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The pharmacology of latent inhibition as an animal model of schizophrenia

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Abstract

The nature of the primary symptoms of schizophrenia and our lack of knowledge of its underlying cause both contribute to the difficulty of generating convincing animal models of schizophrenia. A more recent approach to investigating the biological basis of schizophrenia has been to use information processing models of the disease to link psychotic phenomena to their neural basis. Schizophrenics are impaired in a number of experimental cognitive tasks that support this approach, including sensory gating tasks and models of selective attention such as latent inhibition (LI). LI refers to a process in which noncontingent presentation of a stimulus attenuates its ability to enter into subsequent associations, and it has received much attention because it is widely considered to relate to the cognitive abnormalities that characterise acute schizophrenia. Several claims have been made for LI having face and construct validity for schizophrenia. In this review of the pharmacological studies carried out with LI we examine its claim to predictive validity and the role of methodological considerations in drug effects. The data reviewed demonstrate that facilitation of low levels of LI is strongly related to demonstrated antipsychotic activity in man and all major antipsychotic drugs, both typical and atypical, have been shown to potentiate LI using a variety of protocols. Very few compounds without antipsychotic activity are active in this model. In contrast, disruption of LI occurs with a wide range of drugs and the relationship with psychotomimetic potential is less clear. Although reversal of disrupted LI has also been used as a model for antipsychotic acticity, mostly using amphetamine-induced disruption, insufficient studies have been carried out to evaluate its claim to predictive validity. However, like facilitation, it is sensitive to both typical and atypical antipsychotic agents. The data we have reviewed here demonstrate that facilitation of LI and, perhaps to a lesser extent, reversal of disrupted LI fulfil the criteria for predictive validity.

Theme: Disorders of the nervous system

Topic: Neuropsychiatric disorders

Keywords: Schizophrenia; Animal models; Antipsychotic agents; Psychotomimetics; Attention

Contents

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1. Introduction

The term schizophrenia as it is used today was introduced by Bleuler in 1911 [25], who used it to replace *dementia praecox*, a term first used by Kraepelin to collectively describe several syndromes, such as hebephrenia and catatonia, which he believed to have a common organic basis. Bleuler considered that neither dementia nor precocity were the defining features of the disease and invented the term schizophrenia to reflect dissociation of various aspects of the psyche, which he viewed as fundamental to the disease. The characteristic signs and symptoms of schizophrenia are now widely accepted [9], and are typically divided into two categories, positive and negative, although other classification schemes have been proposed [159,160]. Positive symptoms are those that appear to reflect an excess of normal function and include disordered thinking, delusions and hallucinations. Negative symptoms, in contrast, can be thought of as representing a loss of normal function and include flattened affect, avolition (lack of energy) and anhedonia (lack of pleasure) [9,237]. In addition to these symptom clusters there is an increasing emphasis on cognitive deficits in schizophrenia and the possible relationship between such deficits and the symptoms of schizophrenia [79,104]. Although schizophrenia has been viewed as a functional psychosis for much of the last 100 years, both Kraepelin and Bleuler considered schizophrenia to be an organic disease. Nowadays, there is considerable evidence that schizophrenia is indeed an organic disease, possibly a neurodevelopmental disorder [110,111,197,220,270,272,278] and although several brain regions have been implicated, the site of the primary abnormality (if such a thing exists) has yet to be identified [10,111,308].

Direct experimental investigation in animals of the biological systems that might subserve schizophrenia is therefore especially problematic, firstly because of our lack of knowledge of the underlying cause and secondly because of the nature of its primary symptoms. Complex psychological symptoms such as delusions, hallucinations and disordered thought are not readily observable in animals (even assuming such phenomena exist in non-human species), making it difficult to identify animal models of the disorder. Because of this, animal models of schizophrenia have centred largely on behavioural changes that occur in rodents or primates following administration of drugs such as the dopamine-releasing agent amphetamine or, more recently, the glutamatergic antagonist phencyclidine (PCP), which are known to produce psychotic symptoms in humans [69,129,132,212,246,254]. Many of these behaviours such as hyperactivity or abnormal exploratory patterns can be reversed by drugs that are known to have antipsychotic properties in the clinic [49,151]; however they bear little relevance to schizophrenic symptoms. Such models may be of use in identifying new drugs that act in a similar way to those already in use in the clinic but are limited in that their predictive value is unclear where novel mechanisms of action are concerned.

A newer approach to investigating the biological basis of schizophrenia has been to use information processing models of the disease to link psychotic phenomena to their neural basis. Several authors have attempted to define schizophrenia as a deficit in the treatment of information (expressed variously in terms of attentional systems, control systems or information processing models) (e.g., Refs. [36,112,113]). At the core of all these approaches is the idea that manipulation and/or monitoring of pertinent information is impaired in schizophrenia, either through insufficient or inappropriate processing. For example, Hemsley [112,113] has suggested that the basic disturbance in schizophrenia involves a ‘‘weakening of the influences of stored memories of regularities of previous input on current perception’’. Thus, whereas memories evoked by contextual cues would normally allow more focussed processing of those stimuli particularly relevant to that context, it is suggested that this does not occur to

the same extent in schizophrenia: thoughts and behaviour are poorly controlled by the context, leading to such symptoms as distractibility and disordered thinking.

Frith [78,79] has proposed that the underlying deficit is in systems that oversee self-generated actions, both in terms of difficulty generating willed action (leading to negative symptomatology) and in monitoring of self-generated actions and thoughts (leading to misattribution of the source of the sensory input, a feature that Frith has used to explain hallucinations, thought insertion, alien control, etc.). Specific deficits in tests of reality monitoring (e.g., discrimination of self- versus externally generated events) in schizophrenic patients have been reported by Brébion et al. [30] who correlate this with selective attention deficit as measured by the Stroop colour–word interference task, a widely used test of selective attention in which subjects are required to name the ink colour in which colour words are printed, this process taking longer when there is a conflict between the ink colour and the word (e.g., the word 'red' printed in blue ink). Brébion et al. [30] argue for a specific role of a selective attention deficit in the reality monitoring failure in schizophrenia and Gray et al. [96] have recently attempted to integrate the approaches of Frith and Hemsley, stressing the importance of selective attention as the major control process in the passage of information. It is therefore possible, on the basis of deficits in selective attentional processes, to suggest how the various signs and symptoms of schizophrenia can arise, although it is stressed that the positive symptoms of schizophrenia are more satisfactorily explained by this approach than the negative symptoms [96].

Disorders of attention have long held a prominent place in definitions of schizophrenia. Green has recently reviewed the early characterisation of attentional deficits in schizophrenia [104], including Kraepelin's characterisation of attentional deficits in schizophrenia and his association of them with different phases of the disease. Bleuler [25] listed deterioration of attention as one of the signs of the disease and disorders of attention in early schizophrenia have been particularly highlighted in the work of McGhie and Chapman [43,181,182]. Descriptions of the deficits that schizophrenics have in different aspects of attention (e.g., vigilance, selective and divided attention) have been the subject of several recent reviews [26,50,200]. Thus, there are numerous tasks assessing selective attention in which schizophrenic patients are deficient, such as the Stroop test [30,206,223] or the '2 and 7' test of Ruff (in which subjects are required to cross-out the numbers 2 or 7 embedded in strings of either numbers or letters, the later measuring more automatic processes and therefore faster) [226,301]. Fortunately for the development of animal models of schizophrenia, there are also a number of experimental cognitive tasks of information processing and selective attention in which schizophrenics have been shown to be deficient which can also be evaluated in animals. These include sensory gating tasks such as pre-pulse inhibition [87] and tasks involving selective attention such as Kamin blocking and latent inhibition (LI) [20,97,100,134,202] (although Swerdlow et al. failed to find an LI deficit in patients [257]). It is important to note that selective attention deficits in schizophrenics are detectable early in the course of the disorder and prior to administration of antipsychotic medication [20,100,134, 173].

Thus, studying the neural basis of experimentally induced dysfunction in attentional tasks such as LI and pre-pulse inhibition of the startle response (probably the two most widely used approaches) in animals and relating them to dysfunctions in schizophrenic patients provides a potentially powerful approach to modelling schizophrenia. A major advantage is that it circumvents the difficulties of producing the behavioural symptoms of psychosis in animals. LI describes a phenomenon whereby prior experience that a stimulus does not have a consequence makes it more difficult to subsequently form an association with that stimulus, in a manner directly proportional to the amount of prior experience. It is described in more detail below. The startle response is a rapid and characteristic muscle contraction response to an unexpected stimulus of sufficient intensity. If it is briefly preceded by a lower intensity stimulus (the prepulse), insufficient in itself to elicit a startle response, the amplitude of the startle response is reduced. The neuroanatomy of the startle response and prepulse inhibition have been worked out in some detail [54,256], and is similar in animals and humans. The prepulse inhibition serves to allocate attentional resources to appropriate modalities and its dysfunction might therefore lead to poor use of these resources and the type of attentional deficits occurring in schizophrenia. Prepulse inhibition and its relation to schizophrenic symptoms have been extensively reviewed elsewhere and will not be discussed to any great extent in this review [65,113,256].

LI has been demonstrated in numerous mammalian species including humans (for review see Ref. [169]) and is conserved across a wide variety of experimental protocols from conditioned emotional response learning in rats to auditory number learning in humans. Initially LI was mainly of interest to learning theorists because it posed problems for accounts of how animals learned basic associations but it subsequently became important in the development of a number of theories of attention. The theoretical basis of LI remains the subject of much debate. However, most contemporary accounts of LI agree that it reflects some form of selective attention in that it corresponds to our ability to selectively attend to important information in our environment and to ignore the unimportant [169,174]. LI and pre-pulse inhibition are probably not measuring exactly the same thing as despite many similarities, several differences between them have been noted, such as deficits in prepulse inhibition but not LI following social isolation [303] or following injection of

selective dopamine antagonists into the pre-frontal cortex [67].

A number of studies have indicated that LI is disrupted in high schizotypal subjects and acute schizophrenics [20,97,100,105,273]. Furthermore, Braunstein-Bercovitz and Lubow [28,29] have recently demonstrated a role for selective attention in human LI by showing that manipulating attention during pre-exposure, such as by depletion of attentional resources with a masking task, attenuated LI in schizotypal subjects. The LI deficit in schizophrenics has consequently been used as evidence of a selective attention deficit in schizophrenia [96,171]. LI is also disrupted in normal volunteers by amphetamine [99,262], a psychotomimetic dopamine-releasing drug, a finding that is consistent with the hypotheses concerning dopamine overactivity in schizophrenia [39,40]. The neuro-anatomical basis of LI has been well studied and there is much evidence from lesion studies and microdialysis studies to suggest an involvement of the limbic system and, in particular, mesolimbic dopamine systems in the phenomenon [33,68,96,102,138,260,297,313,314]. In rats LI is also disrupted by amphetamine, an effect that can be reversed by typical antipsychotic drugs such as haloperidol and also by atypical antipsychotics such as clozapine (see Section 4 and Table 8). The fact that LI can be studied in both animals and humans and can be disrupted by amphetamine in both species, has engendered interest in the paradigm as an animal model of schizophrenia.

Animal models of psychiatric disorders can be classified as having predictive, face or construct validity depending on a variety of criteria defined by Willner [307]. It has been suggested that LI fulfils many of the criteria for construct validity (i.e., similar underlying neurophysiological concept, such as the postulated role of selective attention deficits in both schizophrenia and in LI), face validity (i.e., similarity of measured end-points in clinical and experimental models, such as the observation of impaired LI in acute schizophrenia) and predictive validity (i.e., similar pharmacological profile in clinical and experimental studies, such as the effects of amphetamine and haloperidol in animal models of LI) as an animal model [65,72,74,96]. In addition, studies examining the neural circuitry involved in LI (reviewed in Refs. [65,96,284]) have drawn attention to the major role played by the limbic system and the potential role of these circuits in the signs and symptoms of schizophrenia. Initially, the predictive validity of LI rested largely on the effects of a limited number of antipsychotic agents. However, because LI appears to have good face and construct validity compared to many existing models, there has recently been an increasing number of studies investigating the pharmacology of LI in animals (Fig. 1), particularly with a view to identifying antipsychotic therapies with novel mechanisms of action. A review of these studies therefore forms the core of this paper, in an attempt to consolidate the literature that presently exists in this field and also to discuss some of the methodological and conceptual issues that arise when examining the effects of pharmacological intervention on LI.

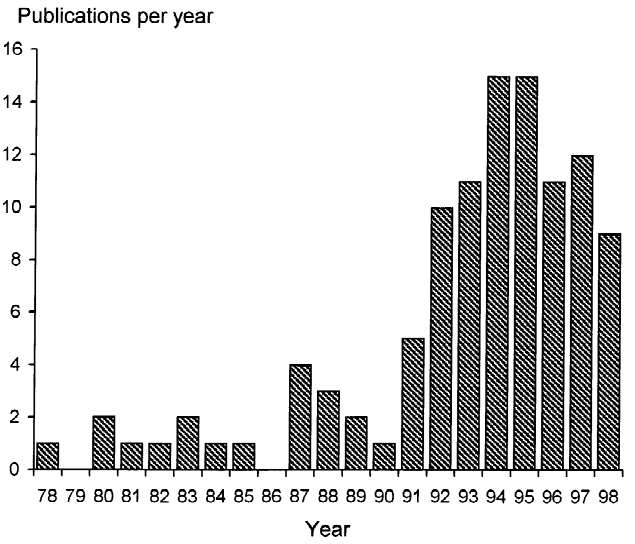

Fig. 1. Number of publications per year concerning the pharmacology of LI (references cited in this review used as source).

Finally, it is important to note that LI is a cognitive process and the problem we are faced with is to determine how best to exploit LI as an animal model for evaluating potentially antipsychotic compounds: it is this which will ultimately determine its validity as an animal model of schizophrenia. The value of LI is that protocols exist to evaluate it in both animals and man and that the underlying cognitive processes are similar in both. Furthermore, it has been argued that this underlying cognitive process is relevant to at least some aspect of schizophrenia (see the above-cited reviews for more in-depth discussion of these matters). There are essentially two ways in which LI is being used in this way: reversal of disrupted LI and facilitation of a low level of LI. The former is hampered by the need to attenuate LI by, for example, drugs or lesions. How well these are able to mimic schizophrenia is open to much debate. The latter depends on drugs acting on an intact system to enhance LI and therefore makes the assumption that such systems remain functionally intact in schizophrenia. Both approaches have advantages and disadvantages and one of the aims of this review is to help researchers coming into this field to determine which is most appropriate for them.

2. Methodological considerations

Since the original studies carried out by Lubow and Moore [172] with goats and sheep as subjects, the fundamental LI methodology has been considerably elaborated upon using a variety of classical and instrumental conditioning procedures in several mammalian species,

including man. Efforts to demonstrate the LI effect in non-mammalian species, such as pigeons, goldfish or bees have not, to date, succeeded [22,48,240,264,310]. Numerous protocols exist for demonstrating LI but in all cases it is made evident when conditioning to a stimulus is retarded or reduced in subjects that have been pre-exposed to that stimulus compared to subjects receiving no pre-exposure (between-subject protocols) or compared to conditioning to a different non-pre-exposed stimulus (within-subject protocols). All protocols therefore include a pre-exposure phase, during which a stimulus is presented without consequence, followed by a conditioning phase, where the same stimulus is paired with the unconditioned stimulus. The principal difference between the various protocols used is the way the strength of this conditioning is demonstrated. Procedures using animals as subjects include discrimination learning, conditioned freezing, conditioned suppression, conditioned avoidance, conditioned taste aversion, conditioned eye blink and conditioned magazine responding. Not all of these procedures have been used as extensively as others to examine drug effects on LI and this section will therefore be restricted to discussing those procedures which have contributed most to the pharmacology of LI in animals.

The magnitude of the LI effect is related to a number of parameters which include the number and duration of pre-exposure trials [6,56,207,280], the unconditioned stimulus (US) intensity [109,147,193], contextual cues [14,53,108,184,198], the interval between the pre-exposure, conditioning and test phases [1,5] and exposure to other conditioned stimuli [18,216]. In addition, experiments have demonstrated that early maternal separation [66] or non-handling [70,286,288] of animals can disrupt LI when measured in the adult animal. Although the literature contains a vast amount of information on the importance of these parameters to the LI effect itself, it is important to note that there are few investigations into how changing these parameters may influence the effects of drugs on LI (see Section 2.4). In addition, even fewer systematic studies have been carried out to examine the effects of species, strain and age differences on LI or on the effects of drugs on LI.

LI has been investigated using the conditioning of both aversively motivated behaviours and appetitively motivated behaviours. Within the majority of these procedures the extent of conditioning to the conditioned stimulus (CS) is indexed by the suppression or enhancement of conditioned responses associated with eating or drinking (e.g., lever pressing for food, licking for water, etc.). This requires that animals be deprived to some extent of either water or food, an experimental procedure that in itself has been shown to modify conditioning [176,252]. For this reason, when examining the effects of drugs on LI it can be difficult to determine if a change in conditioned responding is due to specific or non-specific effects of the drug, affective motivational changes or to other unconditioned responses that interfere with consumption, problems common to many animal models. In addition, the motivational state of the animal (e.g., hungry or thirsty) can be part of the context at the time of pre-exposure and attenuate LI if different to the conditioning context [144], producing another potential source of interaction with drug treatments. Certain other procedures require animals to make a motor response (e.g., active avoidance). Many of the compounds discussed in the following sections have well established effects on a variety of these parameters, such as the effects of dopaminergic and serotonergic drugs on locomotion, food consumption and reward mechanisms (e.g., Refs. [86,189,243]).

LI methodology can be also be divided into on-baseline and off-baseline procedures. On-baseline procedures assess the magnitude of the LI effect during the conditioning phase of the experiment. Thus, LI is present when the pre-exposed group exhibit slower conditioning than the non-pre-exposed group. This method allows one to see the development of LI across a number of conditioning sessions and for this reason more conditioning trials are required than in an off-baseline procedure and repeated administrations of the drug are needed across conditioning sessions. In contrast, the conditioning phase of an off-baseline procedure employs a pre-determined number of conditioning trials and the assessment of the LI effect usually takes place within one drug-free test session after conditioning, where no US is present and the degree of conditioning is assessed during a single presentation of the CS. This tends to produce an all-or-nothing LI effect that may render off-baseline techniques less sensitive to subtle changes in associative strength. However, the absence of drug during testing remains a major advantage. Another concern with off-baseline procedures is that, unlike on-baseline procedures, the animal is not allowed to exhibit consummatory responses during the pre-exposure and conditioning phases. This can increase the variability in baseline consummatory behaviour upon testing. Some recent studies have included a ‘rebaseline’ phase between conditioning and testing phases during which animals can exhibit consummatory responses and it is claimed that this reduces response variability during testing [75].

The relative advantages of on- or off-baseline procedures have been the subject of much debate [135,147–149]. Much of the discussion has concerned the interaction of dopaminergic compounds (in particular amphetamine) with different components of the two LI procedures and how this might affect the magnitude of the measured LI effect. The difficulty of separating dopaminergic modulation of LI from its effects on perception of reinforcer strength (both the positive reinforcement used to maintain behavioural responding and the unconditioned stimulus used in the conditioning phase) is one of several important issues raised by this discussion that are not yet entirely resolved. However, it highlights the importance and usefulness of having several methods with which to measure LI

so that such possibilities can be examined: in principal the LI effect should be independent of the method used to measure it. Unfortunately, as the discussion in the above-cited papers shows, the method used can also add elements with which drugs can interact.

Lastly, it is possible with most LI procedures to use either between-subject or within-subject protocols. In the former, separate groups are used for the two pre-exposure conditions. In within-subject methods the animals are presented with two CSs during the conditioning phase: one CS that has already been pre-exposed and one CS that has not. This within-subject protocol allows each animal to act as its own control [146,183,312] although it is important to counterbalance the stimuli to control for any overshadowing effects in addition to examining the unconditioned effects of novel stimulus presentations.

2.1. Aversively motivated procedures

Within the literature concerning the pharmacology of LI, studies employing aversive stimuli as the US during the CS−US conditioning phase are far more common than those involving appetitive stimuli. Several LI procedures make use of aversively motivated behaviours including conditioned suppression (also, referred to as conditioned emotional response; CER), conditioned avoidance, conditioned taste aversion (CTA), conditioned eyeblink and conditioned freezing. The latter two methods have not been used as extensively as the others to examine drug effects on LI and only isolated examples exist [141,221].

The majority of studies examining drug effects on LI have employed CER procedures using suppression of drinking behaviour as the dependent variable [193,195,276,280,281]. This is probably due to the rapidity with which this off-baseline protocol can be carried out and also because testing can be carried out in the absence of drug treatment, thus any drug effects on consummatory behaviour should not interfere with measurement of LI. In a typical protocol rats are first trained to drink in an experimental chamber, this behaviour subsequently being used to determine the strength of conditioning. Then, in the absence of the drinking spout (i.e., off-baseline) a CS (typically a tone) is paired with footshock. When the tone is presented during a test session in which the rat can drink, the CS-footshock association leads to a CER, measured as an inhibition of ongoing behaviour (in this case drinking). Pre-exposure of the CS prior to pairing with footshock results in a weaker association and a less marked CER compared to animals not pre-exposed, i.e., LI. An on-baseline CER procedure using conditioned suppression of the animals' lever pressing for food as the dependent variable has also been used [121,148,222]. Similar results concerning the facilitation of LI by neuroleptics [64,148] and disruption of LI by systemic amphetamine [146,193,290] have been obtained using both procedures.

Conditioned avoidance procedures have mainly been used to examine the neural mechanisms underlying LI [17,248,249] but have also been used effectively to show facilitation by haloperidol [287] and disruption of LI by amphetamine [250]. In fact, the investigations by Solomon et al. [250] and Weiner et al. [285] during the early 1980s were the first demonstration that amphetamine could disrupt LI, suggesting that it might prove useful as a model for the attentional impairments seen in acute schizophrenia. More recently a conditioned avoidance procedure was successfully used to demonstrate abolition of LI by phencyclidine [235], a glutamate antagonist that can induce psychotic symptoms in man [106,254]. Conditioned avoidance procedures typically use active avoidance training in which animals learn to use a cue stimulus to move from one side of a chamber to the other in order to avoid receiving a footshock. LI is demonstrated when pre-exposure to the stimulus used as the cue impairs learning relative to non-pre-exposed animals. Such procedures often run the pre-exposure and conditioning phases consecutively within the same session. This makes the procedure more rapid than other LI methods but a disadvantage of this is that drug effects during each phase cannot be dissociated, which can be an important factor as will be discussed in a later section.

Passive avoidance has been used much more rarely for LI [57,164,165,167], possibly because this procedure presents certain problems for LI. In passive avoidance a contextual cue (i.e., the apparatus) is used as the CS during CS−US pairings and it is well-established that LI is context-dependent [95,107,120,184,198]. The role of the context in such experiments is therefore akin to that in foreground contextual conditioning (i.e., conditioning the US to context in the absence of a discrete CS), whereas in most LI experiments the context plays a role similar to that in background conditioning (i.e., conditioning to context during pairing of a discrete CS with US). The neuronal systems involved in such foreground and background conditioning may be different [91,209,210,255] and therefore the pharmacology of LI using the passive avoidance protocol may be different from that of other, more widely used, protocols. However, a few other protocols have made use of context pre-exposure to demonstrate LI, using reduced conditioned freezing to context as the measure of LI (e.g., Ref. [142]).

There are an increasing number of studies which use conditioned taste aversion (CTA) to evaluate LI [4,21,57,67,68]. CTA is a phenomenon whereby a novel rewarding taste CS (typically sucrose or saccharose solution) is associated with illness (induced by injection of LiCl immediately after the CS) resulting in avoidance of that flavour. LI is demonstrated when animals pre-exposed to the CS show less aversion as a result of its subsequent association with LiCl: thus they will consume more of the CS solution than non-pre-exposed animals when it is presented to them after the conditioning. The use of CTA

to study drug effects can be confounded by a number of factors. Firstly, as the sucrose solution/water solution acts as a CS during pre-exposure and conditioning, drugs which reduce or increase fluid consumption will change the amount of pre-exposure. Such an effect can be easily monitored by examining fluid intake in pre-exposed and non-pre-exposed groups. Secondly, during pre-exposure, injection of the drug may itself induce CTA. Although examination of fluid intake on the second day of pre-exposure can give an indication as to whether the drug is itself causing the animal to avoid the CS, such an effect is less easily detectable in non-pre-exposed animals, who have no reason to avoid water. Instead, the animals may become habituated to feeling ill and the LiCl induced-sickness may lose some of its associative value, resulting in apparently poor learning in the non-pre-exposed group. Similarly, drugs may also modify the aversiveness of the LiCl injection, which can only be evaluated in separate experiments (e.g., does the drug facilitate the aversiveness of a lower dose of LiCl?). Finally, in a CTA protocol animals are not learning to ignore the CS during pre-exposure as would be required for LI, in fact quite the opposite: they are learning to appreciate the sweet taste. Thus despite its ease of use, the taste aversion protocol for LI has a number of problems which may limit its usefulness.

2.2. Appetitively motivated behaviours

The majority of publications concerning LI that examine appetitively motivated behaviours have centred their efforts around parametric issues and lesion effects [60,108,120,140,216]. Only a few studies have examined the use of appetitively motivated behaviours to investigate the effects of drugs on LI [147,183]. Typically, these procedures are on-baseline, i.e., the magnitude of the LI effect is examined during the conditioning phase of the experiment. For this reason, this type of study takes longer which may explain why it has not been used extensively for studying drug effects on LI (although one study has shown an appetitive LI procedure only lasting 1 week [183]). On-baseline studies of this kind have often alternated pre-exposure or conditioning days with intervening drug-free days.

2.3. Timing of drug administration

Although LI can be disrupted by acutely administering a wide variety of drugs (for further details see Section 4) the timing of drug administration can be a critical factor. For example, it was initially reported that amphetamine needed to be administered at both pre-exposure and conditioning phases to disrupt LI in a CER procedure, having little disruptive effect when administered at either phase alone [285]. The majority of drug studies of LI have used a similar off-baseline CER protocol in which pre-exposure, conditioning and testing are carried out on separate days and, in most of these studies, drugs have been administered during both pre-exposure and conditioning. However, evidence is emerging that, for dopaminergic agents in particular, the important phase for drug effects is during conditioning. In the case of amphetamine, it seems important that the dopamine release it provokes be dependent on nerve impulses in order for it to disrupt LI [277] and this can be obtained with a single treatment if a sufficiently long pretreatment time is used (i.e., 45 rather than the usual 15 min) [194]. Several studies had in fact already demonstrated disruption of LI with a single dose of amphetamine using protocols in which pre-exposure and conditioning were carried out in a single session, probably thereby ensuring a sufficiently long pretreatment time [60,180]. It should also be pointed out that only a single dose of amphetamine is required to disrupt LI in man where pre-exposure and conditioning are run in a single session and drug pretreatment times are at least 90 min [99,262]. The cholinergic agonist nicotine, which like amphetamine also increases dopamine release, can also disrupt LI when administered at only the conditioning phase [138]. In addition, it has been demonstrated that a reversal of amphetamine-induced disruption of LI can only occur if the reversing drug, e.g., haloperidol, is present during the conditioning phase [137]. Similar results have been obtained with facilitation of LI where it has been shown that presence of haloperidol during the conditioning phase of the experiment is necessary for facilitation of LI to occur [207]. In contrast, drugs acting on the serotonergic system appear to act primarily during pre-exposure. The $5HT_{2A/2C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) only disrupts LI when given during the pre-exposure phase [116,183] and the $5\text{-}HT_{1A}$ antagonist WAY100,635 only facilitates LI if administered during pre-exposure [150].

Some of these studies raise the possibility of state-dependent learning effects in LI. That is, disruption of LI by injecting drugs in different phases of the experiment may cause transfer failure from one phase to another because of the change from a drugged state to a non-drugged state [130,203]. This kind of effect can be difficult to dissociate from any disruptive effects of the drug itself and only a few experiments have directly controlled for it [4,150], although in many cases there exist separate studies demonstrating that administration of the compound during several stages of the LI procedure has similar effects. The contribution of such internal contextual effects to LI have yet to be fully explored but it is likely that they will prove to be important. Contextual control of LI is one of its more robust features [107,145,184], and the more similar the pre-exposure and conditioning context are, the greater the LI effect. Even the US presentation during conditioning can be part of a contextual shift between phases and thereby reduce LI. Killcross and Dickinson [145] have recently demonstrated this by using explicitly unpaired

exposure to the US during the pre-exposure phase to increase the magnitude of LI.

Apart from its role in context shift between phases of the LI procedure, internal context has also been shown to play a role in learning about the to-be-CS during pre-exposure. In a series of elegant experiments, Killcross and Balleine [144] demonstrated that the non-pertinence of the pre-exposed stimulus is probably only valid with reference to the motivational state of the animal during pre-exposure. This motivational state (e.g., hunger or thirst due to food or water deprivation, both of which are common features of LI protocols) is also part of the internal context and changing this between pre-exposure and conditioning (i.e., pre-exposure while animals are hungry and then conditioning while they are thirsty) attenuated LI [144]. The possibility of state-dependent effects was effectively ruled out by employing a within-subjects design. They explain their results by suggesting that during pre-exposure animals learn that the CS is unrelated to events of relevance to their current motivational state. Studies such as these suggest numerous ways in which drugs can interfere with our ability to study the LI effect: they can act as internal cues themselves, modify an animal's motivational state (or its perception of this) and modify reinforcer strengths.

2.4. Influence of parametric manipulations on drug effects in LI

An increasing number of studies demonstrate that changing experimental parameters of an LI procedure in ways that do not affect the size of the measured LI effect can profoundly affect the interactions of drugs with LI. De la Casa and Lubow [55] have demonstrated that the duration of the pre-exposure phase is an important variable in LI and that with longer total CS pre-exposure times the effect of amphetamine to disrupt LI is abolished [56]. Another recent study demonstrated that under two different pre-exposure conditions, each giving 'maximal' LI, the effects of nicotine were in diametrically opposed directions [222]. Using pre-exposure conditions comparable to other studies with nicotine [138,193] these authors observed a disruption of LI with nicotine. However, when they used a much greater amount of stimulus pre-exposure (which in itself did not change the magnitude of the LI effect) they found an enhancement of LI with nicotine. Other studies have also demonstrated that changing CS parameters affects drug interactions with LI. Weiner et al. [300] reported that changing the CS from a steady to a flashing light could counteract the disruptive effects of amphetamine, a finding that can be extended to the facilitatory effects of haloperidol [227]. These findings suggest that stimulus salience is an important factor (a flashing light being more salient than a steady light) although the authors discuss other interpretations including the role that the duration of stimulus pre-exposure might play.

Other studies have demonstrated that changing US intensity can modify drug effects on LI. For example, increasing US intensity can abolish the enhancing effects of the neuroleptic α-flupenthixol [148] and lowering the US intensity (shock or food) results in a less effective disruption of LI by amphetamine [147]. This latter finding was not replicated in a subsequent study by Weiner et al. [300] who also carried out a meta-analysis of 23 previous studies which also failed to support a modification of learning in the non-pre-exposed group with amphetamine treatment (which might be expected if reinforcer strength had been affected). The role of drug modulation of reinforcer strength in mediating drug effects on LI remains a matter of dispute.

2.5. LI methodology in humans

The present review is concerned primarily with evaluating the pharmacological validity of animal models of LI. However, it should be noted that there are an increasing number of pharmacological studies being carried out in humans. At present this is limited to those using amphetamine, nicotine and haloperidol [99,262,305] and the results obtained to date are comparable to those obtained in animal studies (however, see Ref. [306]). The methods used for measuring LI in humans are, in general, quite different from those used in animals [7,23,98,170,171, 234,242,273] and will not be discussed here.

3. Facilitation of LI

There are several ways in which the LI effect can be exploited to provide a preclinical test for antipsychotic drug activity. However, in terms of defining its pharmacology, it is the potentiation of low levels of LI that has received by far the most attention and is, in fact, the only LI protocol which can be said to have been validated pharmacologically as a test for detecting potential antipsychotic agents.

The most widely used procedure for demonstrating facilitation of LI by a drug treatment has been the CER, using tone and shock as the CS and US, respectively, and using drinking as the dependent variable. However, all of the principal methods used for demonstrating LI in animals have successfully been used to show facilitation. There are at least two ways of demonstrating facilitation, which usually depends on the method being used. Thus in off-the-baseline experiments, such as most of those using CER and CTA procedures, facilitation of LI is usually shown by using conditions which, in control animals, result in very weak or negligible LI. Weak LI is achieved by using fewer pre-exposure trials than would be necessary to demonstrate robust LI (e.g., using 10 pre-exposures to the to-be-conditioned stimulus compared to 30). In other procedures, such as the CAR and some CER protocols using lever-pressing as the dependent measure, facilitation of LI is

shown by slower conditioning during CS−US pairing trials.

3.1. Antipsychotic agents

The antipsychotic compounds that have been tested for their ability to facilitate LI are listed in Table 1. It is immediately apparent that the majority of studies have examined the effects of the typical antipsychotic agent haloperidol. Haloperidol shows a remarkable consistency in its ability to facilitate LI, with all authors reporting positive effects. Facilitation of LI by haloperidol has also been reported in humans [304,305]. It is noteworthy that haloperidol is able to facilitate LI in experiments using a variety of different methods and that the doses required are broadly similar between protocols. In addition, these doses (around 0.03–0.3 mg/kg) are similar to those active in a variety of pharmacological tests for dopamine antagonist activity, considered to be relevant to its antipsychotic activity [16]. Although most protocols studying facilitation have used fewer CS presentations than would normally be required to produce LI, Weiner et al. [299] have recently shown that increasing the number of conditioning trials also attenuates LI and that under these conditions haloperidol and clozapine are able to reinstate LI. It should also be noted that in addition to facilitating LI in normal animals under conditions which generate weak LI, haloperidol (0.1 mg/kg i.p.) is also able to facilitate the development of LI in non-handled males (i.e., the animals remained undisturbed between birth and weaning), which do not display LI using conditions which allow its development in handled animals [70]. Gray et al. [103] have reported that injection of haloperidol directly into the nucleus accumbens results in enhanced LI. This effect was obtained with a single administration prior to the conditioning phase of a standard CER procedure and suggests a role for dopaminergic activity in the nucleus accumbens and during the conditioning phase of LI. The role of the nucleus accumbens in LI remains controversial however. Several authors have reported little or no effect of intra-accumbens amphetamine [146,153,154], whereas others find disruption of LI [103,247]; lesions of the accumbens have been reported to have no effect on LI [68,114] to disrupt LI [297] and to enhance LI [103]. Additional support for a role of nucleus accumbens dopamine comes from a recent microdialysis study which reported that pre-exposure to a stimulus attenuated dopamine release in the accumbens during subsequent conditioning to that stimulus [314].

A variety of other neuroleptic agents have also been tested for their ability to facilitate LI with essentially the same outcome, although in most cases results with these compounds have been reported only once in the literature and usually only a single dose has been examined, based on doses active in other preclinical tests of antipsychotic activity (an exception to this is clozapine which will be discussed in more detail later). In fact, most of these results come from a single study by Dunn et al. [64] who examined the effect of eight antipsychotic compounds, all of which (except clozapine) enhanced LI. They also examined the effects of several compounds which lack antipsychotic activity, none of which were active. Although this is a valuable study and remains the most extensive pharmacological examination of LI to date, the interpretation of these results is difficult for two reasons. Firstly, the use of only a single dose of each compound makes the negative effects difficult to interpret as, in a subsequent dose–response study from the same group, clozapine was reported to be active, albeit at a single, very low, dose [61]. This raises the question as to what effect other apparently inactive compounds might have had if a wide enough dose-range had been tested (although the doses appear to have been well chosen). Secondly, all treatments were subchronic (7 days) as the authors were unable to demonstrate an effect of haloperidol following a single administration, whereas other studies have been able to (e.g., Ref. [207]). Weiner and Feldon [283] have suggested that this may be because Dunn et al. [64] had pre-exposure and conditioning sessions on the same day, as this type of protocol can significantly affect the results obtained with amphetamine [290]. However, LI can be demonstrated using a variety of protocols with different delays between pre-exposure and conditioning, which (in theory) are not important to the LI effect itself [72,169], and studies with haloperidol demonstrate a positive effect of the drug given prior to both pre-exposure and conditioning (see Table 1) or just before conditioning alone [207]. One might therefore expect a single haloperidol administration to work in the Dunn et al. [64] protocol. In a subsequent response to the comments of Weiner and Feldon [283], Dunn suggested that other differences such as tone versus light, CS and US parameters, drug dosage schedules and age and strain of rats are likely to be just as important and need to be explored more fully [60], with which we would agree. However, Dunn [60] also reported in this response that a single dose of haloperidol was able to facilitate LI using their protocol. As an additional complication Dunn and Scibilia [62] have reported that a single administration of haloperidol or clozapine into the nucleus accumbens can enhance LI using the same 1-day exposure/conditioning protocol as before. It is interesting and relevant to this discussion that studies in acute schizophrenic patients demonstrating an LI deficit were carried out using a single session pre-exposure/conditioning protocol [20], as were studies showing a single dose of amphetamine could disrupt LI in normal humans [99].

In contrast to the effects of haloperidol and other neuroleptic agents tested, there is less consistency with the atypical antipsychotic drug, clozapine. Although a consensus is starting to emerge that it is able to facilitate LI, following either systemic injection [61,188,193,267,283] or directly into the nucleus accumbens [62], earlier studies

Table 1
Neuroleptic/antipsychotic compounds tested for facilitation of latent inhibition

Compound	Mode of action[a]	Dose range tested	Active doses/effect	Method used[b]	References[c]
Haloperidol	Dopamine	0.1 mg/kg i.p.	0.1 mg/kg	CER, sound/shock, drinking	[280]
	antagonist	0.1 mg/kg i.p. (a) before PE and C, (b) before PE only	(a) 0.1 mg/kg (b) inactive	CAR, sound/shock, avoidance learning; on baseline	[287]
		0.02–0.5 mg/kg i.p.	0.1, 0.5 mg/kg	CER, sound/shock, drinking	[73]
		0.1 mg/kg s.c.	0.1 mg/kg	CER, sound/shock, drinking	[192]
		0.1 mg/kg i.p.; before both PE and C or C only	0.1 mg/kg	CER, sound/shock, drinking	[207]
		0.003–3 mg/kg i.p. 7 days	0.03, 0.3 mg/kg	CER, light/shock, drinking	[64]
		0.3 mg/kg i.p.	0.1 mg/kg	Same day PE/C	*[60]*
		Not indicated	'Strengthened LI effect'	CTA, saccharin/LiCl, consumption of saccharin solution	*[114]*
		0.1 and 0.25 mg/kg	0.1, 0.25 mg/kg	CER, flashing light/shock, drinking	*[265]*
		(a) 0.03–0.2 mg/kg i.p. before PE and C	(a) 0.03, 0.1, 0.2 mg/kg	CER, sound/shock, drinking. Low basal LI obtained by extended conditioning rather than less PE	[299]
		(b) 0.1 before C only	(b) 0.1 mg/kg		
		0.1 mg/kg i.p., 4 different CS used	0.1 mg/kg, but only with flashing house-light CS	CER, 4 different visual stimuli/shock, drinking	[227]
Clozapine		1–10 mg/kg i.p.	Dose-dependent reduction of LI	CER, CS/US not indicated, measure not indicated	*[44]*
		10 mg/kg i.p. for 7 days	No effect	CER, light/shock, drinking	[64]
		2.5–10 mg/kg, route of administration not indicated	Dose-dependent enhancement of LI	CER, sound/shock, drinking	*[283]*
		0.01–3 mg/kg i.p. for 7 days	(a) inhibition by 1.3 mg/kg (b) enhanced at 0.1 mg/kg	CER, light/shock, drinking	*[61]*
		0.3–10 mg/kg s.c.	1, 10 mg/kg	CER, sound/shock, drinking	[193]
		5, 10 mg/kg i.p.	5 and 10 mg/kg	CER, sound/shock, drinking	[298]
		(a) 5 mg/kg i.p. before PE and C (b) 5 mg/kg i.p. before PE only (c) 5 mg/kg i.p. before C only	(a) facilitation of LI (b) no effect (c) facilitation of LI	CER, sound/shock, drinking. Low basal LI obtained by extended conditioning rather than less PE	[299]
		0.16 mg/kg s.c.	0.16 mg/kg	CER, sound/shock, drinking	[188]
		2.5, 5 and 10 mg/kg i.p.	10 mg/kg	CER, light/shock, drinking	[267]
Olanzapine	Clozapine-like	(a) 0.1–3 mg/kg i.p. (b) 0.03–0.3 mg/kg i.p. for 7 days	(a) inhibition at 3 mg/kg (b) enhanced at 0.1 mg/kg reduced LI at 0.3 mg/kg	CER, light/shock, drinking	*[61]*
α-Flupenthixol	Dopamine antagonist	0.23 mg/kg i.p. using two methods	0.23 mg/kg in both paradigms	(a) CER, sound/shock, lever pressing; on-baseline (b) Appetitively motivated conditioning, sound/sucrose solution, lever pressing; on-baseline	[148]
Fluphenazine		0.3 mg/kg i.p. for 7 days	0.3 mg/kg	CER, light/shock, drinking	[64]
Thiothixene		1 mg/kg i.p. for 7 days	1 mg/kg		
Chlorpromazine		10 mg/kg i.p. for 7 days	10 mg/kg		
Thioridizine		10 mg/kg i.p. for 7 days	10 mg/kg		
Mesoridazine		2 mg/kg i.p. for 7 days	2 mg/kg		
Metoclopramide		5 mg/kg i.p. for 7 days	5 mg/kg		
Remoxipride		1, 5, 10 mg/kg i.p.	1, 5 mg/kg	CER, light/shock, drinking	[266]
Sertindole	D_2/5-HT_{2A}/α_1 antagonist	5 mg/kg s.c.	5 mg/kg	CER, sound/shock, drinking	[292]

[a] This is the principal action of the compound, rather than a definitive list of all its activities.
[b] Three elements of the method are indicated: the basic protocol, the CS and US, and the behavioural method used to assess LI. CER, conditioned emotional response; CAR, conditioned avoidance response; CTA, conditioned taste aversion. All experiments are 'off baseline' except where indicated. All compounds administered prior to both PE and C unless otherwise stated. Other abbreviations: PE, pre-exposure; and C, conditioning.
[c] References in italics indicates that it is not a full paper.

had demonstrated both a lack of effect [64] and an inhibition [44] of LI by clozapine. One study even reported all three effects at different doses [61]. This variety of effects has been obtained, by and large, in different studies using similar CER paradigms, although as discussed above minor methodological differences may prove important. Part of this variability is clearly due to the doses used, as there is a strong tendency for clozapine to disrupt the development of the CER at higher doses (generally those of 5 mg/kg and above), but this effect varies between experiments (see Ref. [193] for example). It should be noted here in passing that haloperidol, at doses superior to those required to facilitate LI, has also been shown to disrupt the CER [73,276] (our own unpublished data). Further studies are clearly required in order to more fully characterise the effects of clozapine in LI models and to understand the methodological factors which contribute to its positive effects and those that might attenuate its ability to facilitate LI. This variable effect, in large part related to the doses used (e.g., Ref. [61]), demonstrates the importance of dose–response studies in LI.

This generally reproducible and consistent enhancement of LI by neuroleptic agents, including some that can be broadly labelled 'atypical', such as sulpiride [73] and more recently clozapine [61,62,193,267,283], olanzapine [61] and remoxipride [266], has provided one of the main supports for its use as a test for detecting novel and, hopefully, atypical antipsychotic agents. It is clear from the preceding discussion, however, that there are many important areas where further work is needed, particularly in determining the role that methodological factors play in determining pharmacological effects.

3.2. Other compounds reported to facilitate LI

Although the initial studies of drug effects in LI concentrated on compounds with known antipsychotic activity in the clinic, a substantial number of recent studies has centred around compounds with a high affinity for one or more of the 5-hydroxytryptamine (5-HT) receptor subtypes (see Refs. [123,122,177] for recent reviews of 5-HT receptor subtypes). This work has been fuelled by the mounting evidence of a role for 5-HT in schizophrenic symptomatology [24] and antipsychotic drug action, where affinity for 5-HT receptors may be important [158,224,233], as well as the wider availability of compounds with selectivity for subtypes of the 5-HT receptor. Also important is the extensive work showing the importance of brain 5-HT systems in LI. Thus, lesions of serotonergic input to the hippocampus, either by 5,7-dihydroxytryptamine lesions of the fornix-fimbria [42], or lesions of the median raphé nucleus [17,162,167,249], abolish LI.

The effects of serotonergic compounds on facilitation of LI are shown in Table 2. Those compounds that facilitated LI include the 5-HT_{1A} receptor antagonist WAY 100,635 [150] and the 5-HT_3 receptor antagonists dolasetron [192] and ondansetron [276]. In addition to these antagonists, the 5-HT uptake inhibitors fluoxetine and sertraline have also been reported to facilitate LI [128,163]. In view of the deleterious effects of serotonergic lesions on LI, the facilitatory effects of the antagonists appear unexpected. Killcross et al. [150] suggest that the effect of WAY 100,635 is via blockade of somatodendritic 5-HT_{1A} receptors, thereby increasing serotonergic activity in the

Table 2
Serotonergic compounds tested for facilitation of latent inhibition[a]

Compound	Mode of action	Dose range tested	Active doses/effect	Method used	References
Buspirone	5-HT_{1A} partial agonist	5 mg/kg i.p.	No effect	CER, sound/shock, lever press	*[128]*
WAY 100,635	5-HT_{1A} antagonist	0.5 mg/kg s.c. prior to PE, C or PE+C	0.5 mg/kg when administered prior to PE or PE+C	CER, sound/shock, leverpressing	[150]
M 100,907	5-HT_{2A} antagonist	0.1–3 mg/kg i.p.	No effect	CER, sound/shock, drinking	*[195]*
S 16924	5-HT_{1A} agonist, 5-$HT_{2A/2C}$ antagonist, D_4 antagonist, α_1 antagonist	0.08 mg/kg s.c.	0.08 mg/kg	CER, sound/shock, drinking	[188]
Dolasetron	5-HT_3 antagonist	0.01 and 0.1 mg/kg s.c.	0.1 mg/kg	CER, sound/shock, drinking	[192]
Ondansetron	5-HT_3 antagonist	0.01 mg/kg i.p.	0.01 mg/kg	CER, sound/shock, drinking	[276]
Fluoxetine	5-HT uptake inhibitor	5 mg/kg ip	5 mg/kg	CER, sound/shock, lever press	[128]
Sertraline	5-HT uptake inhibitor	5 mg/kg i.p. prior to PE	5 mg/kg	Passive avoidance, context/shock, avoidance	[163]
Imipramine	5-HT and NA uptake inhibitor	10 mg/kg i.p. for 7 days	No effect	CER, light/shock, drinking	[64]

[a] Notes as for Table 1.

hippocampus and cortex [84,117,125]. However, the effect of WAY 100,635 on raphé cell firing is weak [77] and a role for blockade of postsynaptic 5-HT_{1A} receptors, which are particularly prevalent in the hippocampus and cortex, cannot be ruled out. The 5-HT_3 receptor antagonists may be acting by modulating dopaminergic activity in the nucleus accumbens [51] although this remains controversial.

The effects of some of the more recent antipsychotic compounds should also be noted here as several, including sertindole [292], combine dopamine receptor antagonism with 5-HT_2 receptor antagonism. Some recent novel potential antipsychotics, such as S 16924, also combine 5-HT_{2A} antagonism with other activities (including dopamine D_4 and 5-HT_{2C} antagonism and 5-HT_{1A} agonism [187]) and are effective in facilitating LI [188]. However, antagonism of 5-HT_2 receptors alone, with the selective antagonist M 100,907, appears to be insufficient to facilitate LI [195], suggesting that under normal conditions these receptors are not activated.

Notable by their absence from this list are compounds acting at glutamatergic synapses. Increasing evidence suggests that a hypofunctioning glutamate system better explains the symptoms of schizophrenia than a hyperactive dopamine system does [106,115,131,155,259,268], and recent clinical studies are providing evidence that this theory has practical relevance too [89,155,259]. The absence of data on glutamatergic agonists in LI is a potentially weak aspect of its pharmacological validation and studies using the compounds becoming available [190,191] will be eagerly awaited.

3.3. Miscellaneous studies

In addition to serotonergic compounds, a few other potentially antipsychotic compounds have been tested as facilitators of LI (Table 3). These include the sigma receptor antagonist BMY-14802, the angiotensin-converting enzyme (ACE) inhibitor ceranopril, nicotinic agonists and amphetamine. The latter pair might appear somewhat paradoxical, in view of the use of nicotine and, particularly, amphetamine as inhibitors of LI (see below). However, there are logical reasons for having tested them as facilitators of LI.

In the case of nicotine, it was originally used in LI as a stimulator of dopamine release in the nucleus accumbens [138], a process thought by some authors to be critical to the disruptive effects of amphetamine in LI. However, there are also suggestions that schizophrenic patients may self-treat with nicotine as prevalence of smoking is particularly high in schizophrenics, possibly because it helps reduce extrapyramidal side-effects [90]. Although the original finding of Joseph et al. [138] has been repeated, albeit using essentially the same protocol [193], a recent study by Rochford et al. [222] has examined the effect of nicotine and the nicotinic agonists cytisine and lobeline in LI using a CER procedure in which lever pressing for food served to indicate the degree of conditioning. They found

Table 3
Miscellaneous compounds tested for facilitation of latent inhibition[a]

Compound	Mode of action	Dose range tested	Active doses/effect	Method used	References
Amphetamine	Induces carrier mediated release of dopamine	4 mg/kg	LI retained under conditions of CS−US pairings which abolished LI in controls	CER, sound/shock, not given	*[76]*
BMY-14802	Sigma antagonist	5–30 mg/kg i.p.	15, 30 mg/kg	CER, sound/shock, drinking	[294]
Ceronapril	ACE inhibitor	5, 50 and 500 μg/kg i.p.	50 μg/kg	CER, sound/shock, drinking	[291]
Proglumide	CCK antagonist	0.25, 0.5, 1 mg/kg i.p.	0.5 and 1 mg/kg	CER, flashing light/shock, drinking	[93]
Naloxone	Opiate antagonist	(a) 2 mg/kg s.c. immediately after PE	(a) 2 mg/kg	CER, sound/shock, heart rate conditioning in rabbits	(a) [80]
		(b) 1.5 μg into medial septal area	(b) not quite significant facilitation (P=0.06)		(b) [81]
Cytisine	Cholinergic agonist	2.5 and 5 mg/kg i.p.	5 mg/kg	CER, sound/shock, lever press	[222]
Lobeline	Cholinergic agonist	5 and 10 mg/kg i.p.	10 mg/kg		
Nicotine	Cholinergic agonist	(a) 0.2 and 0.4 mg/kg i.p. (base) before PE and C (b) 0.4 mg/kg i.p. before PE (c) 0.4 mg/kg i.p. before C	(a), (b) and (c) 0.4 mg/kg		
Chlordiazepoxide	Benzodiazepine agonist	10 mg/kg i.p. for 7 days	No effect	CER, light/shock, drinking	[64]
Trihexyphenidyl	Muscarinic antagonist	1 mg/kg i.p. for 7 days	No effect		
Promethazine	Histamine antagonist	20 mg/kg i.p. for 7 days	No effect		
Pentobarbital	Barbiturate	5 mg/kg i.p. for 7 days	No effect		

[a] Notes as for Table 1.

that all three compounds enhanced the expression of LI, and that this effect could be antagonised by mecamylamine and the peripheral nicotinic antagonist hexamethonium. Although this result is in complete contrast to those obtained by Joseph et al. [138] and by Moran et al. [193] using similar doses of nicotine (0.4–0.6 mg/kg), the conditions used by Rochford et al. [222] were unusual in that the amount of stimulus pre-exposure used was substantially more than was needed to obtain a maximal level of LI under their conditions. Indeed, they demonstrated that by reducing the amount of pre-exposure from 60 presentations of 60s duration each to 40 presentations of 5 s each (an 18-fold reduction down to levels comparable to those used by Joseph et al. [138]) the level of LI they obtained was unchanged but that nicotine administration now significantly inhibited LI. They suggest that the role of nicotinic receptors in LI may be different depending on whether it is 'robust' or 'labile'. In view of the activity of cytisine (which poorly penetrates the CNS) and the ability of the quaternary antagonist hexamethonium to block the facilitatory effects of nicotine it is likely that this facilitation of LI by nicotinic agonists is peripherally mediated. Exactly what this effect might be is not at all clear, although nicotine has several actions outside the CNS, including well-known cardiac and gastrointestinal effects. The authors themselves suggest that nicotine is stimulating catecholamine release from the adrenal glands and that this subsequently affects cognitive function. Further support for different mechanisms in these diametrically opposed effects of nicotine comes from the ability of lobeline to facilitate LI as it is much less potent than nicotine in mediating dopamine release [31,32,46,94], a mechanism clearly implicated in the ability of nicotine to disrupt LI [101,138,208]. Another interesting difference to the inhibitory effects of nicotine on LI is that the facilitatory effects were observed after pretreatment with nicotine prior to pre-exposure *or* conditioning. This demonstration that changing pre-exposure parameters can have such major consequences for drug effects on LI, although somewhat fortuitous in view of the extreme conditions of pre-exposure used, is an important observation that deserves following up, particularly under conditions of pre-exposure more generally used.

Clinical studies show that an LI deficit is apparent during the acute phase of the illness, but that LI is apparently normal during the chronic phase. Feldon et al. [76] have hypothesised that this might be due to increasing dopaminergic hyperactivity during the chronic phase resulting in perseveration in ignoring irrelevant stimuli. Thus, whereas low doses of amphetamine disrupt LI, higher doses will lead to a behavioural perseveration in ignoring the conditioning stimuli and thus produce 'super-LI'. That is, whereas LI can normally be overcome by increasing the number of CS−US pairings, this effect should be absent after high doses of amphetamine. This is indeed what they found: using a standard CER protocol, a high dose of amphetamine (4 mg/kg) made LI more resistant to the effect of increased CS−US pairings. This is a potentially important result that needs exploring using other protocols as it may shed light on some of the disparate findings obtained with amphetamine in different LI paradigms in the past. Perhaps more importantly, it may provide an understanding of the dynamics of LI in schizophrenic patients (i.e., its reinstatement with disease chronicity) and give insights to the disease process itself.

A few other miscellaneous drugs have been tested as facilitators of LI. Sigma receptors have recently been targets for antipsychotic drug development as several neuroleptics have high affinity for the sigma receptor and agonists of this site have psychotogenic potential [246]. Compounds have recently been developed that show some selectivity as antagonists for this receptor, and one of them, BMY-14802, has been shown to facilitate LI [294]. Recent clinical studies suggest however, that sigma antagonists may be devoid of antipsychotic activity [85].

Acute treatment with the ACE inhibitor ceronapril was also recently found to facilitate LI, having been tested on the basis that the angiotensin-converting enzyme might be involved in the metabolism of cholecystokinin, a peptide that may modulate dopamine release in the limbic system [291]. However, chronic treatment with ceronapril disrupted LI [293], and a recent study demonstrated facilitation of LI with the cholecystokinin antagonist proglumide [93]. These diverse effects may reflect the complex interaction of cholecystokinin with dopamine systems or with other neurotransmitters (see Ref. [93] for discussion of these issues).

Finally, as part of a series of studies evaluating the role of opioid mechanisms in learning, the effect of post-exposure naloxone has been evaluated in an LI model following either parenteral [80] or intra-septal injections [81]. In both cases evidence for facilitation of LI was obtained.

3.4. Compounds that do not facilitate LI

Few studies have been carried out to explicitly examine the validity of LI models by testing compounds that lack antipsychotic effects in man. The exception to this is the study of Dunn et al. [64] (see also Section 3.1 for additional discussion of this study), where several compounds were tested following 7 days administration. They showed that a tricyclic antidepressant (imipramine), a benzodiazepine (chlordiazepoxide), an antimuscarinic agent (trihexyphenidyl), an antihistamine (promethazine) and a barbiturate (pentobarbital) were all incapable of facilitating LI. Although such studies are of great importance in demonstrating the relevance of LI to attentional deficits of schizophrenia, further work is needed as, in the same study, clozapine failed to facilitate LI although a subsequent dose–response study demonstrated an effect (see Section 3.1).

Table 4
Effect of local intracerebral injection of compounds on facilitation of LI[a]

Compound	Dose and site	Active dose/effect	Method	References
Haloperidol	0.5 μg intra-accumbens prior to C	0.5 μg	CER sound/shock, drinking	[103]
Haloperidol	0.05 μg intra-accumbens	0.05 μg	CER, light/shock, drinking	*[62]*
Clozapine	1 μg intra accumbens	1 μg		
Naloxone	1.5 μg into the septal region	'Modest' increase', not quite significant ($P=0.06$)	CER, sound, heart-rate conditioning in rabbits	[81]

[a] Notes as for Table 1.

Low doses of apomorphine, which reduce dopamine release by selective activation of dopamine autoreceptors, might be expected to facilitate LI like the neuroleptics. However, no clear evidence for facilitation has been published. In one study, which examined the effects of low doses of apomorphine, no facilitatory effect was observed [75]. A more recent study has examined the effect of prefrontal cortex administration of apomorphine and although not significant, there was a suggestion of enhanced LI which could not be clearly defined due to ceiling effects and decreased suppression in the non-pre-exposed animals [33].

3.5. Anatomical and neurochemical systems involved in facilitation of LI

Lesion studies have identified certain brain structures and systems, including the hippocampus, nucleus accumbens, subiculum and median raphé nuclei, as being of particular importance for the development of LI. This is an extensive literature and will not be dealt with here in detail. Briefly, however, lesions of the hippocampal formation have variable effects which seem to depend to some extent on the site of the lesion and the method used to assess LI [45,82,120,140,213,217,311]. Lesions of the nucleus accumbens have been also been reported to have variable effects on LI [114,154,258], which may depend on the part of the accumbens affected, as lesions of the shell, but not the core, of the accumbens abolished LI [295]. More consistently, removal of the serotonergic input to the hippocampus is widely reported to abolish LI [17,42,162,167,249]. Studies on the mechanisms by which drugs may facilitate the development of LI have therefore started by investigation of these areas, either by studying the effect of haloperidol following a central lesion that abolishes LI, or by direct injection of drugs into brain structures. To date, however, only a limited number of studies have been reported and these are summarised in Tables 4 and 5.

Although it would be desirable to be able to make correlations between the doses active in LI and those active in the clinic, very few dose–response curves have been established apart from those for haloperidol and, more recently, clozapine. Much of these data is therefore of a qualitative nature and does not allow any deeper validation at a more quantitative level, nor to make correlations between affinities for various receptors and activity in LI. This latter possibility would be particularly interesting with some of the more recent compounds with mixed activity at dopamine D_2/D_3 receptors and D_2/5-HT_2. It is therefore very difficult to make firm conclusions about receptor subtypes involved in LI until either such studies are carried out or more selective compounds are used.

One neurochemical system that has received little attention, as far as drug studies of LI are concerned, is the noradrenergic system. This is somewhat surprising in view of the postulated role for noradrenergic mechanisms in other aspects of attention [52,225], and the publication of several reports (over 10 years ago) that selective lesions of

Table 5
Effect of haloperidol following lesions which abolish LI[a]

Lesion	Dose of haloperidol	Effect on LI	Method	References
Knife-cut to subicular input to the n. accumbens	0.2 mg/kg	Reinstatement	Not indicated	*[260]*
Bilateral electrolytic lesions of n. accumbens shell region	0.2 mg/kg i.p.	Reinstatement	CER, sound/shock, drinking	[297]
5,7-DHT lesion of median raphé nucleus	0.5 mg/kg i.p.	Reinstatement	Conditioned passive avoidance, context/shock, passive avoidance response	[166,167]
Retrohippocampal NMDA lesion from entorhinal cortex to central subiculum	0.2 mg/kg i.p.	Reinstatement	CER, flashing light/shock, drinking	[311]

[a] Notes as for Table 1.

noradrenergic systems could attenuate LI [13,162,179]. However, more recent studies failed to find an effect of lesions of the noradrenergic dorsal bundle [269].

4. Disruption of LI

As shown in Table 6, a large number of compounds have been shown to disrupt LI. In most cases these effects have only been reported once, except for the effects of amphetamine, nicotine and DOI, which have been shown to disrupt LI by at least two laboratories. In the case of amphetamine, its disruptive effects on LI have also been demonstrated using a wide range of different LI experimental protocols, suggesting that like the facilitation of LI by neuroleptics, the disruption by amphetamine is independent of the method used to study LI.

4.1. Amphetamine

Numerous studies have shown that the indirect dopamine agonist amphetamine, when given at both pre-exposure and conditioning phases, disrupts LI in rats (Table 6). Initial studies suggested that amphetamine needed to be administered at least twice, before both the pre-exposure and conditioning phases, to disrupt LI [285,290]. It was suggested that the amphetamine-induced dopamine release needed to be calcium dependent for it to be able to inhibit LI and this only occurs after a second injection, the initial effect being calcium-independent [277]. Gray et al [103] have suggested that the first injection of amphetamine has an action on the ventral tegmental area, having a sensitizing effect for a second action of amphetamine in the nucleus accumbens. They showed that a systemic administration of amphetamine, followed 24 h later by intra-accumbens amphetamine successfully disrupted LI. In contrast, nicotine-induced dopamine release is calcium-dependent following the first administration, and correspondingly, only a single treatment prior to conditioning is required to disrupt LI [138]. However, single administrations of amphetamine can be effective in abolishing LI in man [99], and recent studies suggest that the same is true in rats [180,194]. McAllister [180] reported abolition of LI with a single dose of amphetamine given 30 min prior to pre-exposure and conditioning (which were run consecutively). This was subsequently confirmed by Moran et al. [194], who describe abolition of LI with a single dose of amphetamine administered 45 or 90 min prior to the conditioning phase, but not when it was administered 15 min before, a pretreatment time used in the majority of studies. Moran et al. [194] hypothesise that with the longer pretreatment time the dopamine release induced by amphetamine becomes progressively more calcium-dependent. Comparisons of dose–response curves under these different conditions have yet to be made, and no comparative pharmacological studies have been carried out.

The dose–response relationship of amphetamine's effects on LI appears to be inverted U-shaped, with low to moderate doses disrupting LI, but high doses having no effect [289]; indeed, as already discussed above, high doses of amphetamine can result in what has been called 'super-LI' (see Section 3.3). Because low doses of amphetamine preferentially release dopamine in the nucleus accumbens, whereas high doses seem to affect primarily striatal dopamine [102], it has been hypothesized that dopamine in the nucleus accumbens plays a significant role in LI [102]. Experiments measuring dopamine release in the nucleus accumbens by microdialysis found that in non-pre-exposed animals, CS presentation elicited dopamine release during conditioning, but this conditioned dopamine release was not exhibited by animals that had been pre-exposed to the to-be-conditioned stimulus [313,314]. In addition, intra-accumbens amphetamine has been shown to disrupt LI [103,247], although others have not replicated this effect [68,146] (see Table 7).

An alternative hypothesis for the mechanisms underlying LI disruption by amphetamine has been suggested, related to modifications of reinforcer strengths [143,147]. In a series of experiments, it was found that disruption of LI by amphetamine could be prevented by decreasing the intensity of the US. The authors hypothesize that amphetamine disrupts LI by modifying the animal's perception of the US during the conditioning process. Thus, properties of the US such as intensity or duration could influence the effect of amphetamine on LI. This remains the subject of much debate (see Section 2).

4.2. Other dopaminergic compounds

The direct D_1 agonist SKF 38393 and the direct D_2 agonist quinpirole have been reported to disrupt LI [63] and to have no effect [75]. These disparate results cannot be explained simply as dose differences because similar doses were used in the two studies. The disruption by quinpirole and SKF 38393, although in agreement with the idea that increased dopaminergic activity should disrupt LI, is difficult to evaluate further because it has only been reported in abstract form [63]. The lack of effect seen in the other study [75] has been interpreted to indicate that direct stimulation of dopamine receptors does not have the same effect on LI as indirect stimulation with amphetamine. Support for this interpretation comes from a further experiment demonstrating that the direct D_1/D_2 agonist apomorphine also had no effect on LI. Differential effects of amphetamine and apomorphine have also been seen with other behavioural measures [178,218]. It has also been pointed out that amphetamine can induce psychotic symptoms in humans, whereas apomorphine does not [11,156]. Thus, if LI reflects an attentional process that can be disrupted by psychosis, one might expect a parallel disruption with amphetamine but not with apomorphine.

Two groups in The Netherlands have studied the effects

Table 6
Compounds which have been tested for their ability to disrupt LI[a]

Compound	Mode of action	Dose-range tested	Active doses/effect	Method used	References
DL-Amphetamine	Induces carrier mediated release of dopamine	1.5 mg/kg i.p. for either 14 days, during PE only, or for 15 days (including PE)	(1) No effect. (2) LI abolished (3) No effect (4) LI abolished	(1 & 2) CER, sound/shock, drinking. PE and cond. on same day. (3 & 4) As above but PE and cond. separated by 24 h.	[285]
		6 mg/kg i.p. acutely or for 5 days	No effect	CER, sound/shock, drinking	[289]
		1.5 mg/kg i.p.	1.5 mg/kg	(1) CER, sound/shock, drinking (2) CAR, sound/shock, trials to criterion	[290]
D-Amphetamine		1 and 4 mg/kg s.c. for 5 days. Last administration 45′ prior to CAR training	4 mg/kg	CAR, sound/shock, trials to criterion for acquisition of CAR	[250]
		2×1 mg/kg, 24 h and 15′ prior to PE, C and testing (all in single session)	Abolished LI	CER, tone:flashing light/shock, drinking. Within subject method; pre-exposure, conditioning and testing on same day.	*[312]*
		1.5 mg/kg i.p. tested with different stimulus PE durations (3″, 30″, 150″).	1.5 mg/kg only at 30″ PE duration	CER, sound/shock, drinking	[56]
		(1) 0.5, 1.5, 3 mg/kg i.p. (2) 0.5 mg/kg i.p. with different shock intensities	(1) Suggestion (not overall significant) of attenuated LI at 1.5 mg/kg. No effect of other doses (2) Amphetamine attenuated LI, an effect abolished by reducing the intensity of footshock	(1) Appetitive conditioning, tone/food reward, magazine entries (2) CER, sound/shock, lever press for food reward	[147]
		Not given	'Attenuation of LI'	CTA, saccharin/LiCl, consumption of sacharin solution	*[114]*
		1.5 mg/kg i.p.	Abolished LI	CAR, tone/shock, % avoidance	[19]
		0.1–1 mg/kg s.c.	1 mg/kg	CER, sound/shock, drinking	[193]
		1 mg/kg i.p., 4 different CS used	1 mg/kg, but only with flashing house-light CS	CER, 4 different visual stimuli/shock, drinking	[227]
		0.32 mg/kg s.c., before single session PE and C	Abolished LI	CER, sound+light/shock, lever pressing for food reward	[180]
		0.1–0.5 mg/kg i.p.	0.25 and 0.5 mg/kg	CTA, sucrose/LiCl, consumption of sucrose solution	[68]
		0.25 and 0.5 mg/kg i.p.	0.5 mg/kg 0.25, 0.5 mg/kg	Passive avoidance, context/shock, avoidance CTA, sucrose/LiCl, consumption of sucrose solution	[57]
Amantadine	DA releaser/non competitive NMDA antagonist	25 and 50 mg/kg i.p. prior to conditioning	50 mg/kg	Passive avoidance, context/shock, avoidance	[124,164]
Nomifensine	DA uptake blocker	10 mg/kg i.p. before C	10 mg/kg		
Buproprion	DA uptake blocker	30 mg/kg i.p. before C	30 mg/kg		
SKF 38393	D_1 agonist	3, 10 mg/kg s.c.	'Dose-related attenuation'	CER	*[63]*
Quinpirole	D_2 agonist	0.1, 0.3, 0.56 mg/kg	'Dose-related attenuation'		
SKF 38392	D_1 agonist	1, 5, 10 mg/kg s.c.	No effect	CER, sound/shock, drinking.	[75]
Quinpirole	D_2 agonist	0.1, 0.3, 1 mg/kg s.c.	No effect		
Apomorphine	Dopamine agonist	0.03, 0.3, 1.5 mg/kg s.c.	No effect		
Clozapine	Atypical antipsychotic	1, 5, 10 mg/kg i.p.	'Dose-dependent reduction of LI'	CER	*[44]*
amperozide	Atypical antipsychotic	1 mg/kg i.p. for 7 days	'Significantly decreased LI'	CER	*[63]*
Fluperlapine	Atypical antipsychotic	10 mg/kg i.p. for 7 days	'Significantly decreased LI'		

Table 6. Continued

Compound	Mode of action	Dose-range tested	Active doses/effect	Method used	References
(−)-Nicotine	Cholinergic agonist	(a) 0.2–0.8 mg/kg s.c. (nicotine base); 0.6 mg/kg s.c. (b) before PE or (c) before C	(a) 0.4–0.8 mg/kg. 'The loss of LI at 0.8 mg/kg was less clear cut' (b) no effect; (c) abolished LI	CER, tone/shock, drinking	[138]
		0.3, 0.6, 1.2 mg/kg s.c. (=0.11, 0.21, 0.42 mg/kg of base)	All doses abolished LI, but the effect was clearest at 0.6 mg/kg	CER, tone/shock, drinking	[193]
		0.4 mg/kg i.p. (base)	0.4 mg/kg	CER, tone/shock, lever pressing	[222]
8-OH-DPAT	5-HT_{1A} agonist	0.19, 0.38 mg/kg i.p.	No effect on LI but increased suppression in all groups	CER, tone/shock, drinking	[41]
RU 24969	5-HT_{1B} agonist	0.5, 10 mg/kg i.p.	0.5, 10 mg/kg		
Ritanserin	5-$HT_{2A/2C}$ antagonist	0.67, 2 mg/kg i.p.	2 mg/kg	CER, tone/shock, drinking	[41]
DOI	5-$HT_{2A/C}$ agonist	0.01, 0.1, 1 mg/kg	1 mg/kg	Conditioned response, sound/sucrose reward, anticipatory nose-poking for reward during CS presentation. Within subject method	*[183]*
		0.3–5.6 mg/kg s.c., prior to PE or PE+C	Disruption of LI when given during PE only (1–5.6 mg/kg). No effect when given during both PE and C	CER, tone/shock, drinking	[116]
Phencyclidine (PCP)	Noncompetitive NMDA antagonist	0.5, 1, 3, 7 mg/kg i.p.	No effect	CER	*[44]*
		1 and 5 mg/kg i.p.. PCP was administered either prior to PE, C or both	No effect	CER, tone/shock, drinking	[281]
		2.5 mg/kg i.p. (15 min pretreatment) or 8.6 mg/kg i.p. (20 h pretreatment)	No effect of 2.5 mg/kg. Abolished by 8.6 mg/kg	CTA, sucrose/LiCl, sucrose consumption	[271]
		1 or 5 mg/kg/day s.c. via slow release pellet or 1 or 5 mg/kg i.p. per day for 5 days	5 mg/kg/day slow release pellet	CAR, light-sound/shock, avoidance	[235]
Ketamine	NMDA antagonist	25 mg/kg i.p.	Abolished LI when given before PE but not if given before C and test. Authors suggest that the effect is due to state dependency	CTA, sucrose/LiCl, sucrose consumption	[4]
		50 mg/kg i.p. immediately after each saccharin PE	Abolished LI	CTA, saccharin, saccharin consumption	[83]
MK-801	NMDA antagonist	0.1 mg/kg s.c. for 5 days prior to PE	No effect	Classically conditioned rabbit nictitating membrane response to tone	[221]
Strychnine	Glycine antagonist	0.75 mg/kg i.p.	Abolished LI	CAR, tone/shock, % avoidance	[19]
Caffeine	Adenosine antagonist	10 mg/kg s.c.	No effect on LI, but increased overall performance on CAR		
Chlordiazepoxide	Benzodiazepine agonist	5 mg/kg i.p. either prior to PE, C or both	Abolished LI if given prior to PE but not if given prior to C	CER, tone/shock, drinking	[71]
SR 48692	Neurotensin antagonist	Not given	'Dose-dependently attenuated'	No details given	Kilts (1993), unpublished abstract; ACNP meeting
Substance P	Neuropeptide	100 μg/kg s.c. prior to PE, C or PE+C	Abolished LI when given before PE+C or C	Passive avoidance, context/shock, avoidance	[165]
Ceronapril	ACE inhibitor	50 μg/kg i.p. (chronic)	Abolition of LI	CER, sound/shock,drinking	[293]
LiCl		0.15 mEq/kg for 6 days	Impaired LI	CAR, sound/shock, trials to criterion and escape latencies	[38]
Testosterone	Anabolic steroid	13.5 mg/kg, 7 times during 17 days prior to and concurrent with LI procedure	Prevented the development of LI	CER, context exposure/shock, conditioned freezing to context	*[141]*
Nandrolone	Anabolic steroid	Equimolar dose to that of testosterone indicated above. Same schedule	No effect		

[a] Notes as for Table 1.

Table 7
Effect of local intracerebral injection of compounds on abolition of LI[a]

Compound	Mode of action	Doses and site	Active doses/effect	Method used	References
D-Amphetamine	Induces carrier mediated release of dopamine	10 μg/0.5 μl for 5 days into: (1) n. accumbens (2) Caudate putamen	(1) LI abolished (2) No effect	CAR, sound/shock, trials to criterion for acquisition of CAR	[247]
		(1) 3 and 10 μg/μl intra-accumbens (2) 0.5 mg/kg i.p.	(1) Authors report no significant effects, but one dose (unclear which due to typographical error) appears to have reduced LI. (2) Abolition of LI.	CER, sound/shock, lever press for food reward; within subject	[146]
		1 mg/kg i.p. prior to PE and 5 μg intra-accumbens prior to C	Abolition of LI	CER, sound/shock, drinking	[103]
		10 μg/0.5 μl (during PE and C) into (1) n. accumbens (2) dorsal striatum	(1) No effect (2) LI abolished	CTA, sucrose/LiCl, consumption of sucrose solution (during fixed period or time to drink fixed volume)	[68]
Apomorphine	Dopamine agonist	9 μg/side; medial prefrontal cortex	No effect	CER, flashing light/shock, lever pressing	[33]
cis-Flupenthixol	Dopamine antagonist	12 μg/side; medial prefrontal cortex	Abolition of LI		
SCH 39166	Dopamine D_1 antagonist	500 ng/0.5 μl/side; medial prefrontal cortex	No effect	CTA, sucrose/LiCl, consumption of sucrose solution	[67]
Sulpiride	Dopamine D_2 antagonist	12.5, 25, 100 ng/0.5 μl/side; medial prefrontal cortex	No effect		
Morphine	Opiate agonist	8 μg into the right n. accumbens prior to PE	No effect on LI, but abolished context specificity	CER, sound/shock, freezing	[302]

[a] Notes as for Table 1.

of injecting dopamine agonists or antagonists into the medial prefrontal cortex (see Table 7), an area thought to be intimately involved in the cognitive deficits of schizophrenia (see Refs. [96,278]). Broersen et al. [33] administered the non-selective dopamine agonist apomorphine and the non-selective dopamine antagonist flupenthixol bilaterally into the medial prefrontal cortex. Flupenthixol, but not apomorphine disrupted LI. This result is the opposite of what has been reported following systemic administration of these compounds [75,148] but is in agreement with the hypothesis that subcortical and cortical dopamine systems act reciprocally [59,168,214]. However, the disruption reported for flupenthixol may not actually represent disruption of LI itself but rather a disruption of the ability to detect it as the non-pre-exposed groups showed decreased learning, rather than the pre-exposed groups showing improved learning as would be required for disruption of LI. Using more selective antagonists of the dopamine D1 or D2 receptor (SCH 39166 and sulpiride, respectively), Ellenbroek et al. [67] recently failed to demonstrate an effect on LI, suggesting, perhaps, that blockade of both D1 and D2 receptors in the prefrontal cortex are necessary for disruption of LI.

4.3. Nicotine

Disruption of LI by the cholinergic agonist nicotine has been demonstrated in three studies in animals [138,193,222]. This disruption has been attributed to nicotine's ability to release dopamine selectively in the nucleus accumbens [138], thus acting as an indirect dopamine agonist similar to low doses of amphetamine. This finding lends further support to the hypothesis that LI is disrupted by indirect but not direct dopamine agonists. The nicotine-induced disruption can be reversed by treatment with antipsychotics that have dopamine antagonist activity (see next section), again in agreement with the idea that it is acting as a dopamine agonist.

In order to disrupt LI, it is only necessary to administer nicotine prior to the conditioning phase of the experiment [138]. This supports other studies demonstrating that this is the phase most sensitive to dopaminergic pharmacological manipulations [207,285,287] (however see Refs. [71,116]). Further evidence that the effect of nicotine is mediated by the dopaminergic system has been provided by Warburton et al. [277] who showed that impulse dependent release of dopamine by nicotine is important for its disruption of LI.

In contrast to the results in rats, it has been difficult to show an effect of nicotine on LI in man. Thornton et al. [262] studied the effects of smoking and of subcutaneous nicotine in non-smokers on LI and failed to find an effect. However, Allan et al. [8] have reported that LI is reduced in smokers, a finding that was not replicated in a smaller group of subjects in a subsequent study by the same group [305]. Although no clear explanation is currently available, various suggestions for the discrepancy between animal and human studies have been offered by the authors of these studies and may relate to the limit on the dose of nicotine that can be given before nausea occurs in man.

4.4. Serotonergic compounds

Many of the results obtained with compounds or lesions affecting serotonergic activity indicate that reduction of serotonergic transmission leads to disruption of LI. This has been shown with serotonin depletion by *p*-chlorophenylalanine [248], median raphe lesions [249] and stimulation of the 5-HT_{1B} presynaptic autoreceptor [41]. Selective destruction of the serotonergic innervation of the hippocampus with 5,7-dihydroxytryptamine lesions of the fimbria-fornix also disrupts LI, suggesting a locus for the disruption of LI by serotonin-reducing manipulations [42].

In contrast, the 5-$HT_{2A/2C}$ agonist DOI has been shown to disrupt LI in both appetitive [183] and aversive [116] conditioning procedures. These results appear contradictory to the hypothesis that decreased serotonergic activity disrupts LI but, in fact, systemic administration of DOI has been shown to inhibit 5-HT neuronal firing in the dorsal raphe and decrease extracellular 5-HT in the frontal cortex [309]. Although this offers an interpretation that is consistent with previous findings, a definitive explanation of the effects of various serotonergic manipulations on LI remains to be established. The disruption of LI by DOI is in agreement with the findings that DOI is hallucinogenic in humans [88,201,241] and that hallucinogenic potency of DOI, LSD and several related hallucinogens is correlated with 5-HT_{2A} receptor affinity [88,263]. DOI has also been shown to disrupt prepulse inhibition [204,244], an animal model of sensorimotor filtering processes which, like LI, is disrupted in schizophrenia [27]. Thus, disruption of LI by DOI is consistent with the hypothesis that LI reflects an attentional process that is disrupted in schizophrenia and by psychotomimetic agents, and also with the increasing evidence that 5-HT_2 antagonism is an important component of atypical antipsychotic activity [186]. In this context, it is not surprising that the 5-HT_{2A} antagonist and potential antipsychotic M 100,907 reverses the disruptive effects of amphetamine and DOI on LI [116,195]. Similar effects were obtained with antipsychotics possessing 5-HT_{2A} antagonist activity such as clozapine, haloperidol, and risperidone [116] (see next section). It is not clear, however, why numerous compounds with 5-HT_2 antagonist activity (not necessarily selective), including ritanserin and amperozide, and the atypical antipsychotics clozapine and fluperlapine, have also been shown in some cases to disrupt LI [41,44,63].

An unusual feature of DOI's disruption of LI is that it can only be obtained if DOI is administered only at the pre-exposure phase [116,183]; administration at both pre-exposure and conditioning phases did not significantly disrupt LI except at a dose which caused disruption of the CER itself [116]. Reasons for differential effects of DOI at pre-exposure and conditioning are presently unclear, although the involvement of state-dependent learning, anxiolytic effects or contextual shift effects is plausible.

4.5. Glutamatergic compounds

As well as dopaminergic and serotonergic mechanisms, glutamatergic systems are also thought to play a major role in schizophrenia [40,155,161,259] (see also Section 3.2) and a range of compounds interacting with the glutamate receptor complex have been studied. The *N*-methyl-D-aspartate (NMDA) antagonist ketamine has been reported to disrupt LI [4,83], but its effects appear to be due to state-dependency as disruption was only observed when the compound was administered at the pre-exposure phase, but not when it was administered at pre-exposure, conditioning and testing phases [4].

It was also initially reported that NMDA antagonists, such as MK-801 and phencyclidine (PCP) do not disrupt LI [221,281]. However, closer inspection of the results obtained with PCP by Weiner and Feldon [281] suggests that the 1-mg/kg dose may have disrupted LI when administered only at the pre-exposure phase, but the LI effect in vehicle-treated animals was too small for this to be significant. PCP did not disrupt LI when administered prior to all phases of the experiment, however, indicating that any effects obtained with administration at the pre-exposure phase may have been similar to those reported for ketamine and due to state-dependency. This lack of effect of PCP was interpreted to indicate that LI models an attentional process that is only deficient during manifestations of positive symptomatology and, as such, should only be affected by dopaminergic manipulations (such as amphetamine) but not by glutamatergic manipulations [281]. This interpretation is supported by the findings that LI deficits only occur in acute schizophrenia and disappear in the chronic disease state [97], which can be characterized by a preponderance of negative symptomatology. However, this interpretation does not fit with the findings that ketamine and PCP produce both positive and negative symptoms, rather than negative symptoms only.

More recently, two studies have shown that PCP can indeed disrupt LI under appropriate conditions. One study used the relatively high dose of 8.6 mg/kg of PCP given 20 h prior to pre-exposure and conditioning in a conditioned taste aversion protocol was able to abolish LI [271]. The authors suggest that high doses are necessary to

disrupt LI and that the long pretreatment time was necessary to avoid relatively short-lasting motor-impairment effects of PCP. A more recent study by Schroeder et al. [235] used a slow-release pellet to administer PCP continuously over 5 days (1 or 5 mg/kg per day) and compared this with repeated daily injections of the same doses (1 or 5 mg/kg i.p.). The low dose was without effect after either mode of administration. In contrast, the higher dose abolished LI, but only when given continuously—the repeated daily injections were without effect. The authors of this study evaluated the treated animals in several additional tests and the results shed some light on why the early studies failed to show a clear impairment of LI with PCP. Repeated daily treatment with PCP increased anxiety (as measured by open-arm entries on an elevated plus-maze) and also increased locomotor activity [235], whereas the continuous administration of the same total daily dose had no effect on these parameters. The anxiety and locomotor effects of acute PCP may explain the absence of a clear disruption in earlier studies and explain the need for long pretreatment times as used by Turgeon et al. [271] as the locomotor stimulant effects disappear relatively quickly [2]. Thus, whereas in man a psychotic state can be identified after even quite high doses (including after overdose) despite the occurrence of other symptoms [127,212], it is necessary to use a dosing procedure that eliminates these other effects in animal studies as they interfere with our ability to detect a 'psychosis-like' state.

4.6. Antipsychotic agents

Perhaps surprisingly, several antipsychotic agents have been reported to disrupt LI, including haloperidol (in both rat and man) [276,306], clozapine [44,61,193], amperozide and fluperlapine [63]. In general these effects have been observed with high doses, beyond the range at which enhancement of LI takes place. In addition, the reduction of LI is often due to disruption of learning or reduced conditioning in the non-pre-exposed group.

4.7. Other compounds

A variety of neuropeptides interact with brain dopaminergic systems and a few studies have explored the effect of modulating peptidergic activity on LI. The neurotensin antagonist SR 48692 has been reported to disrupt LI (Kilts, unpublished data presented at ACNP Meeting, 1993). This finding is consistent with the hypothesis that neurotensin agonists might have antipsychotic potential, as it has recently been demonstrated that neurotensin itself and the neurotensin agonist NT1 exhibit antipsychotic profiles in preclinical behavioural tests [230]. As a close functional relationship between neurotensin and dopamine exists in the mesolimbic pathways [199], it is possible that the effects of SR 48692 on LI are mediated through this dopaminergic pathway. Numerous peptidases control extracellular concentrations of neuropeptides, one of which is the angiotensin-converting enzyme (ACE). Inhibition of ACE increases cholecystokinin levels, which are thought to modulate dopamine release in the nucleus accumbens. Chronic administration of the ACE inhibitor ceronapril has been reported to disrupt LI [293], in contrast to its acute effect of LI enhancement [291]. To our knowledge, possible differential effects of acute versus chronic administration of ceronapril on receptor state or modulation of dopamine release have not been explored. Finally, the effect of peripheral administration of substance P on LI has been examined. It was found to disrupt LI when administered prior to conditioning or conditioning and pre-exposure, but not when given before pre-exposure alone [165]. This effect was antagonised by haloperidol.

Lithium chloride, used in the treatment of mania, has also been shown to disrupt LI using a CAR procedure [38]. The authors hypothesize that lithium disrupted LI by increasing attention to the to-be-CS (tone presented during pre-exposure). However, lithium also impaired learning in the non-pre-exposed animals, suggesting that disruption of conditioned responding itself may explain the results. Lithium is not reported to have any major impact on schizophrenic symptoms [58,133].

Strychnine, an antagonist of the glycine-gated chloride channel, has also been reported to impair LI using the CAR protocol [19]. However, this too may not be a specific effect on LI as strychnine increases reactivity to noxious stimuli [22], suggesting that it may have disrupted LI by increasing the salience of the footshock US used by Bakshi et al. [19], a parametric manipulation shown to reduce LI [148].

It has been reported that the benzodiazepine agonist chlordiazepoxide disrupts LI when administered during pre-exposure or during both pre-exposure and conditioning [71]. Typically, disruption of LI is characterized by *improved* learning in non-pre-exposed animals. However, in this experiment, inspection of the data suggests that this disruption is actually due to *impaired* learning in the pre-exposed group, as well as in the non-pre-exposed group. It is therefore difficult to consider this effect as disrupted LI. The authors ruled out state-dependent effects between pre-exposure and conditioning because of the similar findings with treatment during pre-exposure alone or during pre-exposure and conditioning. However, state-dependent effects might also be apparent between conditioning and testing phases in such off-baseline procedures, requiring administration during all three parts of the experiment to completely rule it out. Alternatively, these findings could be explained by anxiolytic effects of chlordiazepoxide, especially at the conditioning phase, in which shock was used as the US.

The effects of anabolic steroids on LI have been examined using CER with context conditioning in male rats [141]. This abstract reported disruption of LI by chronic administration of testosterone prior to and concur-

rent with the LI procedure, or with administration 10 months earlier during the rats' adolescent stage of development. Nandrolone also disrupted LI with administration 10 months earlier, but had only marginal effects when administered prior to and concurrent with the LI procedure. These results suggest that androgenic (testosterone and nandrolone) versus estrogenic (metabolism of testosterone) effects have differential influence on LI [141]. It is possible that these findings may have some relation to the finding that LI is disrupted only in male nonhandled rats [70], and have some relevance to the greater proportion of male schizophrenics with early onset disease. A variety of other manipulations which are either stressful or are known to affect hormone levels have been examined for their effects on LI. These include maternal separation and social isolation. Interestingly, the former disrupts LI [136], but the latter does not [303].

In summary, the only compounds shown to disrupt LI in at least two studies by separate laboratories are amphetamine, nicotine, and DOI. This lends support for the postulated roles for dopaminergic and serotonergic systems in LI. In addition, a good case can be made that the disruptive effects obtained with some other drugs are due to modulatory influences upon these systems. Recent data suggest that the glutamatergic antagonist PCP can be added to this list, supporting an involvement of the glutamatergic system in LI, an important advance given the increasing importance postulated for this system in schizophrenia [40,106,161].

5. Reversal of disrupted LI

As discussed in the previous section, there are many treatments which can prevent LI from being established, but only amphetamine-induced disruption has been extensively used for drug studies. The only others that have been studied to date are nicotine-, DOI-, substance P-, non-handling- and selective breeding-induced disruption of LI. Compounds which have been tested for their ability to reverse amphetamine-induced disruption of LI are listed in Table 8, and include haloperidol, clozapine, olanzapine,

Table 8
Compounds tested for their ability to reverse amphetamine-induced disruption of LI[a]

Compound	Mode of action	Dose of amphetamine	Doses tested	Active doses/effect	Method	References
Haloperidol	Dopamine antagonist	1 mg/kg i.p.	0.2 and 0.5 mg/kg i.p.	0.2 and 0.5 mg/kg	CER, sound/shock, drinking	[276]
		1.5 mg/kg s.c.	0.1 mg/kg s.c.	0.1 mg/kg	CER, sound/shock, drinking	[188]
Chlorpromazine	Dopamine antagonist	4 mg/kg s.c. for 5 days	1 mg/kg s.c. for 5 days	1 mg/kg	CAR, sound/shock, trials to criterion	[250]
Clozapine		1 mg/kg s.c.	1, 2, 3, 5, 10 mg/kg s.c.	2 & 5 mg/kg. Some disruption of CER at 3 and 10 mg/kg	CER, sound/shock, drinking	[193]
		1 mg/kg i.p.	5 and 10 mg/kg	10 mg/kg	CER, sound/shock, drinking	[298]
		Not given	Not given	'Antagonises amphetamine-induced disruption'	CER, sound/shock, drinking	*[282]*
		1.5 mg/kg s.c.	5 mg/kg s.c.	5 mg/kg	CER, sound/shock, drinking	[188]
		1 mg/kg i.p.	10 mg/kg i.p.	10 mg/kg	CER, light/shock, drinking	[267]
Olanzapine		1.5 mg/kg i.p.	0.003–1.25 mg/kg	0.31 mg/kg	CER, sound/shock, drinking	*[92]*
S 16924	5-HT_{1A} agonist, 5-$HT_{2A/2C}$ antagonist, D_4 antagonist, α_1 antagonist	1.5 mg/kg s.c.	2.5 mg/kg s.c.	2.5 mg/kg	CER, sound/shock, drinking	[188]
Sertindole	D_2, 5-HT_{2A}, α_1 antagonist	1 mg/kg, route not indicated	5 mg/kg s.c.	5 mg/kg	CER, sound/shock, drinking	[292]
Risperidone	D_2, 5-HT_{2A}, α_1 antagonist	1 mg/kg s.c.	0.3, 1, 3 mg/kg s.c.	1, 3 mg/kg	CER, sound/shock, drinking	Hitchcock et al., unpublished data
M 100,907	5-HT_{2A} antagonist	1 mg/kg s.c.	0.1, 0.3, 1 mg/kg i.p.	1 mg/kg	CER, sound/shock, drinking	[196]
Ritanserin	5-$HT_{2A/2C}$ antagonist		0.1, 1, 10 mg/kg i.p.	no effect		
Ondansetron	5-HT_3 antagonist	1 mg/kg i.p.	0.01, 0.1 mg/kg i.p.	0.01 mg/kg	CER, sound/shock, drinking	[276]
BMY-14802	Sigma ligand	1 mg/kg i.p.	15, 30 mg/kg i.p.	30 mg/kg	CER, sound/shock, drinking	[294]
Ceronapril	ACE inhibitor	1 mg/kg i.p.	0.05 mg/kg i.p.	no effect	CER, sound/shock, drinking	[291]

[a] Notes as for Table 1.

risperidone and sertindole. It is apparent that reversal of amphetamine-induced disruption of LI has been far less studied than facilitation of LI and that the compounds tested are all known antipsychotic agents or compounds expected to have antipsychotic activity. Thus, unlike facilitation, there is not the range of psychotropic agents tested which are known to lack antipsychotic activity in the clinic. Most of the compounds listed in Table 8 have also been tested as facilitators of LI and, in most cases, the results are similar in that LI is reinstated from a baseline where it is essentially absent or at least greatly attenuated. The only exceptions to this are M 100,907, which reversed the effects of amphetamine but was inactive in facilitating LI [195] and ceronapril, which facilitated LI but failed to reverse the amphetamine-induced attenuation [291].

In general, the range of compounds tested against amphetamine has been too narrow (i.e., no compounds expected to be inactive) for any firm conclusions to be drawn about its validity as a predictive model for antipsychotic activity. It is perhaps not surprising that the non-selective dopamine antagonists haloperidol and chlorpromazine reverse the effects of amphetamine [250,276]. However, the potential utility of this model is greatly increased by the effects of the atypical antipsychotics clozapine and olanzapine [92,193,282,298] as well as the putative atypical antipsychotic agents sertindole [292] and risperidone (Hitchcock et al., unpublished data) both of which have higher affinity for dopamine D_2 receptors compared to D_1 [158,229]. It is interesting that the latter two compounds also have very high affinity for the 5-HT_{2A} receptor [158,224,229], as the selective 5-HT_{2A} receptor antagonist M 100,907, which has negligible affinity for dopamine receptor subtypes [205], also reversed amphetamine-induced inhibition of LI [196]. It may therefore seem surprising that ritanserin, which also has a high affinity for 5-HT_{2A} receptors [158], failed to reverse the effects of amphetamine on LI [195] and has even been reported to disrupt LI [41]. One explanation is that the equally high affinity of ritanserin for 5-HT_{2C} receptors [205,224] has a deleterious influence on LI, as neither M 100,907 nor risperidone have high affinity for this receptor [158,205]. However, as some antipsychotic agents, notably clozapine, as well as some novel potential antipsychotics such as S 16924, have high affinity for the 5-HT_{2C} receptor [187,224] and also reverse the amphetamine-induced impairment of LI [188,193,282,298] it seems likely that some other explanation must be sought. Despite this, the ability of M 100,907 to reverse the effects of amphetamine suggests that a role for the 5-HT_{2A} receptor in antipsychotic drug activity cannot be excluded. Schmidt et al. [231–233] provide evidence that 5-HT_{2A} receptor activation is permissive for the increased dopamine release observed after administration of amphetamine analogues, suggesting a mechanism by which M 100,907 might prevent the impairment of LI by amphetamine and, perhaps, suggesting why it does not facilitate LI, as these receptors do not appear to be involved in basal, physiological dopamine release.

A few other compounds have been tested against amphetamine in LI, as indicated in Table 8. These include the sigma antagonist BMY-14802, which also facilitates LI [294]. Although many antipsychotic compounds have affinity for the sigma site and selective sigma ligands are effective in many preclinical tests for antipsychotic drugs [47,211,261], there is no convincing evidence that it is responsible for their antipsychotic-like effects, particularly as clozapine has little affinity at this site [157]. The positive effects of this compound in facilitating LI and antagonising the amphetamine-induced disruption of LI may represent a ‘false positive’, as a recent open clinical study with BMY-14802 failed to demonstrate significant antipsychotic activity [85].

Compared to amphetamine, relatively little use has been made of the other possible ways of disrupting LI. Joseph et al. [138] have shown that haloperidol can reverse the effects of nicotine on LI, primarily with the aim of demonstrating the role of increased dopamine release in the disruptive effects of nicotine. More recently, clozapine has also been shown to reverse the effects of nicotine [193]. There is also a report that the D_1 antagonist SCH 23390 and the D_2 antagonist raclopride are effective against nicotine [139]. Interestingly, the 5-HT_{2A} receptor antagonist M 100,907, which can antagonise the disruptive effects of amphetamine [196], was unable to reverse the effects of nicotine [195]. This result may be consistent with the differences in the mechanisms of dopamine release provoked by nicotine and amphetamine [277] and the data of Schmidt et al. [231–233] demonstrating that the 5-HT_{2A} receptor is involved in amphetamine-invoked dopamine release but not physiological release. A recent study has made use of the ability of the hallucinogenic 5-$HT_{2A/2C}$ receptor antagonist DOI to disrupt LI. Hitchcock et al. [116] demonstrated that pretreatment with clozapine, haloperidol, risperidone and M 100,907 were all able to prevent the disruptive effects of DOI in LI. Finally, there is a report of reversal of substance P-induced disruption of LI by haloperidol in a study using pre-exposure of the experimental chamber in a passive avoidance protocol [165].

Only one non-pharmacologically induced disruption of LI appears to have been used to test anti-psychotic agents. Non-handled male rats have a long-term deficit in LI [288,286], and this deficit can be reversed by 0.1 mg/kg haloperidol using a typical CER procedure [70].

6. Conclusions

The number of studies on the pharmacology of LI has shown a steady increase over the last 10 years (Fig. 1) and it is now possible to draw some general conclusions. Firstly, in terms of the predictive validity of the various

ways of exploiting LI, it is facilitation that has been best characterised pharmacologically as a model for antipsychotic drug action in the clinic. This is largely due to the fact that protocols employing disrupted LI have, almost exclusively, only used drugs with known, or suspected, antipsychotic activity. One of the complications with using reversal of disrupted LI is the choice of agent or intervention to be used for disruption. Even if we limit this choice to protocols which have examined antipsychotic agents it remains extensive: the disruptive effects of amphetamine, nicotine and DOI, deficits induced by selective breeding or non-handling as well as a variety of lesions have all been reversed with at least one antipsychotic drug (usually haloperidol). In addition to these manipulations, another 16 compounds have been reported to disrupt LI (see Table 6). However, most studies restrict themselves to amphetamine, probably because it is considered to have more construct validity. With the recent demonstration that PCP can disrupt LI (see Section 4.5) it is anticipated that this approach will be increasingly used for drug studies, given the current emphasis on the role of glutamate in schizophrenia. Weiner and Feldon [284] have recently suggested that disruption of LI is a ''much more specific and restricted behavioural effect than has previously appeared to be the case''. However such a view is not readily supported by the data presented in this review. Although some of the compounds reported to disrupt LI are not renowned for their ability to induce psychotic symptoms in man (e.g., nicotine, ACE inhibitors or LiCl), it should be noted that a recent survey listed 149 drugs and drug classes which have been reported to induced psychotic symptoms in man [12]. We should not be too surprised, therefore, if a wide range of drugs disrupt LI and this might not detract from the validity of LI as a model of psychosis. However, the fact that a compound can induce signs of psychosis does not necessarily mean that it represents a process involved in schizophrenia. This makes the choice of a disruptor in LI experiments a difficult one.

In addition to the use of drugs to disrupt LI, only limited use has so far been made of other ways of disrupting LI. As noted above, non-handling has successfully been used to disrupt LI [70,239], as has maternal separation [136] and selective breeding for mice non-responsive to neuroleptic-induced catalepsy, which show impaired prepulse-inhibition and LI [152]. However, the only drug study appears to be the reversal of non-handling-induced disruption of LI by haloperidol [70]. Social isolation, which disrupts PPI, was not found to affect LI [303] using a conditioned suppression protocol.

Secondly, increasing evidence suggests that the pharmacology of the pre-exposure and conditioning phases are different. Thus dopaminergic interventions appear to act primarily during conditioning, whereas serotonergic interventions affect LI during pre-exposure. These effects have been demonstrated for both facilitation [103,150,207, 287,299] and disruption of LI [116,285]. Interestingly, where appropriate studies have been carried out, the effects of other non-dopaminergic compounds can also be attributed to an effect at pre-exposure, including naloxone [80], chlordiazepoxide [71] and ketamine [4]. In some cases this has been attributed to state-dependency [4,116], and there is clear evidence that benzodiazepine ligands and glutamate antagonists are capable of producing state-dependent phenomena in other experimental situations [126,175]. It should also be noted that some early reports of the effects of amphetamine in LI raised the issue of state-dependency [289]. However, nicotine, which can produce state-dependent effects under appropriate conditions [275], does not affect LI when given during the pre-exposure phase only [138]. In addition, whereas it is easy to understand how state-dependency can explain disruption of LI, it is hard to imagine how the facilitation of LI by the 5-HT_{1A} receptor antagonist WAY 100635 when administered during pre-exposure only can be attributed to state-dependency, particularly as this study is one of the few to carry out the parallel experiment of administering the compound only during conditioning and obtaining no effect. The comparable experiment has also been carried out for enhancement of LI by clozapine. Weiner et al. [299] demonstrated that enhancement of LI could be obtained when clozapine was administered only prior to conditioning but not when administered only before pre-exposure. Thus, although typical LI protocols are open to state-dependency effects, this does not necessarily occur and does not explain all the experimental phase-dependent effects observed. The pair of experiments using WAY 100635 and clozapine represents a compelling basis for the suggestion that serotonergic and dopaminergic mechanisms are involved in different phases of the LI process [103,287,299], and the data on disruption of LI by amphetamine and DOI during conditioning and pre-exposure, respectively [116,285], although open to several interpretations, support a similar dichotomy.

Why should dopaminergic systems be involved in processes important during conditioning and serotonergic systems during pre-exposure? Any answer at this stage is largely speculative but there are several possibilities. Most published work has concentrated on explaining the effect of dopaminergic compounds during conditioning and there have been several suggestions for this. For example, it has been suggested that the effects of dopaminergic drugs on LI are not mediated by processes related to stimulus processing but, rather, that their actions are mediated via their influences upon reinforcement mechanisms [143]. This interpretation was supported by experiments demonstrating that modification of US intensities in the LI procedure could attenuate drug effects on LI [147,148]. Whether these actions are actually reinforcer-mediated however, is not clear as other groups have demonstrated that the effect of amphetamine upon the impact of the CS–US contingency can also be manipulated by increasing the number of conditioning trials (CS–US pairings) [299]

or by changing the nature of the to-be-conditioned stimulus, such that disruption by amphetamine and facilitation by haloperidol seemed to depend on the nature (saliency?) of the stimulus (flashing versus non-flashing lights) rather than the strength of the reinforcer [227,300]. Another interpretation of the LI process, which in part integrates previous suggestions, is to describe drug effects on LI in terms of a switching model [279,284]. That is, dopaminergic mechanisms are not involved in the acquisition of stimulus irrelevance but rather determine the subsequent expression of this learning during conditioning. Thus, when contingency conditions are changed between pre-exposure (CS–no consequence) and conditioning (CS+US), drugs that increase dopaminergic transmission promote rapid switching of responding (i.e., from that based on pre-exposure contingencies to that based on conditioning contingencies) and thus disrupt LI. Drugs that decrease dopaminergic transmission reduce the ability to switch responding according to the new CS–US contingency, and drug-treated animals continue to respond to the stimulus according to the information acquired in pre-exposure, thus, enhancing the LI effect. Interestingly, there is evidence for a switching deficit in schizophrenics [219,245].

In addition to these explanations for the effect of dopaminergic compounds in LI, we would like to propose a third possibility which provides interesting links with some of the information processing theories of schizophrenia discussed in the Introduction. Mesolimbic dopaminergic neurons have a well-documented role in signalling stimulus salience, i.e., to serve as an alerting system to indicate that a stimulus has occurred which predicts events relevant to the context within which the animal finds itself [236,238]. Thus, whereas midbrain dopaminergic neurons increase their activity *following* the first exposure to reward, this activity subsequently shifts to events that occur *prior* to the reward, i.e., which predict its occurrence [238]. Signalling of reward-related stimuli would be an important part of any process involved in stimulus selection based on the expected value of such stimuli to the current needs of an organism: disruption of such signalling would lead to inappropriate use of previously learned associations. Although the work of Schultz [236] is concerned primarily with positive reinforcement, a role for dopamine in signalling negative reinforcement (i.e., footshock) has also been demonstrated, in the context of an LI protocol. Young et al. [314] showed that application of mild footshock to rats increases dopamine release within the nucleus accumbens and that this is further increased if a novel tone stimulus precedes the shock; subsequent presentation of the tone alone elicited dopamine release. Both of these effects of the tone presentation were attenuated or abolished by pre-exposure to the tone, showing that the conditioned dopamine release is susceptible to LI. In these same experiments there was no change in dopamine release during pre-exposure to the tone. Thus drugs acting via dopaminergic mechanisms have no intrinsically active system to modify during pre-exposure, whereas increasing dopamine release or blocking its effect during conditioning will modify a physiologically relevant dopaminergic signal and thereby abolish or facilitate LI, respectively. Interestingly, these properties of the dopaminergic system provide a link to the information processing models of schizophrenia presented in the Introduction, as in any such system a method for indicating pertinence would be an essential component in order to maintain attention directed to salient stimuli (both of internal and external origin) and thus avoid information overload and rapid switching of attention to irrelevant stimuli. Furthermore, the dopaminergic system also signals when an expected reward does not materialise [119], thereby giving it some of the characteristics of a monitoring system, suggested to be deficient in schizophrenia by several authors (see discussion of information processing models of schizophrenia in the Introduction).

In contrast to the conditioning phase, where only dopaminergic agents have been shown to act selectively, the pre-exposure phase is affected by a much wider range of pharmacological activity. As discussed above, this is particularly well documented for serotonergic agents, with disruption of LI by the 5-HT_2 agonist DOI or the 5-HT uptake inhibitor sertraline [71,163] and facilitation by [4,83,116] the 5-HT_{1A} receptor antagonist WAY 100,635 being reported following their administration during pre-exposure only. A number of other compounds have also been shown to affect LI via an action specifically during pre-exposure, including disruption by ketamine and chlordiazepoxide [71] and facilitation by naloxone and nicotine [80,150,222]. Although there is insufficient data to draw firm conclusions, one possibility is that an interaction with memory processes might explain these effects. There exists extensive data supporting a role for 5-HT in learning and memory processes [34,253], and the benzodiazepine chlordiazepoxide and the NMDA antagonist ketamine also have well established effects on memory and learning [3,35,185,274]. In some cases this interaction with LI appears to be due to state-dependent learning effects but this is clearly not a satisfactory explanation for all these compounds and, as explained above, has been explicitly ruled out for some (e.g., WAY 100,635 [150]). This type of approach, examining drug effects on pre-exposure and conditioning separately, remains rare for the moment [4,71,116,150]. However, in order to better understand the pharmacology of the pre-exposure phase as it relates to the LI effect (rather than state-dependency) such protocols should be be more widely employed.

It remains unclear, however, why learning about stimulus contingencies during pre-exposure should be disrupted but not learning about stimulus contingencies during conditioning. Recent studies using a CER protocol for LI in conjunction with c-fos production (which can be used as a measure of neuronal activity) suggest that

different brain regions are activated in the various combinations of pre-exposure and conditioning typically used in such protocols [215,251]. Although, neither experiment directly addressed the question as to which brain regions might be activated during different phases of an LI experiment, various nuclei of the amygdala seemed to be particularly important for conditioning. Radulovic et al. [215] refer to non-presented data which suggest that exposure to the CS alone had no effect on c-fos production in the central nucleus of the amygdala, unlike shock or shock-CS pairing. Further studies will be necessary to pursue this approach in the context of selective drug action during pre-exposure or conditioning. It will also be necessary to examine other LI protocols, as activation of the amygdala nuclei might be related to the fear-conditioning component of the CER procedure rather than being related to LI itself [15,37]. The lack of effect of amygdala lesions on LI would support this suggestion [118,296].

It will be interesting to see if the difference between serotonergic and dopaminergic interventions has any consequences for the clinical profile of the more recently developed compounds with high affinity for the 5-HT receptors. There is, in fact, already some evidence that this may be the case: Bleich et al. [24] have reviewed evidence on the role of 5-HT in schizophrenic symptomatology and suggest that dopamine hyperactivity is related to type 1 schizophrenia where positive symptoms predominate whereas a hypersensitive serotonergic system is involved in type 2 schizophrenia, characterised by negative symptoms. Relating such clinical phenomena to different phases of an LI protocol in rodents might prove a difficult task, but already there are some interesting results, such as those concerning 'super-LI' [76] (see Section 3.3), which might point us in the right direction.

There are a number of other issues which may prove to be important in defining the pharmacology of LI but for which we have insufficient data at present or which are the subject of much debate. These include the ability to compare drug effects obtained using different protocols and the role that reinforcement parameters might play [228].

The LI literature contains a number of recurring methodological problems which have already been discussed in some depth [202] (see also Section 2). One of the difficulties in investigating the effects of drugs on LI has been caused by the numerous different methodologies used. Although the availability of a wide range of paradigms does allow examination of the generality of findings (e.g., on positively and negatively motivated responses), the major disadvantage remains, in that results can be difficult to reproduce between laboratories and subtle changes in methodology can lead to conflicting reports which in turn complicate interpretations. In addition, in common with many learning paradigms, there can be difficulties separating motivational, performance and attentional effects of drugs on LI. However, it is important to note that despite the differences in methodology and stimulus and reinforcement parameters employed in different laboratories there is much agreement in many of the effects reported with a range of compounds.

It is also necessary to be more rigorous in defining the terms of LI. Disruption of the LI effect is theoretically defined as improved learning in the pre-exposed group of subjects. It has often been the case, however, that a disruption of LI is reported when the non-pre-exposed group show impaired learning rather than the pre-exposed group showing improved learning. Of course, when the non-pre-exposed group exhibits impaired learning this does result in a reduction of LI but it is important to examine and define whether this reduction is due to a specific disruption of LI processes or simply a disruption of the conditioned suppression or conditioned responding that is used to measure LI.

Until the underlying cause of schizophrenia is discovered, no model can claim full construct validity. However, the parallels that exist between LI studies in schizophrenic patients and in animal experiments provide convincing evidence that this paradigm is measuring, at least in part, some of the impairments that are seen in schizophrenia. As such, a strong case can be made for it having at least face validity. The data we have reviewed here demonstrate that facilitation of LI and, perhaps to a lesser extent, reversal of disrupted LI probably fulfil the criteria for predictive validity. Frith [78] has recently suggested that rather than try to model schizophrenia in animals, a more successful approach may be to model cognitive processes underlying individual symptoms of schizophrenia. LI clearly falls within this approach and should continue to be a useful tool with which to predict antipsychotic activity and to examine novel mechanisms of drug action.

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