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Historical context of state dependent learning and discriminative drug effects

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ABSTRACT

Drug-induced state dependent learning (SDL), as well as similar effects on memory retrieval exercised by physiological states, have been known since 1830. Before 1950, understanding of this area derived primarily from clinical descriptions of somnambulism, dream recall, fugue states, and cases of multiple personality. After 1950, experimental demonstrations of the properties of SDL and drug discriminations (DDs), along with a series of changes in the DD procedure, have led to the DD paradigm that is currently employed, and which has properties that make it an extremely useful tool for preclinical investigation of a variety of pharmacological and psychological questions. These conceptual and technical developments have resulted in widespread acceptance of the DD paradigm as a preclinical research method. This paper reviews the nineteenth and twentieth century history of clinical observations, concepts, and experiments, that have led to our current status of knowledge about drug discriminations and SDL.

Keywords: State dependent learning – Drug discrimination – Dissociation of learning – Stimulus effects of drugs – Drug cues – Discriminative effects of drugs.

INTRODUCTION

We do not know of any scientific interest in the stimulus effects of drugs before the nineteenth century. In this paper, significant events subsequent to that time will be reviewed chronologically.

State dependent learning in the nineteenth century

Throughout the nineteenth century there was widespread interest in hypnosis, fugue states, somnambulism, multiple personality, and other forms of amnesia (Ellenberger, 1970). Various explanations for these clinical phenomena were proposed including, after 1835, the idea that the physiological and pharmacological state of the organism determined, at each instant in time, which memories were accessible to consciousness. Combe wrote as follows.

"The patient was a girl of 16 [who had episodic somnambulistic attacks]. ... The circumstances [events] which occurred during the paroxysm were completely forgotten by her when the paroxysm was over, but were perfectly remembered during subsequent paroxysms.

"Dr Abel informed me of an Irish porter to a warehouse, who forgot, when sober, what he had done when drunk; but being [again] drunk, again recollected the transactions of his former state of intoxication. On one occasion, being drunk, he had lost a parcel of some value, and in his sober moments could give no account of it. Next time he was intoxicated, he recollected that he had left the parcel at a certain house, and ... it had remained there safely, and was got on his calling for it.

"The only conclusion which seems to arise ... is that before memory can exist, the organs [have] to be affected in the same manner, or to be in a state analogous to that in which they were, when the impression was first received.

"These facts cannot be accounted for in a satisfactory way; but by communicating a knowledge of their existence, attention will be drawn to them, and future observations and reflection may ultimately throw light upon the subject." (Combe, 1835, p. 489-490).

The preceding quotation concludes that physiological state dependent learning (SDL) is responsible for the amnestic phenomena of somnambulism, and that ethanol can also induce SDL. It had been known for a century that memories for the hypnotic state could not be retrieved in the normal waking state, although they clearly persisted in unconscious form (Chastenet de Puysegur, 1809). Somnambulistic

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patients were also sometimes known to have state-dependent recall, as stated in the first sentences of the preceding quotation, and there were sufficient similarities between somnambulism and hypnosis so that hypnosis was often called artificial somnambulism (Ellenberger, 1970). It is not known whether the intellectual zeitgeist of 1835 included the idea that physiological SDL caused the amnestic phenomena of somnambulism. However Combe's report almost certainly went at least one step beyond the prevailing zeitgeist by reporting that a drug state (alcohol) could produce SDL effects and thus be a determiner of memory retrieval.

For many years after Combe's "Irish porter" case was reported, the idea that alcohol could produce state dependent learning (SDL) was carried forward through the medical literature by authors who mentioned Combe's case intermixed with their discussions of somnambulism, hypnosis, fugues, and other amnestic syndromes (Elliotson, 1840, p. 646; Macnish, 1834, p. 78; Macnish, 1835, p. 30; Winslow, 1860, p. 338). The importance of physiological SDL in producing amnesias was not universally accepted; for example, Elam's (1869) description of the subtypes of "somnambulism" (under which label he included dreams, sleepwalking, fugue, multiple personality syndrome and several other amnestic phenomena) discussed the physiological state of the brain during these phenomenon without mentioning SDL. Nonetheless, it appears that the existence and importance of SDL was moderately widely accepted in England and America throughout the second half of the nineteeth century.

In 1868, Wilkie Collins incorporated SDL produced by opium into the plot of his novel "The Moonstone". The novel was published in serialized form, and widely read, thus making the concept of SDL widely available to the public. Whyte (1960, p. 168) records that popular acceptance of the idea of unconscious determination of behavior progressed from being "credible" in 1700 to being "topical" by 1800 to being "fashionable" by 1875.

Early theories for SDL

Current theories for SDL postulate three major causes for SDL; stimulus equivalence, state equivalence, and affect equivalence. The period 1880-1910 saw a major change in the status of SDL, as it was integrated into comprehensive theories of memory retrieval and personality. All three of the twentieth century ideas were anticipated at that time.

Ribot proposed that control of memory retrieval by bodily states was mediated by "organic sensations" which he listed, and which were equivalent to what are now called "interoceptive stimuli" (Ribot, 1891, p. 23-30). Ribot was also explicit in asserting that the stimulus effects of the normal (no drug) state were as salient as those of abnormal states, so that retrieval of memories acquired while in the no drug (N) state could occur only when N cues were again present (Ribot, 1882, p. 108-115). Hence, his theory predicted that equally large impairments in memory retrieval would be produced by drug to no drug (D→N) and by N →D state changes. His was the first mechanistic theory for SDL that is known, and it was a stimulus theory. It asserted that physiological SDL effects determined moment-to-moment changes in the subset of memories that could be retrieved in normal humans instead of only considering SDL to be a process that was active in pathological states.

Semon also explicitly integrated ethanol-induced SDL into his comprehensive model for memory formation and retrieval (Semon, 1904/1921, p. 144-145; 1909/1923, p. 180) by postulating that the "energetic condition" of the brain must be the same at the times of registration and retrieval if retrieval was to occur. His model asserts that both brain state and stimulus conditions influence the likelihood of reinstatement of an engram, includes reference to both physiological and pharmacological SDL, and closely resembles the "brain state equivalence" models later put forward by Hebb (1949) and Overton (1964). Additionally he asserted that overtrained responses would be retrieved in spite of changes in brain state – a conclusion not reached again until Iwahara and Noguchi (1972). Schacter (1978; 1982, p. 185) has recently provided a very interesting discussion of Semon's ideas.

Finally, in a simple case report Corning (1898) asserted that memory retrieval was affect-specific and that mood SDL was responsible for the amnesic phenomena that he observed in what was perhaps a case of multiple personality disorder (MPD). Physiological SDL was not mentioned by Corning, and instead he proposed affect-specific SDL as the cause of MPD.

So, 50 years after it was first reported, SDL acquired enhanced status by being included as one of the properties of memory important enough to be accounted for in comprehensive theories of

learning and recall. These theories attributed SDL to the same mechanisms that are currently believed to produce it.

Rejection of the concept of physiologically based SDL

Even as academic psychologists were finally integrating physiological and pharmacological SDL into their theories, trend setting clinicians were increasingly focusing on other types of dissociation. Starting around 1900 interest in dissociation induced by changes in physiological state first waned and then disappeared. Binet (1896), Janet, Prince, and Sidis were major contributors to the redirection of focus which occurred at this time. They studied hysterics and patients with multiple personality disorder and developed methods such as automatic writing, distraction, and crystal gazing for communicating with the co-conscious or unconscious portion of the brain in such patients. It seems obvious even now that the phenomena that they studied were not based on physiological SDL.

The ideas that there were brain mechanisms allowing dissociation, and that selected engrams might become split off from normal consciousness and hence be unretrievable at a particular moment, certainly remained as shown by the following statements by Prince.

"Abnormal psychology, then, points strongly to the conclusion that there is a normal physiological dissociating mechanism which is [a] function of the [organization of the nervous system]. It is this mechanism which brings about such spontaneous normal states as absent-mindedness, sleep, ... induced states like hypnosis; and through its perversions the dissociations underlying abnormal phenomena" (Prince, 1905, p. 143).

"We may ... lay it down as a general law that during any dissociated state, no matter how extensive or how intense the amnesia, [memories of] all the experiences that can be recalled in any other state, whether the normal one or another dissociated state, are conserved and, theoretically at least, can be made to manifest themselves. And, likewise and to the same extent, during the normal state [memories of] the experiences which belong to a dissociated state are still conserved, notwithstanding the existing amnesia for those experiences" (Prince, 1916, p. 78).

Although dissociation was still in vogue, changes in physiological or pharmacological state were no longer viewed as the mechanism that most frequently caused such splitting. Janet (1907), for example, was outright rejecting of the idea that physiological SDL could be responsible for the instances of dissociation that interested him. He characterized as "pure childishness" the attempt to explain hypnotic suggestibility or somnambulism (a term he used to refer to both multiple personality and hysterical symptoms) in terms of physical brain function (Janet, 1907, p. 63). And although Prince (1916, p. 81) once mentioned reintoxication as a method of aiding retrieval for periods of alcoholic blackout, he did not regard state-equivalence as the mechanism that was responsible for most clinically important instances of dissociation.

For 20 years or so Janet, Prince and other workers accepted dissociation as a common property of memory retrieval and consciousness without really saying much about why it occurred. Then Freud developed the idea that most instances of dissociation occurred because of avoidance of one sort or another, i.e. because of strong emotional reactions that led to a splitting off or repression of memories for some portions of experience. This provided a mechanism that apparently could explain which experiences were dissociated from consciousness, and why.

Ellenberger (1970) characterized the nineteeth century as the era of the "First Dynamic Psychiatry" which he described as primarily concerned with phenomena of somnambulism, catalepsy, multiple personality, hysterical symptoms, and hypnotism (p. 111). The notion of physiological SDL was an integral part of the First Dynamic Psychiatry. Ellenberger also reported that this school of thought was actively rejected starting in 1880 (p. 171), with the usually accepted date for its demise being 1900 (p. 174). During the transition before the "New Dynamic Psychiatry" was firmly established by Freud and others, a few theorists still accepted the existence of SDL, as shown by mention of SDL in the writings of Ribot, Semon and Prince. However, the phenomenon was not considered as important as it had been 50 years earlier, was infrequently mentioned in books published after 1900, and workers were apparently in agreement that it was not the cause of the major symptoms that now concerned them; hysterical symptoms, fugue states, and multiple personality. One of the last mentions of SDL was made by Coriat (1906, 1910*b*) who conducted experiments to show that memories for periods of alcoholic blackout could sometimes be retrieved if special techniques were employed, and tangentially mentioned the Irish Porter case as showing that ethanol SDL occurred.

The loss of emphasis on SDL did not necessarily reflect bad scientific judgment. Hysterical patients were apparently everywhere to be found at this time. However not even a second case of drug-induced SDL had ever been reported, and the whole existence of drug SDL rested on the single case report by Combe. Hence, it was perhaps appropriate that drug SDL ceased to be a central focus of attention.

Incidentally, it is likely that Semon and Prince did not know of Combe's original case report. Prince (1916, p. 81) cited Ribot as the source of the "Irish porter" case, and Ribot in turn described the case as "well known," without explicitly citing Combe (Ribot, 1882, p. 115). Similarly, Coriat (1910*b*) refers to ethanol SDL as "well known," citing only "Ribot's case" as the source of this knowledge. Apparently knowledge of Combe's original case report had been lost.

1910-1940. Virtual loss of the concept of SDL

Although Coriat knew of ethanol SDL, his book "Abnormal Psychology" (1910*a*) does not mention it even though it deals extensively with dissociative and amnestic phenomena. Similarly in a book by Core (1922) that dealt extensively with dissociation and the amnesias resulting from it, physiological SDL was not mentioned. These books provide examples of the shift in focus described by Ellenberger. Twenty years later Miller (1942) in his book "Unconsciousness" distinguished 16 different ways in which the word unconsciousness was used, without referring to exclusion from consciousness due to SDL. He even described Girden's 1937 dissociation studies in connection with the question of whether conditioning required a functioning cortex, without mentioning SDL as a mechanism that could exclude engrams from consciousness. Similarly Cameron (1947) in a long monograph entitled "Remembering" made no mention of SDL even though he did describe many other effects of drugs on memorization and retrieval.

After 1930, experimental psychology apparently became increasingly interested in dissociation of all types. Hilgard (1977, p. 10) has commented on factors that possibly underlay the rapid loss of interest in dissociation, that apparently occurred in the newly developing behavioral psychology of the 1930s. It is his view that interest waned more by social consensus than because of any new data that explicitly reduced the significance of preconscious processes. For whatever reasons, although knowledge of the clinical phenomena of dissociation, somnambulism, fugues, and multiple personality persisted, this writer has not found instances after Prince (1916) in which SDL was explicitly mentioned in the literature.

Prince's book was reprinted at least as late as 1929, Semon's books were translated into English in the 1920s, and some of Ribot's books were reprinted as late as 1910, thereby making the SDL concept available. However little or no attention was apparently paid to SDL at this time.

In 1931 Charlie Chaplin's movie *City Lights* depicted events resembling ethanol-induced SDL (McDonald *et al.*, 1965). However, alternative explanations for the events portrayed in the film are possible. If the film depicted SDL, then where did Chaplin get the idea? Chaplin's autobiography does not clarify the issue (Chaplin, 1964, p. 325); indeed his wording suggests that the film was not intended to portray SDL. Unfortunately, Chaplin's autobiographical statements are highly unreliable (Geduld, 1985), which leaves us with substantial room for doubt about what the film intended to portray. All that can be concluded is that *City Lights* may possibly have reflected a knowledge of SDL by Chaplin.

By 1930 the following ideas had been published, and most had apparently been forgotten. (1) Current physiological, pharmacological, and/or emotional state determines which memories are retrievable at any instant in time, with recall requiring state equivalence. (2) Both the no drug state and abnormal states have an equally important influence on memory retrieval. (3) Control of memory retrieval by bodily states may, or may not, be mediated by the mechanism of interoceptive sensations. The data underlying these assertions included clinical observations of hypnosis, somnambulism, fugue, and multiple personality collected during the nineteeth and early twentieth centuries, and one reported case of ethanol-induced SDL in a delivery man who got drunk on the job around 1830.

Precursors of the rediscovery of SDL and DDs

Direct precursors of the rediscovery of SDL included several developments in the 1930s.

One of these was the extant interest in the role of stimulus context as a factor influencing memory retrieval. This was not a new idea, but Guthrie (1935) had repopularized it by asserting that retrieval of learned responses was conditional on all stimuli present in the environment when the response was learned. A few studies in animal subjects had demonstrated substantial disruptions in the performance of learned

responses when the stimulus context was altered (Hunter, 1911; Carr, 1917; Patrick and Anderson, 1930). A larger number of studies had been conducted in human subjects, investigating the effects of changes in a variety of contextual stimuli, including changes in proprioceptive stimuli produced by alterations in bodily posture (Reed, 1931), changes in the verbal context surrounding a word to be remembered (Pan, 1926), changes in the color of the paper on which words to be recalled were printed (Dulsky, 1935), moving from indoors to outdoors or from one room to another (Farnsworth, 1934; Bilodeau and Schlosberg, 1951; Greenspoon and Ranyard, 1957), as well as other environmental manipulations (Pessin, 1932). In the experiments using human subjects, the effects on memory retrieval produced by changes in stimulus context were usually quite small. Nonetheless, anyone who read the current literature certainly was aware that changes in stimulus context sometimes caused failures in memory retrieval.

A second precursor was the drive discrimination studies. Hull (1943) had asserted that food and water seeking behaviors were conditional on interoceptive stimuli produced by hunger and thirst. During the ensuing decade a large number of experiments on this topic were reported; these are cited and reviewed by Webb (1955). This work focused attention on the role played by interoceptive stimuli, both as contextual cues which modulated retrieval, and as discriminative stimuli.

Third, Girden and Culler (1937) reported an experimental demonstration of drug SDL using the drug state produced by curare extract and the no drug condition. Initially, they studied the conditioned leg flexion response in dogs. Later they expanded their studies to include other response modalities. Girden's experiments had serious methodological difficulties. Also, Gardner's attempt to replicate his findings was largely unsuccessful (Gardner, 1961; Gardner and McCullough, 1962). Nonetheless, Girden's work was apparently accepted by the scientific community and appeared in textbooks of physiological psychology for many years after it was reported (e.g. Morgan and Stellar, 1950, p. 450). Although few of the individuals who studied the stimulus properties of drugs during the following 30 years acknowledged that their work was influenced by Girden's studies, his studies mark the starting point of modern experimental work on SDL.

These three developments took place during the 1930s and 40s. They appear to have provided the intellectual context which provoked rebirth of interest in, and experiments on, SDL and DDs in the 1950s.

Development of the contemporary drug discrimination technique

Developments that directly underlie present drug discrimination (DD) methods started in 1951, and the following 25 years saw a progressive increase in the amount of experimental attention devoted to stimulus properties of drugs. The remainder of this paper will selectively review this history focusing on developments that contributed to the development of the DD method as a practically applicable investigational tool.

Conger (1951) reported the first DD study. He was trying to study the effects of alcohol on approach and avoidance behavior, and realized that the effects he was observing could be caused either by the intrinsic effects of ethanol or by stimulus generalization deficits resulting from a change in drug state between training and testing, i.e. by SDL. In his words:

"The avoidance was established under the condition of sober; one group was then tested under the ... condition of sober, and the other group under the different condition of inebriation. Thus it is logically possible that the decrease in the avoidance response might be due solely to a change in the animal's condition (regardless of the direction of the change) rather than to any specific effect of alcohol [because] it seems likely that a change from sobriety to inebriation (or vice versa) produces a change in the animal's stimulus situation." (Conger, 1951, p. 15).

Conger then made an unprecedented contribution by pointing out that if ethanol did have stimulus effects, then the existence of these effects could be shown by using a discrimination training procedure. In an approach/avoidance task, Conger's rats learned to approach when drunk and avoid when sober, or vice versa, thus becoming the first animals in history to learn a DD in a laboratory setting. Note that Conger's study never answered the question that led him to perform it. By showing that ethanol could exert discriminative control, it showed that ethanol had salient cue effects. This, in turn, indicated that stimulus generalization effects might occur and that the intrinsic effects of ethanol might be confounded with SDL in the state change experiments that Conger had conducted. However his results never answered the questions of whether or to what degree such confounding actually had occurred.

The 2 × 2 experimental design

In the same year, Auld (1951) published the first study that used a 2 × 2 experimental design to detect drug stimulus effects. His experiment tested the effect of tetraethylammonium (TEA) on escape and avoidance performance. No SDL effects were found. This is reasonable because TEA primarily acts outside the brain.

For reference, the following Table describes the structure and properties of the 2 × 2 design.

Group no.	*Drug during training sessions*	*Drug during test sessions*	*Effects present during test session*
1	N	N	None
2	N	D	SDL + Performance deficit + Retrieval deficit
3	D	N	SDL + Memorization deficit
4	D	D	Memorization deficit + Performance deficit + Retrieval deficit

The quantitative size of the effect of presence of drug during training on memory consolidation is computed from test performance in groups 1+2-3-4. Depressant drug effects on performance during test trials cannot be distinguished from drug induced impairments of memory retrieval, and the combined size of these two effects is computed from test performance in groups 1+3-2-4. The SDL effect is computed from test session performance in groups 1+4-2-3. The design assumes that all effects are linearly additive, and that SDL is symmetrical with equally large decrements after D → N and N → D state changes. If any effects other than the postulated ones are present, then the computed effect sizes will be incorrect.

Subsequently, Miller repeatedly proposed the 2 × 2 experimental design as a method for determining the relative strength of SDL effects and other drug effects. He actively promoted use of the 2 × 2 paradigm arguing that it was unwise to try to determine the intrinsic effects of drugs without including the extra experimental groups that would show stimulus generalization decrements if they were present (Miller, 1957; Miller and Barry, 1960; Grossman and Miller, 1961).

SDL studies in the 50s and 60s

Conger had only shown discriminative control after a moderately prolonged series of DD training trials. However, several other investigators soon tested whether the stimulus effects of drugs might be salient enough to produce the generalization decrements postulated by Conger. They conducted 2 × 2 studies, several of which yielded evidence for SDL effects (Murphy and Miller, 1955; Shmavonian, 1956; Heistad, 1957; Heistad and Torres, 1958; Barry *et al.*, 1962; Belleville, 1964; Holmgren, 1964*a*, *b*; Overton, 1964; Otis, 1964; Sachs *et al.*, 1966). Among these studies, Shmavonian obtained the first results actually showing the occurrence of stimulus generalization decrements resulting from a change in drug state, and Overton obtained the strongest effects.

Reasons for the renewed interest in SDL

To clarify the role of the nineteeth century SDL literature, this writer recently conducted telephone interviews with most of the SDL investigators of the 50s. Girden, Auld, Conger, Shmavonian, Miller, Heistad, Barry, and Otis all confirmed that they had no direct knowledge of that literature. Conger attributed the stimulus change explanation for his results as arising from the interest in drive stimuli which was extant at the time, and which made it appear reasonable to him that drugs also could produce similar stimulus effects. Barry (1958) had found state dependent effects of changes in the level of hunger on performance in a straight alley, and he later adopted a similar design when testing the effects of drugs on performance in the same task. Otis had conducted an interesting Ph.D. thesis on the possibility that drive stimuli might act as conditioned stimuli which, if paired with punishment during infancy, could later in life elicit anxiety as a conditioned response (Otis, 1956). He later viewed drugs as a convenient method to induce comparable changes in internal state, and hence used them in his 1964 SDL study. Auld, Conger and Barry were students of Neal Miller, and their 2 × 2 experiments were conducted under Miller's supervision. Miller also reports that he had no knowledge of the nineteeth century literature on drug-induced SDL. Heistad reported that he was strongly influenced by Guthrie and entertained the idea that a large portion of the effects of drugs on behavior might result from stimulus generalization decrements. Shmavonian reports that he used the 2 × 2 design not as a tool to see

stimulus effects, but because it would allow detection of carry-over effects. In summary, the investigators that I interviewed were unanimous in denying any direct knowledge of the nineteeth century work.

Not all SDL studies from this era resulted from the hypothesis that drugs produced stimulus effects. Other models for brain function, later termed "neurological" models by Bliss (1974), also predicted SDL, and some SDL studies were conducted by investigators seeking to test these models (Overton, 1964; Sachs *et al.*, 1966). Holmgren (1964*a,b*) reported SDL without mentioning any theoretical predilection about the sources of the phenomenon.

From the reports of these investigators, it is clear that the SDL studies in the 1950s and 60s occurred because contemporary theoretical and experimental interests, and were not directly inspired by knowledge of the nineteeth century literature on SDL. The theories of Hull (1943) and Guthrie (1935) essentially predicted the occurrence of SDL, even if the phenomenon itself was regarded as undemonstrated, and the experiments were performed for that reason. We should perhaps note that Guthrie's theory was an intellectual descendant of Ribot's nineteeth century theory, and that Ribot's theory had been constructed in a fashion that allowed it to explain SDL. Hence perhaps in this very indirect way, the nineteeth century interest in SDL did promote the SDL studies of the 1950s. However the immediate and apparent cause of those experiments was the intellectual zeitgeist of the 1950s with any linkages to the nineteeth century being extremely indirect.

Theories For SDL

Various mechanisms have been proposed as responsible for SDL. Combe's initial description of SDL did not propose a mechanism by which SDL occurred; it was simply a report of the fact that SDL did occur. As far as we know, Ribot provided the first mechanistic explanation for SDL by postulating that the physiological state of the body was reflected in "organic" sensations, and that reoccurrence of these sensations was a prerequisite for memory retrieval. In 1937, Girden proposed a new model based on the assumption that drugs could functionally decorticate the animal (Girden and Culler, 1937). Conger, Auld, Miller, Otis, and others accepted a stimulus generalization model for SDL. Hebb (1949) and this writer proposed that cell assemblies should be state specific. Indeed, once the scientific world was once again convinced that SDL really existed, a plethora of mechanisms for it were proposed and toward the end of this period a review paper by this author summarized no less than 22 different models that had been suggested as possibly responsible for SDL (Overton, 1978).

Unfortunately, these various competing theories have for the most part never been tested, and so the mechanism underlying SDL and DDs is still unknown. However in recent years the scientific community has come predominantly to support a stimulus interpretation. The widespread acceptance of this formulation both provides ready explanations for many of the phenomena of SDL and DDs, and discourages fundamental research on the mechanisms that underlie them.

Symmetrical DD Tasks

The first improvement in DD methodology after Conger's study was that of using a symmetrical task (Overton, 1961). Overton adopted the 2-response T-maze task after pilot experiments in a straight alley go/no-go maze yielded results that were difficult to interpret precisely because drug effects on rate were confounded with SDL effects in that task. In symmetrical tasks like the T-maze, discriminative control by drug cues is shown by response selection instead of by response failure, and hence the rate depressing effects of drugs are not directly confounded with their stimulus effects (as does happen in single-response go/no-go tasks in which the rate of occurrence of a response is used as an index of discriminative control).

Operant DD paradigms

By 1970, it was possible to list about 20 different behavioral paradigms that had been employed in DD studies by one investigator or another (Overton, 1971). A few of these are identifiable as milestones in the development of the paradigm that is most commonly employed at present.

After adoption of a two-choice task, the next major step was the use of operant tasks (Harris and Balster, 1968). Even the earliest results in operant tasks indicated that they were sensitive to doses much lower than could be detected in the T maze task, and when the symmetrical 2-lever operant DD task was used the operant paradigms provided both high sensitivity and a relatively uncontaminated index of discriminable drug effects (Kubena and Barry, 1969; Morrison and Stephenson, 1969).

One additional important development did not occur until 1975 when Colpaert *et al.* (1975, 1976) introduced the use of a fixed ratio (FR-10) vs

extinction schedule of reinforcement. This schedule produced much higher accuracy of lever selection than previously had been seen in operant tasks, and it was soon adopted by most DD investigators.

How many drug cues are there?

In 1960 it had never been shown whether more than a single drug cue existed, and investigators entertained the possibility that rats might be discriminating "normal" vs "abnormal," irrespective of what drug was used as the training compound. Hence Overton (1966) felt obliged to conduct a series of studies designed to show that atropine and pentobarbital produced two qualitatively different states (or stimulus effects). Stewart (1962) also obtained data showing that at least two different drug states existed.

By the end of the 1960s, however, Overton (1971) could report no less than 10 different types of drugs that were discriminable from no drug and from one another. This led to the generalization that each different type (or class) of drugs would produce a different discriminable effect (the "one cue per pharmacological class" idea), and to the expectation that this pattern might continue to be found as additional types of drugs were tested in the DD paradigm. The proliferation of identified discriminable drugs has continued, leading to the additional generalization that most centrally-acting drugs can exert discriminative control.

The default choice

Studies in operant DD tasks yielded an additional important result. In those tasks, after D (drug) vs N (no drug) training with a particular drug, animals would select the no drug lever when tested with any novel drug. Hence the no drug lever was the "default" response and was selected by trained animals under all drug conditions except the training drug condition and drug conditions closely related to it. This very important finding gradually emerged in the literature and is the most important single property of the DD paradigm for many applications since it underlies the high intrinsic specificity of the procedure.

It should be noted that this result differed from the pattern of results initially obtained by Overton. In his T-maze task, rats made 30-70 percent D choices under most novel drugs, with only a few test conditions leading to consistent selection of the no drug arm of the maze. However the operant task produced a different pattern of results for reasons that have never been adequately explained.

Are SDL and DDs related?

Were the stimulus effects of ethanol that allowed discriminative control in Conger's DD study actually the same effects that produced response decrements in 2 × 2 SDL experiments? The most convincing evidence supporting an affirmative answer to this question was published by Overton (1964) who showed both SDL amnesias caused by changes in pharmacological state and D vs N DDs established by discriminative training in a shock-escape T-maze task. With very high doses of certain drugs, only two sessions were required to learn one response in the drug state and an opposite response in the N state, thus showing SDL. With much lower doses of the same drugs, 30 or 40 training sessions were required to establish D vs N discriminative control. When intermediate doses were tested, the amount of training required to establish D vs N DDs turned out to be inversely proportional to dosage suggesting that high-dose SDL and low-dose DDs were simply two different points on a continuum, and that the same actions of drugs, whatever they might be, were producing both SDL and DDs (Overton, 1974).

However the conclusion is inferential in nature, and there have been few explicit tests of the relationship between the SDL and DDs. Conger asserted that if drug cues produced SDL effects, then the same cues could produce DDs, and vice versa. The phenomenology of DD and SDL data are generally congruent with this hypothesis. However the assertion has mainly been accepted without subsequent attempts at verification.

The presence versus absence theory

In 1975, Colpaert *et al.* introduced an apparently minor restatement of the stimulus theory that in fact caused a basic revision in the predictions of that theory. He argued that rats discriminated presence vs absence of the training drug's cues during D vs N DD training. Around the same time, Frey and Winter (1977) made the same proposal, even more pointedly, referring to it as a "third cue" model. It followed as a prediction that the animals would consistently select the no drug lever during tests with a novel drug that produced cues *different* from the particular cues that the animal had been trained to detect.

This new model differed radically from the one that previously had been accepted by most SDL and DD investigators and which predicted that responding would be equally contingent on D and

on N cues. The new model was not congruent with some data obtained by this writer during tests for substitution in the T maze DD task. However most investigators now used the operant task, and Colpaert's model did match the pattern of results observed in that task, and probably for that reason, the "presence vs absence" model achieved wide acceptance. A variant of this model is also compatible with the frequently reported "asymmetrical SDL" result in which loss of the response occurs after D → N but not after N → D state changes (Overton, 1968, 1988).

Status of SDL and DDs circa 1975

The DD method most frequently employed after 1975 used a composite paradigm incrementally constructed during the preceding 25 years via the process just described. The major components included; (1) simple 2-response tasks in which lever selection was primarily determined by stimulus effects, i.e. tasks that had high specificity in that discriminable effects could be distinguished moderately well from depressant or other drug actions, (2) a paradigm that could be used with almost any type of centrally acting drug, (3) a paradigm providing specificity of recognition of different stimulus effects, such that the stimulus effects of one drug could be distinguished from those of most others, (4) a rational principle for predicting what stimulus effects might be expected from a previously untested drug (the "one cue per class" model), and, perhaps most important, (5) a simple and easy to understand theory (presence vs absence) which made the results of the paradigm appear simple, plausible, and interpretable.

The component pieces that would allow the subsequent widespread use of DDs for investigation of drug effects, causes of drug abuse, and other issues, were all in place by 1975. All that was now required was time for the news to get around, and for members of the pharmacological community to gain confidence in the method. Stolerman has prepared a comprehensive bibliography listing more than 1000 DD studies. It shows that the number of DD publications per year has increased steadily starting in 1970 slightly before the method reached its present stage of development. Most DD studies have been published after 1980, and have used the now popular 2-lever fixed ratio (FR-10) vs extinction D vs N DD training paradigm.

Remembrance of things past

Although several writers had related DDs and SDL to multiple personality or other forms of dissociation during the period 1937 to 1980, not one single citation to the nineteeth century work had been made, and our recent telephone survey appears to confirm that the nineteeth century work had been entirely forgotten. This amnesia was finally lifted by Siegel (1982) after someone attending one of his lectures pointed out the fact that the plot of "The Moonstone" implied knowledge of (1) contextual control of retrieval, (2) SDL, and (3) one-trial tolerance. In "The Moonstone," Collins (1868) quoted the Irish Porter case verbatim, and mentioned Combe's name, and this allowed Siegel to find part of the nineteeth century literature on SDL and publish a description of it (Siegel, 1982, 1983). Not surprisingly, since the nineteeth literature included few empirical data, this has not led to any great modifications in our ideas about SDL or DDs. However it does provide us with a much longer intellectual history than we had previously suspected.

The future of SDL and DDs

The study of dissociation, SDL, and DDs is now at an exciting juncture, having split into several distinct subfields. DDs are used to investigate the neurochemical effects of drugs, and to investigate the stimulus effects of drugs presumed to underlie drug abuse (Overton, 1987). Drug-induced SDL has not been extensively investigated since it was concluded in about 1980 that the doses of psychoactive drugs normally used for outpatient treatment do not produce the phenomenon to an impressive degree (Eich, 1980; but see Lowe, 1982). SDL produced by emotional states is under current investigation as a possible etiological factor in depression and other mental illnesses (Blaney, 1986). At the same time as something approaching 40 distinctively different drug stimuli have been identified in the DD literature, recent years have seen a dramatic resurgence of interest in the multiple personality syndrome, and a redefinition of the clinical syndrome to include "super multiples" reported to have as many as 50 distinct personalities, each partially dissociated from the others. These various studies are being carried out by investigators in several different fields, and a continuing challenge exists to identify findings in one field that may have relevance to another.

From the perspective of this writer, there are still some severe limitations in the DD and SDL methods, as presently employed, and in the scientific knowledge that underlies them. A

proper historical perspective should probably include mention of unsolved problems as well as solved ones, and some of the more serious unsolved problems are the following: (1) Extremely slow production of DD data because of the prolonged training that is required, and the slow production of binary test data. (2) Failure to identify, in even a single case, the actual sensory cues argued to underlie DDs. (3) Failure ever to test definitively whether a sensory mechanism really does underlie either SDL or DDs, or seriously to test the alternate "neurological" models. (4) Failure to conduct many studies aimed at clarifying the properties of stimulus control by drugs so that these properties can be formally compared to those of the stimulus control exerted by stimuli known to be sensory (Overton, 1988). (5) Lack of knowledge about the underlying number of types of drug cues, or even enough knowledge about them to specify whether there are a finite number of drug cue modalities. (6) Use of DD procedures which yield binary data during tests and thus can not provide a linear mapping of cue strength into response choice. (7) Lack of data about overlap between cues produced by dissimilar drugs (which directly results from our lack of methods for measuring such overlap). (8) Lack of any accepted method for controlling the amount of qualitative specificity shown by trained animals. (9) Lack of an adequate method for measuring quantitatively the relative strength or salience of the stimulus effects of pharmacologically dissimilar drugs. (10) Lack of any solid information identifying the subset of discriminable drug effects that are involved in the etiology of drug abuse. (11) Lack of information identifying the list of drug actions in the brain which produce discriminable effects, and distinguishing these effects from those that do not have discriminable consequences. (12) Lack of an experimental design that allows uncontaminated measurement of the strength of SDL effects, and differentiation of SDL effects from the many other drug actions on memory formation, retrieval and expression that have now been demonstrated. (13) Lack of information about the relationship, if any, between the processes that produce physiological SDL (e.g. drive state SDL, dream state SDL) and those that produce drug-induced SDL. (14) An apparent unwillingness to devote much attention to many of the preceding issues, with the degree of avoidance often striking this writer as resembling the defensive dissociation from consciousness of unpleasant experiences presumably responsible for the types of clinical dissociation that replaced physiological SDL as a focus of attention around 1910.

Nonetheless, the history of the SDL/DD area since 1951 has been an impressive success story. With any luck, the selective focus of attention on the successes of the DD method and concomitant avoidance of attention to its limitations will not be entirely comprehensive, and the next 40 years of work will provide answers to many of the questions and problems mentioned in the preceding paragraph.

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