory input to frontal cortical motor systems is switched on, thalamic excitatory input to posterior cortical sensory systems is switched off, and vice versa. The thalamic sensory relay nuclei are connected to appropriate cortical sensory processing regions by the same type of reciprocal excitatory loop that operates between the dorsomedial nucleus and frontal motor systems (Loop I in Swerdlow & Koob's, 1987, model). The GABAergic projection to these thalamic nuclei terminates presynaptically on the descending cortical fibers, so that activation of the nucleus reticularis output is able to bring these excitatory reverberatory loops to a halt.

The overall arrangement depicted in Figure 1 and outlined above is well placed to allow rapid alternation between short periods of time in which (1) the next step in the motor program is organized via the dorsomedial thalamic input to frontal cortical systems and (2) sensory input is processed via the thalamocortical relay nuclei. Considerations advanced elsewhere (J. A. Gray, Feldon, et al., 1991) suggest that the sum of one each of these types of processing periods would take about 100 msec; that is, organization of a step in the motor program would take about 50 msec, and processing of the following epoch of sensory information, similarly about 50 msec. J. A. Gray (1994) has considered how such successive motor steps and the ensuing sensory input need to be integrated in the service of a general goal-directed motor program. Note that, in general agreement with hypotheses proposed by Oades (1985) and Weiner (1990; Weiner & Feldon, 1997) as well as Swerdlow and Koob (1987), dopamine release in the nucleus accumbens plays a key role in this model in switching a motor program on from one step to the next. It does this by terminating the reverberating activity in one coordinated set of neurons and allowing selection (by way of cortical, hippocampal, and amygdalar input to both dorsal and ventral striata; see J. A. Gray, 1994; J. A. Gray, Feldon, et al., 1991; J. A. Gray, Hemsley, et al., 1991; O'Donnell & Grace, 1995, 1998) of the next such set of activated neurons.

Application of the Model

The model outlined above allots to dopaminergic transmission within the nucleus accumbens (and therefore to the nucleus accumbens itself) an equally prominent role in relation to both motor and sensory processing. In consequence, we believe, it can be applied with some success to data sets that otherwise, as we have seen, appear to be in conflict with one another.

The model continues to treat the nucleus accumbens as a nodal structure within an overall motor programming system and indeed is very much in keeping with the seminal view, advanced by Mogenson, Jones, and Yim (1980), of the nucleus accumbens as an interface between the limbic system (source of motivation) and the basal ganglia (organizer of action). It does not, however, treat dopamine release within the nucleus accumbens as a simple "signal of reward" or as directly giving rise to the euphoria reported by users of addictive substances. Nonetheless, the model is consistent with much of the evidence seen as supporting such a "reward" hypothesis—such as, for example, the loss of appetitively motivated goal-directed behavior after lesions of the dopaminergic innervation of the nucleus accumbens, activation of dopaminergic cells in the ventral tegmental area by appetitive incentive stimuli, the association of forward locomotion with dopaminergic activation, and so forth (for reviews of the relevant data sets, see Depue & Collins, 1999; Le Moal & Simon, 1991). But the model is also consistent with the fact that aversive, as well as appetitive, stimuli, both conditioned and unconditioned, activate the mesolimbic dopaminergic system (Salamone et al., 1997; Young et al., 1993). For the sensory processing machinery of a general goal-directed system to serve its functions properly, it is essential that it should keep track, not only of appetitive goals, but also of actual or potential impediments to the attainment of these goals (J. A. Gray, 1994; J. A. Gray & McNaughton, 1996). All these environmental inputs and the associative links in which they are embedded (even those not involving innate biological reinforcers, as in sensory preconditioning), therefore, need to possess a degree of stimulus salience sufficient to activate the enhanced sensory processing that is postulated to derive from dopamine release in the nucleus accumbens and the onward connections via the nucleus reticularis thalami (Figure 1).

Within the model, the fact that drugs of abuse tend, perhaps universally, to elicit dopamine release in the nucleus accumbens (Di Chiara et al., 1992; Di Chiara & Imperato, 1988; Pontieri et al., 1995) can be interpreted in two complementary ways. Accumbens dopamine release should give rise simultaneously to (1) inhibition of the current step in the motor program and (2) selection of goal-relevant stimuli for processing. Excessive and/or prolonged dopamine release would be expected, therefore, to (1) widen this inhibition, preventing the normal passage to the next step in the motor program, and (2) maintain the current selection of stimuli for intensive processing (Joseph et al., 1996). In this light, the drug abuser, as it were, gets stuck at a particular point in the motor program of self-administration of the abused substance and experiences the stimuli associated with that point as being of overwhelming interest. This hypothesis is consistent both with the highly ritualized manner in which drug abusers tend to self-administer their preferred substances

and with the emphasis often found in their self-reports on enhanced perceptual experience.

Application of the model to the database supporting the schizophrenia hypothesis of mesolimbic dopaminergic function is relatively straightforward. This is not surprising, since it was in order to account for these data that the model was constructed (J. A. Gray, 1998). The most central data for this construction concern latent inhibition. It is supposed that preexposure reduces the salience of the CS below a threshold for rapid entry into associative learning—hence the retardation of conditioning that constitutes the phenomenon of latent inhibition. An increase in dopaminergic transmission at the time of conditioning to the preexposed CS is then interpreted as acting via the nucleus accumbens–ventral pallidum–nucleus reticularis–thalamocortical sensory relay nuclei route to provide an additional boost of sensory processing that allows that CS to rise after all above the critical threshold. In relation to prepulse inhibition, enhanced dopaminergic transmission in the nucleus accumbens can be interpreted in a broadly similar manner as providing an additional boost to sensory processing of the pulse, overcoming the inhibitory effects on such processing of the prepulse. More generally, the acute stage of schizophrenic psychosis can be seen as one in which excessive dopaminergic activity in the nucleus accumbens (perhaps occurring, not directly, but in consequence of aberrant input to the nucleus accumbens from the hippocampal system; see J. A. Gray, Feldon, et al., 1991) enhances sensory processing with a variety of dysfunctional consequences. These are likely to include the capturing of attention by apparently salient stimuli of no substantive significance, and excessive broadening of associative links owing to loss of both latent inhibition and the closely related Kamin blocking effect (J. A. Gray, Feldon, et al., 1991; S. H. Jones, J. A. Gray, & Hemsley, 1992) and perhaps also to overextension of sensory preconditioning (J. A. Gray, 1998).

Some of the aberrations of schizophrenic cognitive function that we have attempted to explain in terms of the model in Figure 1 have previously been described as reflecting a breakdown in the normal boundaries between unconscious ("automatic") and conscious ("controlled") processing in schizophrenia (Frith, 1979; Schneider & Shiffrin, 1977). Viewed in this light, the concept of a "threshold for rapid entry into associative learning" utilized in the preceding paragraph becomes another way of talking about the boundary between unconscious and conscious processing. We have considered elsewhere the possibility that our model can be usefully discussed in these terms (J. A. Gray, 1995, 1998; J. A. Gray, Buhusi, & Schmajuk, 1997).

The different data sets relevant to mesolimbic dopamine function briefly considered above are each substantial, as can readily be verified by consulting the review articles that we have cited. Thus, any final model of accumbens function will need to encompass them all. The

model that we have outlined here appears at least in principle to be able to do this; but if it is to be accepted, it first stands in need of extensive direct experimental testing.

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