Integrating Schizophrenia

by Jeffrey A. Gray

Abstract

A neuropsychological theory of the positive symptoms of schizophrenia proposed by J.A. Gray et al. is reviewed in light of subsequent evidence from studies of latent inhibition in clinical populations, healthy volunteers, and rats. It is clear that disrupted latent inhibition is associated with psychosis, but it is uncertain whether this is a state or a trait marker. Much evidence indicates that a similar disruption in latent inhibition can be provoked in rats by excess release of dopamine in the nucleus accumbens, and conversely, that potentiation of latent inhibition occurs when dopaminergic transmission is blocked in this structure. The projection from the hippocampal system to the nucleus accumbens also plays a role in latent inhibition. The theory, therefore, is broadly supported by recent findings. The resulting model of schizophrenia is discussed in relation to the contents of consciousness, positive psychotic symptoms, and alternative theories.

Key words: Latent inhibition, nucleus accumbens, dopamine, positive psychotic symptoms.


The 1991 Theory

The neuropsychological theory of schizophrenia that guides our current research in this field was developed in collaboration with groups in Tel Aviv and Oxford (Weiner 1990; J.A. Gray et al. 1991a, 1991b). The theory is intended to span the complete range of explanation from a malfunction in the brain to the psychological symptoms of the condition, although it is limited to positive symptoms (Crow 1980). It integrates four levels of description (figure 1): (1) A structural abnormality in the brain (in the limbic forebrain, affecting the hippocampal formation, amygdala, and temporal and frontal neocortex) causes (2) a functional neurochemical abnormality in the brain (specifically hyperactivity of transmission in the ascending mesolimbic dopaminergic pathway). (3) This abnormality, in turn, disrupts a cognitive process (the integration of past regularities of experience with current stimulus recognition, learning, and action), and so produces (4) the positive symptoms characteristic of acute psychosis. (For a description of a number of these symptoms, see the section on applying the model to symptoms. See also figure 2 [from Hemsley 1994], which shows how positive symptoms can be derived from the postulates of the psychological component of the overall neuropsychological model of schizophrenia that my colleagues and I have been developing.)

At the neuroanatomical level, the theory draws upon evidence (for detailed references throughout, see J.A. Gray et al. 1991a, unless other references are given) from the postmortem schizophrenic brain that shows pathology in the limbic forebrain. At the neurochemical level, the theory draws upon evidence from studies of psychotomimetic or antipsychotic drugs indicating a relationship between dopaminergic transmission and the positive symptoms of schizophrenia. The third and fourth levels, linking symptoms to underlying cognitive processes, rest upon Hemsley’s (1987, 1993) hypothesis, and its supporting arguments, that positive psychotic symptoms derive from an impairment in the ability to use stored past regularities of experience to aid in the interpretation of elements in current information processing. Integration across these levels of the theory is obtained by a proposed correspondence (figure 3) among the stored regularities and current information processing of Hemsley’s hypothesis (figure 3A); the links (figure 3B, 3C) between the subicular area (origin of the major output from the hippocampal formation) and the nucleus accumbens, a major gateway to the basal ganglia and recipient of a dopaminergic projection that ascends in the mesolimbic pathway from nucleus A 10 in the ventral tegmental area; and input from a comparator system (J.A. Gray 1982a, 1982b) to a motor programming system (figure 3D).

Reprint requests should be sent to Prof. J.A. Gray, Dept. of Psychology, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, United Kingdom.
The proposed correspondence relies on several assumptions:

1. that the limbic forebrain uses stored regularities of previous input to compute a prediction of the next (time being divided into quanta of approximately 0.1 second) state of the perceptual world, given the subject’s current motor program;
2. that the limbic forebrain compares this prediction to the actual state of the world in the following time quantum;
3. that the outcome of this matching operation is transmitted via the projection from the subiculum to the nucleus accumbens (operations 1–3 constitute the comparator system described in detail by J.A. Gray 1982a, 1982b; J.A. Gray et al. 1991a);
4. that this nucleus forms part of a motor programming system in the basal ganglia (Swedo and Koob 1987; Gray et al. 1991a) and that this programming system uses a “match” message from the subiculum to continue the current motor program and a “mismatch” message (“something novel/unexpected has occurred”) to interrupt it;
5. that schizophrenia disrupts the normal input from the subiculum to the nucleus accumbens leading neurochemically to a functional imbalance equivalent to hyperactivity in the mesolimbic dopaminergic pathway and psychologically to an overoccurrence of apparently novel events;
6. that these apparently novel events give rise to positive psychotic symptoms, as considered in detail by Hemsley (1987, 1993, 1994) and reconsidered here in light of subsequent evidence, much of it gathered in studies of the phenomenon of latent inhibition (LI).

LI

If a stimulus is repeatedly presented without other consequence (preexposure) and is subsequently used as the conditioned stimulus (CS) in a standard Pavlovian conditioning paradigm, the preexposed CS develops a weaker association with the unconditional stimulus (US), as measured by the strength of the ensuing conditioned response (CR), than does a nonpreexposed CS. LI is the difference between the CRs evoked by preexposed and nonpreexposed CSs. Most often, different groups of subjects are conditioned with preexposed and nonpreexposed CSs. In that case, LI is measured as the difference in the efficacy of conditioning between the preexposed and nonpreexposed groups. This between-subjects approach may, however, be complemented by within-subject designs, in which all subjects receive both CSs, and LI is measured as the difference in the efficacy of conditioning between the two (Killcross and Robbins 1993; N.S. Gray et al. 1995). Unless otherwise stated, all experiments described here used between-subject designs.

First described by Lubow and Moore (1959), LI has subsequently been the subject of considerable investigation (Lubow 1989) in many species, including humans; many of the resulting data have recently been captured in a neural network model (Schmajuk et al. 1996). The experiments from our own laboratory, reviewed below, have used both rats and human subjects. With rats, we typically assess LI using an off-the-baseline conditioned emotional response (CER) procedure in animals licking for water (Weiner et al. 1984; Feldon and Weiner 1991a; Warburton et al. 1994). In this procedure, after initial baseline training to lick, using animals on restricted water, CS-preexposures and CS-footshock pairings are both conducted without access to water, and the CS is then presented to the rat while it is again licking. CR magnitude is measured by the degree of lick suppression during the CS. Lower licking suppression in response to the CS in the preexposed as compared to the nonpreexposed animals constitutes LI. With human subjects, our usual procedure is based on that of Ginton et al. (1975). Subjects first listen to a tape recording of nonsense syllables, with instructions to count the number of times one of them recurs. In the preexposed condition, bursts of low-intensity white noise (the CS) are randomly superimposed on the recording. Subsequently, while still listening to the tape recording, subjects are asked to predict when a counter display will be incremented; increments (the unconditional stimulus) are preceded for all subjects by the white noise CS,
and the number of trials taken to detect this contingency is the measure of conditioning. LI is shown as a larger number of trials to criterion in the preexposed condition than in the nonpreexposed condition.

The relevance of LI to schizophrenia (or, more exactly, the disruption of LI) lies in LI's resemblance to the deficit in the ability to ignore irrelevant stimuli that has been extensively documented in schizophrenia (for review, see Hemsley 1987). This resemblance was initially pointed out by groups in Massachusetts (Solomon et al 1981) and Tel Aviv (Weiner et al. 1981, 1984). Both groups reported that LI is attenuated or abolished in the...
Figure 3. Further illustration of the theory of schizophrenia proposed by J.A. Gray et al. 1991a

(A) The abnormality of cognitive processing consists of a failure to integrate past regularities of experience with the current control of perception and action. (B) A dysfunctional connection exists between the limbic forebrain and the basal ganglia. (C) The specific pathway carrying the dysfunctional connection is from the subiculum (in the limbic forebrain) to the nucleus (N.) accumbens (in the basal ganglia). (D) The computing functions thus disrupted are the passage of information from a comparator system using stored traces of past regularities (in the limbic forebrain) to a motor programming system (in the basal ganglia) controlling perception and action.

LI in Schizophrenia

For this approach to be taken seriously, however, at least two further empirical observations are essential.

First, it is necessary to show that amphetamine also blocks LI in humans. This is indeed the case, as we have reported (N.S. Gray et al. 1992b) and further replicated twice (Thornton et al. 1997; Kumari et al., unpublished data). Furthermore, as in the rat (Weiner et al. 1984, 1988), the effect of amphetamine is primarily due to increased learning in the preexposed condition and is inversely dose dependent (low doses block or attenuate LI, high doses preserve it). The reason for this inverse dose dependence of the amphetamine effect is unclear. One suggestion is that low doses may release DA more effectively in the nucleus accumbens than in the caudate putamen, the other major region of the basal ganglia to receive ascending dopaminergic afferents (Hitzemann et al. 1980; Porro et al. 1984; DiChiara et al. 1993), and that this may produce the inverse dose dependence of changes in LI (Weiner et al. 1987). Other evidence that DA release in the nucleus accumbens plays a critical role in LI or its blockade is reviewed below. As we shall see, the effects of accumbal DA release on LI also appear to depend on the degree to which such release is impulse dependent or impulse independent. Furthermore, the degree to which amphetamine-induced DA release is impulse dependent appears to involve a phenomenon akin to sensitization (Robinson and Becker 1986; Warburton et al. 1996). It is possible that these three aspects of the action of amphetamine—the inversely dose-dependent effect upon LI, the degree of impulse-dependent accumbal DA release, and sensitization—are in some way linked. For present purposes, however, the important point is that amphetamine blocks LI in both rats and human subjects and, in both cases, in an inversely dose-dependent manner.

Second, it is necessary to show that schizophrenia patients themselves show abnormal LI. Since, however, the effect of amphetamine on LI is reversed in the rat (Solomon et al. 1981; Warburton et al. 1994) by concomitant administration of DA receptor antagonists with antipsychotic properties—a finding that is, of course, itself consistent with the hypothesis that disrupted LI is a model of psychotic behavior—one would not necessarily expect to observe abnormal LI in chronic schizophrenia patients maintained on such medication. One would expect, however, to see disrupted LI in the acute stage of the illness, before neuroleptic treatment has had time—
typically 10–14 days—to exert therapeutic effects. This, indeed, is the case: LI is absent, even marginally reversed, in the first 2 weeks of a schizophrenic episode and is restored to relatively normal levels after 8 weeks of neuroleptic treatment; it is similarly restored in more chronic (> 3 months) cases (Baruch et al. 1988a; N.S. Gray et al. 1992a). As with amphetamine treatment in normal subjects, the effect of acute schizophrenia on LI is due to changes in the preexposed condition. Very importantly, acute schizophrenic patients in this condition actually learn faster than normal subjects, ruling out artefacts due, for example, to poor motivation, distraction caused by psychotic symptoms, adverse drug effects, and so on.

While these results point to a relationship between LI disruption and the early stages of a schizophrenic illness, it is not clear at present how tightly linked such disruption of LI is to positive symptoms. In general, the antipsychotic effects of neuroleptics are exerted principally against these symptoms, and, conversely, the psychotic state sometimes caused by amphetamine is characterized by positive symptoms (Meltzer and Stahl 1976). Moreover, Hemsley (1987, 1993, 1994) has argued that it is these symptoms that would arise from the kind of breakdown in normal information processing that attenuated LI represents. Our first report (Baruch et al. 1988a) of loss of LI in acute schizophrenia was consistent with this emphasis on positive symptoms, since scores on a symptom scale, the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), were positively related to this loss. However, in our second study (N.S. Gray et al. 1992a), the acute and chronic groups of medicated patients were relatively well matched for scores on the BPRS, and yet LI was absent in the former but present in the latter. This result suggests that LI is more sensitive to DA receptor blockade than are positive symptoms, and therefore reflects this pharmacological action fairly directly. This interpretation would be consistent with the fact that acute administration of neuroleptics in rats suffices to enhance LI (Feldon and Weiner 1991b; Peters and Joseph 1993) as well as to antagonize amphetamine-induced attenuation of LI (Warburton et al. 1994). However, in a further study (N.S. Gray et al. 1995), with never-medicated patients and using a within-subject LI paradigm, we found a linear relationship between duration of illness and the magnitude of the LI effect in the absence of drug treatment. LI was absent at the start of the illness, confirming our earlier results using between-group comparisons (Baruch et al. 1988a; N.S. Gray et al. 1992a), but then gradually returned to normal values, the crossover occurring at about 1 year into the episode. This result suggests that antipsychotic medication hastens normalization of LI over the course of a schizophrenic illness.

LI and Schizotypy

The data just reviewed are consistent with the hypothesis that disrupted LI is a state marker, induced either by a drug that enhances DA release or by the acute stages of a schizophrenic episode. To complicate matters further, however, there is clear evidence that the magnitude of LI is also a trait marker from four reports that normal subjects with high scores on questionnaires measuring schizotypy show significantly reduced LI relative to subjects with low schizotypy scores (Baruch et al. 1988b; Lipp and Vaitl 1992; Lubow et al. 1992; De la Casa et al. 1993). Consistent with these effects of schizotypy, we have observed that scores on one measure of this trait (Eysenck's Personality Questionnaire; Eysenck and Eysenck 1975) correlate negatively with DA D2 receptor binding in the basal ganglia, measured in vivo using single photon emission tomography (N.S. Gray et al. 1994).

The fact that LI is reduced both in the acute phase of schizophrenia (Baruch et al. 1988a; N.S. Gray et al. 1992a, 1995) and in normal subjects with high scores on questionnaire measures of schizotypy (Baruch et al. 1988b; Lipp and Vaitl 1992; Lubow et al. 1992; De la Casa et al. 1993) is consistent with a dimensional view (Claridge 1987) of psychosis, in which schizotypia represents one extreme of a continuum of susceptibility to psychosis that extends across the entire population. If this hypothesis is correct, one would expect to see behavior similar to that of normal high schizotypy scorers expressed in first-degree relatives of schizophrenia patients, since these relatives are known from epidemiological studies to carry an elevated risk of the disorder (Kendler et al. 1993). Serra (unpublished manuscript, 1995) tested this prediction in trios of subjects: a chronic schizophrenia proband, a first-degree relative with high schizotypy scores (on questionnaires, diagnostic assessment interviews, or both), and a first-degree relative with low schizotypy scores. The results did not conform to expectation. LI was absent in both first-degree relatives, due not to fast learning in the preexposed condition, but to slow learning in the nonpreexposed condition. Indeed, basic associative learning, as measured in both the LI paradigm and a second task, the Kamin blocking effect, in which schizophrenia patients are impaired (Jones et al. 1992), was extraordinarily poor in the relatives of schizophrenia patients, irrespective of their degree of schizotypy (figure 4). This pattern of results is virtually the opposite of that observed in high schizotypals drawn from the normal population, casting doubt on the dimensional view of psychosis. It suggests the possibility that the increased range of associations formed in acute schizophrenia (as in disrupted LI, as well as in symptomatology) may reflect a...
Neural Basis of Disrupted LI

The issues surrounding the clinical correlates of disrupted LI clearly require resolution. Nonetheless, the data base linking disrupted or reduced LI to the acute stage of schizophrenia and to heightened dopaminergic transmission is now sufficiently strong to warrant detailed study of the mechanisms underlying these links.

We have recently reviewed (J.A. Gray et al. 1995) the evidence implicating in LI the mesolimbic dopaminergic pathway, dopamine release in the nucleus accumbens, and the projections to the nucleus accumbens from the retro-hippocampal region.

The initial observations (Solomon et al. 1981; Weiner et al. 1981, 1984) that LI is attenuated by systemic administration of amphetamine in the rat have been extensively replicated (Weiner 1990) and extended to a second indirect DA agonist, nicotine (Joseph et al. 1993). In each case, the effect on LI is reversed by DA receptor antagonists (Solomon et al. 1981; Joseph et al. 1993; Warburton et al. 1994). In addition, a wide range of DA receptor blockers and other drugs with antipsychotic effects, given without agonist treatment, potentiate LI; that is, the drugged animals show retarded learning in the preexposed condition with too few trials for undrugged animals to show LI (see J.A. Gray et al. 1995). As with all putative drug-induced alterations in cognitive processes, there are potentially less interesting effects that could take on a cognitive mask. However, drug-induced changes in activity, generally learning capacity, or the functional impact of the US coupled with floor or ceiling effects (Killcross et al. 1994) are all more or less ruled out by the overall pattern of reported results, the design of the experiments, or both (J.A. Gray et al. 1995). The reported changes are largely due to changes in the preexposed condition; behavior in the nonpreexposed condition is either unchanged or sometimes changed in the opposite direction.

These data clearly implicate DA in LI. They do not on their own, however, elucidate which dopaminergic system...
influences LI. A number of other lines of evidence indicate specifically the mesolimbic dopaminergic projection from nucleus A 10 in the ventral tegmental area to the nucleus accumbens (J.A. Gray et al. 1995). This evidence (for references, see J.A. Gray et al. 1995) includes the following: blockade of LI by low doses of amphetamine that are considered to produce their effects primarily via the mesolimbic DA system, but not by high doses that act primarily via striatal DA mechanisms; blockade of LI by nicotine at doses that, in experiments using in vivo intracerebral microdialysis, cause DA release in the nucleus accumbens, but not in the dorsal striatum; potentiation of LI by destruction of dopaminergic terminals in the nucleus accumbens, caused by local injection of the catecholamine-specific neurotoxin 6-hydroxydopamine; potentiation of LI by local injection into the nucleus accumbens of the DA receptor blocker haloperidol; reduction of LI after electrolytic or excitotoxic lesions of the principal cells of the nucleus accumbens; and normal LI after lesions of the amygdala (Weiner et al. 1996) or striatum.

In further experiments, we have recently shown that the blockade of LI caused by systemic administration of nicotine can be prevented if accompanied by intra-accumbal administration of haloperidol (Peters et al., unpublished data). Like the other findings summarized above, this result supports the hypothesis (Solomon and Staton 1982) that blockade of LI depends on DA release in the nucleus accumbens. However, this hypothesis has been challenged by Killcross and Robbins (1993), who, unlike Solomon and Staton (1982), failed to affect LI by direct injection of amphetamine into the nucleus accumbens. A recent experiment in our laboratory has clarified the likely reasons for Killcross and Robbins’ (1993) negative results and offers further support for Solomon and Staton’s (1982) hypothesis.

The design of this experiment (Peters et al., unpublished data) was based on the phenomenon of amphetamine sensitization, that is, the increased behavioral effects of this drug after repeated administration (Robinson and Becker 1986). While nicotine blocks LI and haloperidol potentiates LI with a single administration just before the CS-US conditioning trials (irrespective of drug treatment at preexposure), it seemed until recently (see below) that two administrations of amphetamine were needed to block LI. In most experiments, the two administrations of amphetamine have been before preexposure and before conditioning. However, recent experiments in Weiner’s laboratory have demonstrated that the first injection can be given after the preexposure session (see figure 3 in J.A. Gray et al. 1995), consistent with a suggestion (Weiner et al. 1988) that blockade of LI by amphetamine requires sensitization of the response to this drug. Also consistent with this suggestion, Warburton et al. (1996), using dialysis to measure changes in extracellular levels of DA in the nucleus accumbens in response to two injections of amphetamine 24 hours apart (a regimen known to block LI), found an increase in the DA response to the second injection. These researchers further observed that the increased DA response (and only the increased portion) was impulse dependent, in that it was reversed by removal of calcium from the perfusion medium. They therefore refined Weiner et al.’s (1988) hypothesis, proposing that, for DA release in the nucleus accumbens to block LI, this release must be consequent on impulse traffic, and that, in the case of amphetamine, such impulse-dependent accumbal DA release occurs only after sensitization of the DA response by prior administration of the drug.

It has recently been demonstrated that, for behavioral sensitization of the amphetamine response (assessed by changes in locomotor activity), the drug must first act in the ventral tegmental area; expression of the sensitized response requires subsequent action in the nucleus accumbens (Vezina 1993; Cador et al. 1995). If these conclusions apply also to the case of LI blockade, it follows that administration of amphetamine only into the nucleus accumbens, without prior action in the ventral tegmental area, should not block LI, as found by Killcross and Robbins (1993). Conversely, provided there has been prior sensitization in the ventral tegmental area, intra-accumbens amphetamine should block LI. We have recently tested this prediction by administering amphetamine directly into the nucleus accumbens just before the conditioning session, after a first systemic injection just before the preexposure session. This procedure succeeded in blocking LI at least as well as the two systemic injections do. In a further experiment, we administered haloperidol directly into the nucleus accumbens concomitantly with a second systemic injection of amphetamine, just before the conditioning session. This procedure completely prevented the blockade of LI otherwise seen after two systemic injections of amphetamine (Joseph et al., in preparation). Taken together, these results provide substantial evidence for Solomon and Staton’s (1982) hypothesis that amphetamine blocks LI by virtue of its capacity to release DA in the nucleus accumbens, but they indicate that this is so only if the amphetamine response has first been sensitized (presumably by an action in the ventral tegmental area, though we have not yet directly tested this part of the hypothesis).

Although the results of these experiments are largely internally consistent, they raise a problem with respect to the data on human subjects. In the human case, one can block LI with just one administration of amphetamine (N.S. Gray et al. 1992b; Thornton et al. 1997; Kumari et al., unpublished data). This difference from the results obtained with rats may arise because, in the human
nucleus accumbens, DA release following a single administration of amphetamine is impulse dependent, at least under our conditions. Compared to the drug regimen used with rats, our human experiments differ in route of administration (oral vs. intraperitoneal or subcutaneous), delay between administration and test (90 vs. 10 minutes), and dose (5 mg/person vs. 1 mg/kg). These factors, alone or in combination, may result in calcium-dependent (i.e., impulse-dependent) DA release in the human case. They are, however, difficult to investigate at the human level. A better understanding of the mechanisms that underlie impulse-independent versus impulse-dependent release in the rat is therefore required.

Psychopharmacological data have begun to elucidate this problem. In contrast to the earlier findings that a single administration of amphetamine is unable to block LI, two recent articles (Dunn 1994; McAllister 1997) have reported just this result. Paula Moran, in our own group, has followed up these reports, and has shown that, as is the case with nicotine (Joseph et al. 1993), a single administration of amphetamine (1 mg/kg) just before the conditioning session (preexposure having been carried out without the drug) is able to block LI. Further, she showed that this effect depends on the delay between the injection of amphetamine and the start of the conditioning session: If the delay was 15 minutes (as in earlier experiments in which a single administration of amphetamine was ineffective), LI was intact; if, however, it was 45 or 90 minutes, LI was blocked (Moran et al. 1996). Interestingly, the latter delay coincides with the one used in our human experiments (N.S. Gray et al. 1992b; Thornton et al. 1997; Kumari et al., unpublished data). Warburton and colleagues (1996) previously found that the peak DA release elicited by systemic amphetamine in the rat accumbens, which occurs 15–30 minutes after an intraperitoneal injection, is essentially independent of the presence of calcium, but that there is a greater degree of calcium dependence during the exponential decline in extracellular DA observed over the next 45–90 minutes. Thus, Moran’s data are consistent with the hypothesis that blockade of LI depends on that portion of accumbal DA release that is calcium dependent and presumably therefore impulse dependent.

The Hippocampal Connection

Most of the above evidence is consistent with the hypothesis that a critical component determining LI, or its disruption, is release of DA in the nucleus accumbens at the time of formation of the conditioned response. The detailed model proposed by Weiner (1990) and J.A. Gray et al. (1991a, 1991b) went further, however: It claimed that LI is influenced by a specific interaction between the A10 dopaminergic afferents to the nucleus accumbens and the glutamatergic afferents from the subicular area that terminate upon the same gamma-aminobutyric acid (GABA) output neurons in the nucleus accumbens. Much of the evidence is consistent also with this part of the hypothesis. However, it now appears that the component of the hippocampal formation and parahippocampal region that is critical for LI must be expanded beyond the subicular area to include the entorhinal cortex. This part of the temporal cortex projects directly to the nucleus accumbens, as well as indirectly via the hippocampal formation and subicular area. Work from Rawlins’ laboratory has shown that lesions restricted to the subicular area do not block LI, but lesions extending into the entorhinal cortex do (Yee et al. 1995); these authors therefore use the term “retrohippocampal region” to include both the subicular and the entorhinal areas.

Supporting a role for the hippocampal formation, LI is disrupted by large electrolytic or aspiration lesions of this structure (Weiner 1990; J.A. Gray et al. 1991a). A recent report by Honey and Good (1993) has demonstrated, however, that an axon-sparing excitotoxic lesion limited to the major cellular components of the hippocampus (CA1–CA4) and dentate gyrus spares LI, while nonetheless eliminating its normal context dependence (Lubow 1989), that is, dependence on similarity of context between preexposure and conditioning. This result suggests that the complete loss of LI seen after non-axon-sparing lesions of the hippocampal formation reflects, at least in part, damage to fibers of passage. The most likely pathway involved is that from the retrohippocampal region (the subicular and entorhinal areas, both left intact in Honey and Good’s experiment) to the nucleus accumbens, since damage to this region also disrupts LI (Yee et al. 1995). Also consistent with a role for the projection from the hippocampal system to the nucleus accumbens is the observation that LI is disrupted by severance (undercutting the septal area) of this projection (Tarrasch et al. 1992). Other data, however, continue to point to a role for the hippocampal formation itself, extending beyond the context dependence of LI that was affected in Honey and Good’s (1993) experiment, since LI is disrupted by injection of 5,7-dihydroxytryptamine into the fornix-fimbria and cingulum bundle, selectively destroying serotonergic afferents to the hippocampus likely with little additional damage to other regions (Cassaday et al. 1993).

Whatever the exact roles played in LI by the hippocampal formation and retrohippocampal region (a matter that calls for further investigation), they both appear to depend on interaction with a dopaminergic system. This dependence is shown by the fact that the loss of LI after
hippocampal lesions (Christiansen and Schmajuk 1993) or cytotoxic retrohippocampal lesions made using N-methyl-D-aspartate (Yee et al. 1995) is restored by systemic haloperidol, as is the loss of LI after a septal undercut (Tarrasch et al. 1992; Weiner et al., in preparation).

Experiments Using Microdialysis

Measurements of extracellular DA in the nucleus accumbens by microdialysis during the LI paradigm show changes that may account for the effects on LI of DA agonists and antagonists. Thus, if conditioning to a footshock US is carried out using a novel CS, the CS subsequently elicits conditioned DA release; if, however, the CS has first been preexposed, it fails to subsequently elicit conditioned DA release (Young et al. 1993). Concurrent measurement of extracellular DA in the caudate putamen fails to show similar stimulus-related changes (Young et al., in press).

Note that, in these dialysis experiments, the footshock itself elicited DA release in the nucleus accumbens; furthermore, the magnitude of this DA release was enhanced during the Pavlovian pairings of the footshock with a novel but not with a preexposed CS (Young et al. 1993). This finding raises the possibility that conditioning of accumbal DA release to a CS depends on the use, as US, of a biological reinforcer capable of eliciting DA release on its own. Such a possibility would be consistent with the general view, supported by substantial evidence, that accumbal DA release constitutes a critical step in the neural mediation of the reinforcing effects of biologically prepotent stimuli, such as food and pain (Swerdlow and Koob 1987). However, our human LI paradigm does not employ stimuli of this kind, only nonsense syllables as a masking task, bursts of white noise as CS, and counter increments as US. It is therefore possible that the conditioned DA release observed by Young et al. (1993) in response to a CS associated with footshock would not occur in the human LI paradigm. To investigate this possibility, we (Young et al. 1998) therefore applied dialysis to the nucleus accumbens and the caudate in a sensory-preconditioning paradigm. The critical preconditioning phase of this experiment involved CS and US (light and tone) neither of which were biological reinforcers or capable of eliciting detectable accumbens DA release. During Pavlovian pairing of these stimuli, but not in response to randomly intermixed presentations, we observed elevated DA release in the nucleus accumbens but not in the caudate. The behavioral effectiveness of the light–tone pairing was verified by subsequently pairing the tone as CS with footshock as US, and showing that both the tone and the light (itself never directly paired with footshock) acquired the capacity to suppress licking for water. Random intermixing of tone and light did not confer this capacity to transfer conditioned suppression from the stimulus directly paired with footshock to the other. When light and tone were paired during preconditioning, presentation of either alone elicited accumbal DA release; if they were randomly intermixed, only the directly conditioned CS elicited the release.

These results call into question the prevailing view that accumbal DA release is specifically sensitive to biological reinforcers. They suggest, rather, as indeed does the whole body of evidence linking accumbal DA transmission to LI, that this transmitter event reflects the salience or associability of the stimuli that elicit it (Young et al. 1993). In addition, these results increase the likelihood that associative learning in our human LI paradigm is linked to DA release in the nucleus accumbens, even though this paradigm makes no use of biological reinforcers.

Contents of Consciousness

The results of this sensory-preconditioning experiment throw into stark relief a problem already present when the J.A. Gray et al. (1991a, 1991b) model was first proposed. Following common practice (e.g., Mogenson and Nielsen 1984; Swerdlow and Koob 1987), we have treated the nucleus accumbens as the gateway to a basal ganglia motor programming system. But the phenomena of LI and sensory preconditioning do not readily fit into this framework. Blockade of LI, for example, by amphetamine, suggests rather a change in sensory processing, one that allows a stimulus that would otherwise be ignored to reenter current information processing. The symptoms of schizophrenia that J.A. Gray et al. (1991a, 1991b) attempted to relate to blockade of LI similarly suggest changes in perceptual experience rather than motor programming. However, a solution to this problem has recently become apparent from work in Grace’s laboratory. Lavin and Grace (1994) have studied what happens to the outputs from the nucleus accumbens further downstream. Using electrophysiological and tract-tracing techniques, they have demonstrated that the inhibitory GABAergic output from the nucleus accumbens synapses, in the ventral pallidum, upon further GABAergic inhibitory neurons that project to the nucleus reticularis thalami (NRT). The NRT is unusual among thalamic nuclei in that it consists mainly of inhibitory GABAergic neurons; these project to a number of the surrounding thalamic nuclei whose job is to relay impulses originating in peripheral sense organs to the appropriate sensory regions of the cerebral cortex (Jones 1975). The possible
role of the NRT in the selection of stimuli for attention and conscious processing was first pointed out by Crick (1984) and has been incorporated into a neural-network model by Taylor and Alavi (1992). Note that, since the pallidal output to these neurons is itself inhibitory, its activation has the effect of disinhibiting these sensory relay pathways, that is, increasing the entry to the cerebral cortex of those stimuli that are currently engaging the thalamocortical sensory processing loops. Figure 5 presents a diagram of this circuitry. A similar hypothesis, though different in detail, has also been applied to schizophrenia by Carlsson and Carlsson (1990).

Let us consider how the circuitry of figure 5 would be likely to work in an experiment in which an indirect DA agonist, such as amphetamine or nicotine, is used to block LI by causing DA release in the nucleus accumbens. As we know, the basic phenomenon of LI comes from the fact that a preexposed CS is slow to enter into an association with a Pavlovian US. One interpretation (see J.A. Gray 1995a, 1995b) is that it reflects a lack of access to conscious processing by the preexposed CS. If, however, presentation of this CS is accompanied by enhanced DA release in the nucleus accumbens (induced pharmacologically by activation of the retrohippocampal input to the nucleus accumbens, or during acute psychosis), LI is overcome, indicating that the preexposed CS has regained the capacity to engage conscious processing. The circuitry of figure 5 constitutes a mechanism by which this effect can be produced. DA release within the nucleus accumbens inhibits (by acting on DA D₁ receptors; Robertson and Jian 1995) the GABAergic pathway to the ventral pallidum, thus disinhibiting the pallidal GABAergic pathway to NRT, which in turn inhibits the GABAergic projections from NRT to the ascending thalamocortical sensory relay projections, so disinhibiting them. In this way, accumbal DA release should lead to an intensification of processing in whatever thalamocortical sensory relay projections were already operative in the prior instant of time (as defined by the basic comparator circuitry briefly outlined earlier and described in detail by J.A. Gray [1982a, 1982b; J.A. Gray et al. 1991a]). In the LI experiment, this intensification of sensory processing will allow the preexposed CS, which otherwise would not have been fully processed, to enter more readily into association with the US.

The transition in the preceding paragraph to talk about “conscious” processing may, quite properly, have alarmed readers who are aware of the lack of empirical definition of this treacherous term. I have considered some of the tangled issues that constitute the “problem of consciousness” elsewhere (J.A. Gray 1995a, 1995b). I certainly do not presume to offer any substantive solution to this problem. I have, however, proposed a specific hypothesis as to the neuropsychology of the contents of consciousness. According to the hypothesis, they consist

Figure 5. 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 A 10 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.
of the successive outputs of the limbic comparator system, tagged according to the degree to which the different elements making up these outputs are variously expected (i.e., predicted by the comparator circuitry) or unexpected. In neural terms, the hypotheses proposes that the outputs of the comparator system are determined by its feedback to the cortical sensory systems whose inputs to the comparator system have in the preceding instant (with a duration of approximately 100 ms) entered into the process of comparison (for details, see J.A. Gray 1995a, 1995b).

In part, this hypothesis as to the nature of the contents of consciousness springs from the previous neuropsychological model of schizophrenia (J.A. Gray et al. 1991a, 1991b). Applying the hypothesis back again to schizophrenia, we are able to make contact, but in a more fully specified and testable manner, with an older tradition (e.g., Frith 1979; Knight 1984; Venables 1984) in understanding this disorder. According to this tradition, schizophrenia symptoms reflect, using Schneider and Shiffrin’s (1977) widely accepted terminology, a failure in “automatic processing” with a consequent breaking into “conscious processing” of material that would not normally figure there (see J.A. Gray et al. 1991b, for further discussion). In terms of the model outlined here, this transition to conscious processing would, in neural terms, be due to abnormalities in the functioning of the limbic–basal ganglia interface constituted by the projection from the retrohippocampal region to the nucleus accumbens. The consequent overactivity in the dopaminergic projection to the nucleus accumbens (whether direct or due to imbalance between this input and that from the retrohippocampal region) would then boost back into conscious processing; via the NRT and the thalamocortical sensory relays (figure 5), parts of the perceptual world that would otherwise receive only automatic processing. (It remains a mystery that one, but not the other, of these processing types is associated with subjective, conscious experience. That is the hard problem of consciousness, for which no solution is at hand; see J.A. Gray 1995a, 1995b.)

In a recent electronic seminar devoted to consciousness, Newman (1996) discusses a number of hypotheses relating to the “binding” problem; that is, the problem of how the brain manages to put together the various disparate bits of information, spread out in both time and (brain) space, that constitute the integrated contents of a perceptual scene. The various hypotheses he considers all deal implicitly with the putting together of a “neuronal gestalt” in the immediate period of time (approximately the first 100–200 ms; \( t_1 \)) after sense organs first receive stimuli from the environment. But in this period, as is well documented (Velmans 1991), the brain is capable of a high degree of perceptual analysis, extraction of meaningful, cognitive processing, and organization of action, all of which remain entirely unconscious, at least by all normal tests. This initial solution of the binding problem is the one that, for example, the hypotheses of Crick (1984), Crick and Koch (1990), and Llinás et al. (1994) appear to address. But, for this initial solution to lead to the conscious experience of a complex, multimodally specified, coherent scene of some kind, something further has to happen in a following period of time (approximately the next 100–200 ms; \( t_2 \)) for it takes a period of about \( t_1 + t_2 \) after initial stimulation begins for the appropriate experience to enter consciousness (Velmans 1991). To dramatize this part of the hard problem of consciousness, consider world-class tennis: Becker has completed his return of Borg’s serve before he has consciously seen the ball reach the net (McCrone 1993). Thus, all the binding required for Becker’s detection of the ball and organization of the return stroke must have been successfully completed without yet leading to conscious perception of the events that guide this “on-line” behavior.

It was in part to address this problem that I proposed that the contents of consciousness are the outputs of a comparator system that determines whether the outcomes of action plans do or do not go according to plan (J.A. Gray 1995a). If this hypothesis is correct, there are two passes through the thalamocortical system on which the formation of a perceptual description of the world depends (figure 5). The first pass solves the initial binding problem, but leaves the solution still at an unconscious level, though one still capable of providing highly processed guidance for the current step in an on-line action program. Only at a second pass, when the outcome of that step in the program is compared to the expected outcome (predicted by reference to memory stores of regularities of past experience, as described in detail by J.A. Gray [1995a, 1995b; J.A. Gray et al. 1991a]), does consciousness come into play. As noted above, I have conjectured that a critical role is played in the initiation of that second pass by the pathway that links the output from the hippocampal formation via the subiculum to the nucleus accumbens and its dopaminergic afferents from nucleus A 10 in the ventral tegmental area, and from there via the nucleus reticularis thalami to the thalamocortical systems (figure 5). What enters consciousness at the second pass is a mixture of elements that are surprising (i.e., mismatched within the comparator system) and not surprising, with priority given to the former. Ex hypothesi stimuli are more easily tagged as surprising in the state of acute, positively symptomatic schizophrenia due to direct or indirect dopaminergic overactivity in the mesolimbic system (J.A. Gray et al. 1991a, 1991b), leading to an excess of conscious, controlled processing relative to normal individuals.
Applying the Model to Symptoms

The explicit, albeit highly speculative, link now made to the machinery that determines the contents of consciousness is advantageous when we come to apply the model to the symptoms of schizophrenia. I doubt that, even in the heyday of radical behaviorism, anyone has ever proposed that the strange subjective experiences so characteristic of schizophrenia can be dismissed as mere oddities of "verbal behavior." Freedman (1974) has summarized some of these experiences from about 60 autobiographical accounts written by schizophrenia patients during or after their psychotic episodes. The accounts include feelings of enhanced sensory awareness, reports of visual illusions, changes in depth perception, reports of racing thoughts each with an increased range of associations, descriptions of loss of meaning of words or objects, and reports of difficulty in focusing attention and concentrating—not to mention the classic symptoms of auditory hallucinations and delusional beliefs.

The framework developed here (see also figure 2 from Hemsley [1994]) offers a reasonably plausible explanation for at least some of these symptoms. Enhanced sensory awareness is one such symptom: A failure of the comparator system to correctly indicate that an event in the perceptual world is familiar or expected should lead directly to enhanced sensory awareness of that event, just as the occurrence of a genuinely novel event does for normal individuals. Apparently, more basic changes in perceptual experience, as in visual illusions or changes in depth perception, fit less readily with the model. One possibility, however, is that specification of the contents of consciousness depends on the process of differentiation of figure from ground; disturbance in this process would be expected to initiate a range of abnormal perceptual experiences. In line with this possibility, a role for the hippocampus (a key structure in the proposed comparator circuitry) in linking events to their context, especially the spatial context, has often been suggested (see J.A. Gray 1982a for review). And Gaffan (1994) has recently presented evidence that, in monkeys, the hippocampal system is essential for the analysis of visually perceived scenes, that is, objects presented against complex backgrounds. An increased range of associations also falls out naturally from the model. LI, precisely, is a process by which redundant stimuli are normally prevented from entering into associations.

A second process that appears to have the same effect is Kamin's (1969) blocking effect. This phenomenon is demonstrated in a Pavlovian conditioning paradigm in which a CS→US association is set up, then compound conditioning trials are conducted in which CS and CS are jointly presented and followed by the US. This procedure blocks the development of the CR that would occur if CS were paired with the US on its own. Like LI, the Kamin blocking effect appears to limit the formation of associations to those environmental relationships that are of greatest importance (Dickinson 1980): If an event, the US, is fully predicted already by CS, then CS adds nothing to the subject's capacity to prepare appropriate behavior. Also like LI (although the data base is much less extensive), the Kamin blocking effect depends on the integrity of the hippocampal system and normal dopaminergic transmission (for references, see J.A. Gray et al. 1991a), and it is absent in acute, but not chronic, medicated schizophrenia patients, thus showing a similar time course to that of LI (Jones et al. 1992). Disruption of LI or Kamin blocking would have the effect that, in accounting for the occurrence of a significant event (a US), a schizophrenia patient would be likely to attribute causal efficacy to stimuli that normal individuals would ignore, either because they were familiar and had previously occurred without being followed by the significant event, or because the significant event was already predicted by other existing associations. These abnormalities of stimulus processing could clearly give rise to delusional beliefs concerning the importance in the causal structure of the environment of what are in fact trivial events. Indeed, this proposed dysfunction plays a crucial role in the multifactorial model of delusion formation and maintenance suggested by Garety and Hemsley (1994).

A further process of potential importance is sensory preconditioning. As noted above, our dialysis experiments (Young et al. 1998) have shown that sensory preconditioning is accompanied by increased DA release in the nucleus accumbens. It remains to be shown whether this correlation reflects a causal role for accumbens DA transmission in sensory preconditioning. Suppose, however, that it does; in that case, it is likely that the excess accumbens DA release would increase the range over which the phenomenon of sensory preconditioning would come into play. Thus, if I have an existing association between the smell of roses and the color red, and come to form an association between the color red and stopping at traffic lights, might I then interpret the smell of roses as indicating that I should slam on the brakes? This is a dramatic, albeit fictitious, example of the kind of "clang associations" that are well known in schizophrenic speech. Given these possibilities, we plan to determine whether the accumbens DA transmission does in fact play a causal role in sensory preconditioning. It may also be productive to study sensory preconditioning in schizophrenia.

At a more general level, the results of experiments on the pharmacological blockade or potentiation of LI in the rat indicate a potentially critical "psychological locus" of the problems in cognitive processing that beset the schizo-
phrenia patient. That locus lies at the moment of integration of past experience with current information handling, as proposed by Hemsley (1987, 1994). Recall that the LI paradigm involves separate stages of preexposure, conditioning, and a test for the expression of conditioning. In several experiments, we have shown that, when both preexposure and test take place in the drug-free state, it is possible either to block or to potentiate LI by pharmacological manipulations confined to the period of conditioning. This is so for blockade of LI by systemic nicotine (Joseph et al. 1993) or amphetamine (Moran et al. 1996), for reversal of the blockade of LI by systemic nicotine using intra-accumbens haloperidol (Peters et al., in preparation), forn potentiation of LI by intra-accumbens haloperidol (Peters et al., in preparation), and for reversal of the blockade of LI by systemic amphetamine (itself, however, administered twice) using intra-accumbens haloperidol (Joseph et al., in preparation). Assuming that these experimental manipulations can be at least partially mapped onto the brain disorganization that underlies psychosis, the effects obtained suggest that schizophrenia patients may have essentially normal processes of initial familiarization with individual stimuli and normal processes of learning individual associations between stimuli, but difficulty in integrating different experiences with the same or similar stimuli when these require some form of contextually dependent differentiation. This inference is consistent with the one drawn by Hemsley from his experimental and clinical data on human subjects: "It is not claimed that 'memories of past regularities' are not stored . . . rather the suggestion is that the rapid and automatic assessment of significance or lack of significance of aspects of sensory input (and their implications for action) is impaired" (Hemsley 1993, p. 635).

As indicated in our first description (J.A. Gray et al. 1991a), an account of auditory hallucinations requires a slight elaboration of the model. This elaboration is based on Frith's (1987) suggestion that such hallucinations arise because of a failure to distinguish between stimulus and willed intentions, that is, between behavior that is instigated directly by environmental input and behavior that arises from an internal motor program. In consequence, internal speech that is in fact part of an internal motor program is not recognized by the schizophrenia patient as such but is treated as alien. Frith further suggests that failure in recognizing willed intentions is due to a disruption in the efferent copy of the motor program that would normally be sent from the frontal cortex to limbic structures. This hypothesis fits naturally with the general comparator model proposed by J.A. Gray (1982a; J.A. Gray et al. 1991b), since this treats the projection from the frontal cortex via the entorhinal cortex to the hippocampal system as conveying information about current steps in the motor program, which the comparator then uses to compute the next predicted state of the perceptual world.

Integrating Models of Schizophrenia

This treatment of auditory hallucinations constitutes a specific example of a more general compatibility between our model of the neuropsychology of schizophrenia, with its emphasis on the projections from the temporal lobe (entorhinal cortex, subicular region, and hippocampal formation) to the nucleus accumbens and the mesolimbic dopaminergic pathway, and other models that stress the importance of the frontal cortex, the links between it and the basal ganglia, and the mesocortical dopaminergic pathway (Swerdlow and Koob 1987; Geyer et al. 1990; Weinberger 1991). Postmortem pathology is found in schizophrenia in both the temporal and the frontal lobes (Bogerts 1991, 1993), so that it is likely that any final theory will need to include both areas and their respective functions in an integrated model. Numerous pathways link both regions. The ones that presently appear most likely to determine schizophrenia symptomatology are those that involve dopaminergic transmission. In particular, there appears to be an inverse reciprocal link between dopaminergic transmission in the frontal cortex and the nucleus accumbens, respectively; the operation of this link depends on the retrohippocampal region. Thus, Lipska et al. (1993) have shown that lesions of the latter region in the neonatal rat lead, in adulthood, to increased activity of DA in the nucleus accumbens coupled with decreased activity in the frontal cortex. Such a decrease in frontal cortical DA transmission may underlie, or at least contribute to, the hypofunction of the frontal cortex reported in neuroimaging studies (Weinberger et al. 1986).

A further possible route by which heightened dopaminergic transmission in the nucleus accumbens may be associated with reduced activity in the frontal cortex is indicated in figure 5. DA release in the nucleus accumbens, as noted earlier in the discussion of this figure, inhibits the GABAergic output from the accumbens to the ventral pallidum. As well as probably giving rise (via the pallidal projection to NRT, and from there to thalamic sensory relay nuclei) to increased activity in neocortical sensory regions, this pathway should lead, by disinhibition of the ventral pallidal GABAergic projection to the dorsomedial thalamic nucleus, to lowered activity in those frontal cortical regions that receive excitatory input from the dorsomedial nucleus. It is also possible that pathology in the thalamus itself, as recently demonstrated in a neuroimaging study by Andreasen et al. (1994), may both contribute to frontal cortical dysfunction and interrupt output pathways from the nucleus accumbens.
The approach adopted here is probably also compatible with the model developed by the San Diego group (Geyer et al. 1990), who rely principally on a different experimental paradigm, prepulse inhibition (PPI), to measure sensory gating processes in schizophrenia. Like LI, PPI is disrupted in schizophrenia and also by DA receptor agonists in the rat. Furthermore, the brain circuitry that underlies PPI shows considerable overlap with the circuitry underlying LI, with the nucleus accumbens and the mesolimbic dopaminergic pathway again playing prominent roles (Geyer et al. 1990; J.A. Gray et al. 1991a, 1995). However, although both LI and PPI reflect stimulus selection, it would be a mistake to see them simply as alternative ways of measuring the same disruption, associated with schizophrenia, in stimulus selection processes. Not only do the two phenomena operate on different time scales (at least the order of seconds or minutes for LI, and about 100 ms for PPI), they also show different relations to chronicity of illness (LI is disrupted in the acute stage of schizophrenia only, PPI in both acute and chronic stages) and different responses to DA receptor agonists (LI is disrupted only by indirect agonists and this disruption requires impulse-dependent DA release; PPI is disrupted by direct DA agonists, which appear to be more effective than indirect ones) (see Mansbach et al. 1988; Geyer et al. 1990; Feldon et al. 1991).

Clearly, much work remains to be done, both in pursuing each of these models in its own right and in showing how they can be coupled to each other. Nonetheless, existing data already warrant optimism that, despite the bizarre nature of many schizophrenic symptoms and their indelible impregnation with the mysteries of subjective experience, it will shortly be possible to construct a unified neuropsychological account spanning all the levels illustrated in figure 1.

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The Author

Jeffrey A. Gray, Dip. Psychol., Ph.D., is Professor, Department of Psychology, Institute of Psychiatry, London, United Kingdom.

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