Chapter 20

SEQUENCE PRODUCTION PARADIGMS FOR EXPLORING THE ORGANIZATION OF SEQUENTIAL BEHAVIOR

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ABSTRACT

Some of the most interesting features of behavior and cognition are found in animals' responses to sequential problems that require them to organize their behavior through time. If we are to characterize and understand behavior of this complexity, especially how multiple psychological processes act concurrently to produce sequential behavior, then we will have to study forms of sequential behavior that are sufficiently complex that they would likely recruit multiple processes concurrently. Our sequence production paradigm for rats seems to be well-suited for this purpose. In our paradigm, rats rather quickly learn to produce long and elaborate sequences of responses. The sequence production paradigm we use is a functional analogue of nonverbal human pattern learning tasks that require participants to choose buttons or other manipulanda in a spatial array in the proper sequential order that produces a repeating pattern of responses. In our paradigm, rats learn to press levers in a circular array in the proper sequential order that produces a repeating pattern of responses. Our method is an improvement over earlier methods used with rats and even primates because it allows us to study how rats learn long, elaborate serial patterns and because it provides measures of correct-response rates, error rates, and "intrusion" rates (i.e., the number of specific kinds of errors produced at

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particular locations in the pattern) on a trial-by-trial basis throughout the serial pattern. We have applied the sequence production paradigm to examine the psychological and neural systems that subserve sequential behavior and the effects of drugs, toxic chemicals, and brain lesions on these neurobehavioral systems. The sequence production paradigm is a rich and flexible methodology for studying the complex interactions of the multiple psychological and neural processes that mediate the organization of sequential behavior.

INTRODUCTION

Some of the most interesting features of behavior and cognition are found in animals’ responses to sequential problems that require them to organize their behavior through time. Models of sequential learning attempt to describe how humans and other animals learn to predict elements of event sequences or produce response sequences that occur in the same serial order, that is, in serial patterns. Recently, there has been an upsurge in interest in the psychological and neural bases of sequential learning. This type of learning has been shown to be a fundamental human and nonhuman animal capacity involved in “human activities ranging from reasoning to language, and from everyday skills to complex problem solving” (Sun, 2000, p. 1), yet the psychological and neural processes that subserve it have not been identified and properly characterized.

In recent years it has become clear that humans and other animals have much in common in terms of sequential behavior and the processes that seem to be responsible for sequential behavior (Fountain, 2006; Fountain and Rowan, 1995a; Kesner, 2002; McGonigle and Chalmers, 2002; Sands and Wright, 1980; Sands and Wright, 1982; Terrace and McGonigle, 1994). However, rather than a consensus emerging regarding the nature of the mechanisms responsible for sequential behavior, competing hypotheses and theories to describe sequential behavior abound. Sequential learning theories have ranged from those positing simple associative learning mechanisms to those proposing that sequential learning depends on abstract cognitive capacities. The picture of sequential learning that is emerging for rats, for example, like that emerging for primates and humans (Botvinick and Plaut, 2004; Chen, Swartz, and Terrace, 1997; Harris and Washburn, 2005; Keele, Ivry, Mayr, Hazeltine, and Heuer, 2003; Palmer and Pfrodresher, 2003; Terrace, 2005; Treichler, Raghanti, and Van Tilburg, 2003), is perhaps more complex than is generally imagined. Evidence suggests that rats learn to perform complex behavioral sequences by concurrently monitoring several sources of information and encoding the most valid information selected from the stimulus characteristics of pattern elements, the structural relations among elements, the characteristics of extra-sequence cues, and the relative timing of sequential events (Fountain, Wallace, and Rowan, 2002; Fountain, 2006). This idea also fits with recent behavioral and neurobehavioral studies implicating multiple concurrent psychological and neural processes in rat serial pattern learning (Fountain, 2006; Fountain and Rowan, 2000; Fountain and Benson, Jr., 2006).

If we are to characterize and understand behavior of this complexity, especially how multiple psychological processes act concurrently to produce sequential behavior, then we will have to study forms of sequential behavior that are sufficiently complex that they would likely recruit multiple processes concurrently. Our sequence production paradigm for rats
A SEQUENCE PRODUCTION PARADIGM FOR RATS

The sequence production paradigm we use is a functional analogue of nonverbal human pattern learning tasks that require participants to choose buttons or other manipulanda in a spatial array in the proper sequential order that produces a repeating pattern of responses (Hartman, Knopman, and Nissen, 1989; Knopman and Nissen, 1991; Reber, 1989; Restle, 1970; 1973; Restle and Brown, 1970a; 1970b; Willingham, 1998; Willingham, Nissen, and Bullemer, 1989). In our paradigm (Fountain and Rowan, 1995a; Rowan, Fountain, Kundey, and Miner, 2001), rats learn to press levers in an array in the proper sequential order that produces a repeating pattern of responses. Response patterns of this sort are remarkably easy for rats to learn even when patterns are composed of 24, 30, or even more successive elements (Fountain and Rowan, 1995a). In many studies, we have overcome constraints on daily training typically associated with food and water reinforcement procedures by using hypothalamic brain-stimulation reward (BSR) to reinforce correct responses. Because rats do not satiate to the rewarding quality of electrical brain stimulation of the hypothalamus, this form of reward allows us to train rats on patterns composed of many pattern elements with over 100 pattern presentations per day in some experiments. Our method also has the advantage that it allows us to collect accuracy and latency measures on a trial-by-trial basis while the rat performs the task at its own pace. This method is an improvement over earlier methods used with rats and even primates because it allows us to study how rats learn long, elaborate serial patterns and because it provides measures of correct-response rates, error rates, and “intrusion” rates (i.e., the number of specific kinds of errors produced at particular locations in the pattern) on a trial-by-trial basis throughout the serial pattern (Fountain and Rowan, 1995a; Rowan et al., 2001).

Subjects, BSR Electrode Implantation, and Shaping

We have typically used as subjects naïve male hooded rats (Rattus norvegicus) at least 90 days of age. Rats are housed in individual cages with food and water freely available. They are maintained on a 15:9-hr light-dark cycle. Testing occurs during the light portion of the cycle. Both food and water are freely available in the home cage.

For behavioral studies of sequential learning and memory, all rats are implanted with bipolar electrodes (MS301, Plastic Products, Roanoke, VA) for hypothalamic BSR
Prior to stereotaxic surgery, each rat is deeply anesthetized by i.p. pre-injection of xylazine and atropine followed by isoflurane anesthesia. Rats also receive antibiotics (60,000 units penicillin i.m.) following surgery to reduce the chance of infection. They are carefully monitored for infection following surgery and are allowed at least 1 week for recovery from surgery. One important advantage of BSR is that a rat can be reinforced immediately for every correct response without requiring the rat to pause to consume food or water. The result is that rats often produce sequential response rates of 1 response every second or two, similar to sequential response rates observed in analogous human sequence production studies (Fountain and Rowan, 1995a; Restle and Brown, 1970a; 1970b). This can be compared to pattern presentation rates of 1 element every minute or two, or slower, that are common in other sequential learning procedures involving rats and food reinforcement (e.g., Fountain, Henne, and Hulse, 1984; Capaldi, Verry, Nawrocki, and Miller, 1984). An additional advantage of using BSR is that rats do not have to be food- or water-deprived throughout experiments that may last weeks or even months.

Rats are shaped to leverpress for BSR in two shaping chambers (30 X 30 X 30 cm), each equipped with a single retractable response lever mounted 5.0 cm above the floor and a commutating device centrally located in the ceiling. Each box is constructed from clear Plexiglas with a floor of stainless steel rods. Each is enclosed in a sound-attenuating shell made of particleboard (20 X 60 X 65 cm). These shaping chambers are housed in a room separate from those of the test chambers. Both shaping chambers and the sequence production apparatus are controlled from an adjoining room by a microcomputer and interface (interface and Med-State Software, Med Associates, Inc., Fairfield, VT).

Throughout all phases of the experiment, rats receive reinforcement consisting of one or more 200-ms BSR “pulses” of a 60-Hz sinusoidal pulse train from a constant current source of 20-100 µA. Stimulators were fabricated in-house (based on a step-down transformer and a variable potentiometer) and are controlled by the computer and interface. In initial stage of shaping, at the beginning of the session, the lever is inserted into the chamber and remains inserted throughout the 30-min session. Rats are required to make at least 1000 leverpress responses within a 30-min session to be admitted to a study. Rats that fail to meet the criterion within several daily shaping sessions are excluded from the study. The day before starting the sequence production procedure, rats receive one 30-min session of discrete-trial shaping, wherein the lever is retracted briefly then reinserted into the chamber during the intertrial interval (ITI), to familiarize them with the discrete trial procedure they will experience in the pattern production procedure.

The Sequence Production Apparatus: The Circular Lever Array

As shown in Figure 1, the training chamber for the sequence production paradigm (Fountain and Rowan, 1995a, 1995b) is octagonal in shape with clear Plexiglas walls 15 cm wide by 30 cm tall and measures approximately 40 cm between parallel walls. In our apparatus, a retractable response lever (fabricated in-house based on a solenoid to insert the lever arm and springs to affect retraction) is centered on each wall 5.0 cm above the floor producing a circular array of levers around the perimeter of the chamber. We refer to the levers as Levers 1 through 8 in clockwise order with Lever 8 adjacent to Lever 1. Each lever
requires approximately 0.15-N force for activation. Rats in the testing chamber are connected to a stimulator by way of a flexible cord (Plastic Products MS304) and a commutating device centrally located in the ceiling of the chamber.

Figure 1. An octagonal operant chamber equipped with a retractable lever on each wall to form a circular array of levers. Rats are connected by a flexible cord to a commutating device in the ceiling of the chamber so that they can be reinforced with pulses of brain-stimulation reward for correct responses.

Such a chamber is easily constructed from relatively inexpensive but durable materials. To begin, cut an octagonal hole in ¾” melamine particle board large enough to accommodate the 8 Plexiglas walls. In each piece of Plexiglas that will serve as a wall, pre-drill a hole for the lever aperture and any supporting hardware, 2 holes for wood screws at the bottom of the wall, and 2 holes for small nuts and bolts at the top of the wall. Use wood screws to attach the bottom of each wall to the inside of the octagonal hole so that the bottom of each wall is flush with the bottom of the melamine board. Use small nuts and bolts to attach a lightweight metal strap around the outside top of the walls to hold the walls rigidly in place. Your Plexiglas can be lightweight (1/8” thickness) if the levers you use rest on the melamine board, or you may need to use heavier Plexiglas (e.g., ¼” thickness) if the walls must support the levers. Use a hinge to attach an octagonal Plexiglas ceiling to the top of one wall of the chamber using the nuts and bolts that also hold the strap in place.

The chamber rests upon a floor of stainless steel hardware cloth. We have found it convenient to cut a second melamine board with a corresponding round hole slightly larger than the octagonal hole of the chamber, then add approximately 2-cm blocks on each side of the bottom of the support structure to serve as spacers. The hardware cloth sits on this support structure with the chamber atop it. As shown in Figure 2, the spacers allow us to slide standard bedding trays in and out below the hardware cloth floor for cleaning. The weight of the chamber immobilizes the hardware cloth, yet it is easy to remove the hardware cloth for cleaning simply by lifting one edge of the chamber.
Two such operant chambers are side-by-side in each of two testing rooms (approximately 2.0 X 2.6 m); the two chambers in each room are separated by a vertical partition and illuminated throughout testing by fluorescent lighting. The only major distal cues in the rooms are wall-mounted electrical outlet panels on two walls, the partition separating chambers, and white curtains on the remaining side. Mounted above each chamber is a closed-circuit television camera so that rats' activity can be monitored and shaped as necessary throughout testing from the computer and interface located in an adjoining room.

Figure 2. The octagonal operant chamber raised on one side to reveal the arrangement of the stainless steel hardware cloth floor, support structure, and bedding tray.

The Sequence Production Procedure

The sequence production procedure is a discrete-trial 8-choice procedure with correction. At the beginning of each trial, all 8 levers are inserted into the chamber. If the rat makes a correct choice, BSR is immediately administered and all levers are retracted for the next ITI. For incorrect choices, all levers but the correct lever are withdrawn and the rat must locate the correct lever and respond correctly; after the correct response, BSR is immediately administered and the lever is retracted for the next ITI. On each trial, the lever chosen and the latency to the first response are recorded. Rats learn to perform sequences of responses that involve pressing the eight levers in serial patterns. Two of the patterns we have found to be most useful are:


Violation “Runs”  123-234-345-456-567-678-781-818
Integers in the patterns refer to the clockwise position of the levers in the octagonal chamber and the correct order they are to be pressed. Dashes indicate temporal pauses that differ from other ITIs and serve as “phrasing cues” that can dramatically affect pattern learning (Fountain et al., 1984; Fountain and Rowan, 1995a; Stempowski, Carman, and Fountain, 1999; Fountain, Benson, and Wallace, 2000). Phrasing cues can be either longer or shorter temporal intervals than other ITIs (Stempowski et al., 1999). In our studies, we typically use 1-sec ITIs and 3-sec phrasing cues or, more recently, 2-sec ITIs and 0.5-sec phrasing cues. Intervals can be set to the same length as ITIs, phrasing cues, or can be discriminably longer to mark the beginning of each new pattern, for example, by using a 9-sec interval. Phrasing cues typically facilitate pattern learning (Stempowski et al., 1999) when they correspond to the inherent structure of patterns, that is, when they are positioned at formally defined chunk boundaries and thus cue chunk boundary elements (Fountain et al., 1984). In this pattern, elements within chunks obey a simple rule, namely, move one to the right until the phrasing cue is encountered. Underlined integers at the end of the patterns indicate where the patterns differ. The underlined element, “2,” in the Perfect “Runs” pattern fits with the general rules governing elements in all other 3-element chunks. This pattern is formally simple—described by few such rules—with no exceptions and is easily learned by rats to a high criterion within a week of training. The underlined element in the Violation “Runs” pattern does not obey the same rule; it is a “violation” or “exception-to-the-rule” and is difficult for rats to learn. Rats can learn to anticipate this particular violation element and produce the correct response in this particular pattern in 2-3 weeks of daily training of 20 patterns per day.

An advantage of this procedure is that rats begin the first day of the sequence production training experiencing the entire pattern under exactly the same procedure that will be maintained throughout the acquisition phase. No pre-training on simpler patterns or under simpler forms of the procedure is necessary as is often the case in other sequential tasks involving patterns of this length and complexity (cf. Fountain, 1990). Even so, the transition from the 1-lever shaping procedure to the 8-lever sequence production task can be difficult for rats and their response rate in the first day of training is often quite slow. Early in acquisition, shaping is typically required and the number of pulses of BSR may need to be increased to maintain responding. A few rats simply fail to make the transition and have to be excluded from the study. However, most rats become completely independent within the first day or two of acquisition (20-50 patterns) and their sequence production rate increases rapidly over the first few days of training. To make training more manageable during the first few days, we often break the “Day 1” block of training into several days of fewer patterns. For example, if daily training should consist of 20 patterns, we may train the equivalent “Day 1” block over three days of 5, 5, and 10 patterns, then train 20 patterns per day from Day 2 onward.

**Considerations in Constructing Serial Patterns**

Our past research has indicated several factors to consider in constructing sequential patterns for rats so as to avoid potential biases or artifacts. Although rats will learn almost any pattern of responses under the sequence production procedure, patterns that are highly structured are easier to learn than repeating pseudorandom patterns. Past research has shown that the number of simple rules that are required to describe the serial pattern, rather than
pattern length or other factors, is the best predictor of the difficulty of the pattern (Fountain and Rowan, 1995a).

Rats also appear to be sensitive to the distance they are required to travel between levers from trial to trial such that learning responses farther away seems to be more difficult than learning responses on adjacent levers, so equating this factor across trials within patterns is advisable if relative trial-by-trial acquisition rates are of interest. Similarly, equating this factor between patterns is important if comparing acquisition rates between pattern groups is critical.

Rats seem to use whatever cues are available to facilitate learning in this task; one particularly salient cue appears to be unused levers or those with nearby salient cues. For example, our original studies with a sequence production method used a horizontal array of levers along one long wall of an oblong operant chamber, but our results were affected by rats’ tendency to use end walls adjacent to levers at each end of the array as cues for responses on those levers (Fountain, 1990). The circular array was adopted to remove those cues. We have since observed that rats are sensitive to the presence of any levers in the chamber they are not required to press and can use those as cues to guide responses in their vicinity, so we typically create patterns so that all levers are used in the course of any pattern the rats must learn.

**Transfer and Probe Procedures**

Our recent work has shown that transfer procedures and probe patterns can be very efficient and informative procedures for characterizing the psychological and neural processes that underlie rats’ behavior in sequential learning tasks (cf. Fountain, 2006). Rats can easily be trained on a single pattern for 20 to 50 pattern repetitions per day during acquisition until a high criterion is met, then they can be transferred to another pattern in a transfer phase for one or more days. This approach allows detailed scrutiny of the effects of pretraining in one pattern on learning of another over the course of acquisition of the second pattern.

Recently, we developed a more efficient approach modeled after probe tasks often associated with pigeon conditioning studies. In our probe procedure, rats are trained on a single pattern for 20 to 50 pattern repetitions per day during acquisition until a high criterion is met (no more than 10% errors on any pattern element within a day), then we increase the number of pattern repetitions each day if necessary to accommodate the number of probes we wish to introduce. Next, we begin a 10-day probe phase where we introduce probe patterns randomly interspersed with blocks of 5 training patterns within daily sessions. Rats receive one of each type of probe pattern each day; the order of presentation of probe patterns is randomized. We thus obtain data for 10 probe trials for each of several probe patterns for each 10-day probe phase. Multiple probe phases can be conducted; between probe phases, rats are returned to normal training for a minimum of 3 days to assure that they still meet criterion performance before going to the next probe phase. This method allows us to present patterns with as few or as many features changed as we wish so that we can determine the factors that control performance and, in the case of pharmacological or lesion studies, the psychological processes that are compromised by psychobiological manipulations. Fountain (2006) provides detailed examples of this approach.
VARIATIONS ON THE SEQUENCE PRODUCTION PROCEDURE FOR STUDIES INVOLVING OTHER SPECIES, PSYCHOPHARMACOLOGY, AND BRAIN LESIONS

Several situations call for a sequence production method that avoids using BSR for one or more reasons. For example, studies with mice or other species may be impractical if they involve implanting electrodes for purposes of reinforcement. Another example is lesion studies that would be difficult or impossible to conduct because the manipulations interfere with BSR or are impractical with the BSR electrode present. Yet another example is developmental studies that would be compromised by electrode implantation. For these situations, we have developed a variation on our standard sequence production paradigm that involves a nosepoke response reinforced by water. We have used this procedure with rats and mice (Fountain, 2006; Fountain, Krauchunas, and Rowan, 1999). The procedure has the disadvantages that animals must be water deprived and that daily training is severely constrained in terms of the number of pattern presentations that are possible per day. However, it has the advantage of not requiring surgical implantation of BSR electrodes.

The Sequence Production Procedure with Nosepoke for Water Reinforcement

As shown in Figure 3, the nosepoke apparatus is an analogue of the BSR apparatus in that the test chamber used is also octagonal in shape and composed of clear Plexiglas walls with a floor of hardware cloth. The nosepoke chamber for rats has identical dimensions to the BSR chamber, whereas the nosepoke chamber for mice is half the diameter and height of the rat chamber, with 7.5 cm wide and 15 cm tall walls and approximately 20 cm between parallel walls. Centered on each wall is a nosepoke receptacle made of a PVC pipe end cap with an indicator light mounted in the back. This receptacle also contains a small line to deliver a 0.025 ml water droplet into the bottom of the receptacle from a syringe reservoir and solenoid on each wall. Nosepoke responses into the receptacles are detected by infrared emitter/detector pairs mounted in holes on opposite sides of the receptacles. Experiments are controlled from an adjoining room by a microcomputer and interface.

The nosepoke procedure is an analogue of the BSR procedure. At the beginning of each trial, all 8 indicator lights are illuminated in the 8 nosepoke receptacles. If the rat makes a correct nosepoke choice, a water droplet is immediately administered and all indicator lights are extinguished for the next ITI. For incorrect choices, all indicator lights but the correct one are extinguished and the rat must locate the correct receptacle with the illuminated indicator light and respond correctly; after the correct response, a water droplet is immediately administered and the remaining indicator light is extinguished for the next ITI. On each trial, the receptacle chosen and the latency to the first response are recorded. Rats learn to perform sequences of responses that involve choosing the 8 receptacles in the proper serial patterns.
Advantages and Disadvantages of the BSR Versus Water Reinforcement Procedures

The principal disadvantage of the BSR procedure is the need to implant BSR electrodes in all rats whereas the principal disadvantage of the water reinforcement procedure is the severe limitation imposed on training and testing by satiation to the water reinforcer. The number of pattern repetitions per day that rats and mice can complete in the nosepoke procedure will depend on the species, the length of the pattern, and other factors such as effects of drug exposure on thirst and satiation in pharmacological studies, but typically rats can be trained or tested on no more than ten 24-element patterns per day. This limitation effectively doubles or triples acquisition times and precludes the kinds of probe studies that have proven to be so useful in the BSR procedure for an analytical approach to characterizing the processes involved in rat sequential learning. On the other hand, not having to implant electrodes and instead using water reinforcement simplifies the sequence production procedure sufficiently that it should make the procedure more generally accessible to animal learning and cognition researchers. The water reinforcement procedure also allows researchers to do lesion studies, drug studies, and developmental studies that are impossible or impractical when BSR is involved.

Figure 3. An octagonal operant chamber equipped with a nosepoke receptacle on each wall to form a circular array. Rats nosepoke for water reinforcement for correct responses.
An Analogue of Our Sequence Production Procedure for Studies of Human Serial Pattern Learning

We have also developed an analogue of the rat sequence production procedure to examine the correspondence between human and animal sequential learning. Fountain and Rowan (1995a) compared rats’ and humans’ performance on similar variants of the original task. The human variation of this task required college students to learn to produce a response sequence on a computer. Subjects first read a simple set of instructions that was presented on the computer screen. They were informed that they would see eight circles on the screen and that they were to use an arrow (cursor) key to move a smaller circular cursor to the circle of their choice. They should then press the spacebar to choose the circle. The instructions required the participants to locate and use the right and left arrow keys and the space bar before the experiment began. Subjects were then informed that they would be given feedback as to the correctness of their choice. They were told not to be concerned if they made errors, to guess when necessary, and to follow instructions in the box at the top of the screen if they forgot what to do. At the beginning of the testing session, eight circles (13 mm in diameter) appeared on the screen along with a message in the help box at the top of the screen instructing the participant to make a choice. The circles were equally spaced in a circular arrangement (opposite circles were 104 mm apart). Subjects moved the cursor to one of the circles and selected it by pressing the space bar. If the subject selected the correct circle, then “CORRECT” was displayed on the center of the computer screen during the ITI. If the subject selected an incorrect circle, the correct one remained displayed, and the other incorrect circles were removed. The subject was then instructed to choose the correct circle.

Both rats and humans were trained using their respective sequence production procedures to learn the same set of patterns. They learned either completely hierarchical patterns or linear patterns created from the hierarchical patterns with elements rearranged so as to maintain the same pairwise associations found in the hierarchical patterns but with the overall pattern structure disrupted. Three experiments compared rats’ and humans’ learning of patterns with increasing hierarchical complexity. Experiment 1 compared rats’ and humans’ performance in learning either a pattern which could be expressed with two rules and had perfect structure or the same pattern elements rearranged so that the simple structure was disrupted. Pairwise associations between the elements were the same in the two patterns. Experiment 2 examined the effects of disrupting the structure in a pattern whose structure could be described by three rules; Experiment 3 examined this phenomenon in a hierarchical pattern described by four nested rules. Pattern difficulty and the error profiles generated by humans and rats were parallel indicating that rats were using similar cognitive strategies to those humans employed to learn these patterns (Fountain and Rowan, 1995a). More generally, these types of studies with analogous sequence production procedures can be very useful for establishing bridges between human and nonhuman animal cognitive research and between human and animal research on the neurobiology of cognitive processes, particularly those processes that contribute to the organization of complex, intelligent behavior through time.
Sequence Production Paradigms and the Study of the Psychological and Neural Mechanisms of Cognition

Sequence production paradigms are powerful tools for studying the psychological and neural processes that underlie the organization of sequential behavior. In our lab, they have been used to study a variety of psychological processes that contribute to the structure of ongoing behavior, including hierarchical and linear rule learning (Fountain, 1990; Fountain and Rowan, 1995a), phrasing and its effects on cognitive chunking (Fountain and Rowan, 1995b), phrasing as discrimination learning (Fountain et al., 2000; Stempowski et al., 1999), species differences in response to pattern structure and phrasing (Fountain, Krauchunas, et al., 1999), cognitive “sorting” of interleaved patterns driven by subpattern structure (Fountain, Rowan, and Benson, Jr., 1999; Fountain and Benson, Jr., 2006), the role of discrimination learning in sequence production (Fountain, 1990; Fountain and Rowan, 1995a; Fountain et al., 2000; Stempowski et al., 1999), and the role of multiple concurrent cognitive process in sequential behavior (Fountain, 2006; Fountain and Benson, Jr., 2006; Fountain and Rowan, 1995a; Fountain et al., 2002).

Procedures for studying sequence production in humans have also become popular tools for examining and characterizing the effects of pharmacological manipulations and brain dysfunction on complex cognitive processes (cf. Hartman et al., 1989; Knopman and Nissen, 1991; Reber, 1989; Willingham, 1998; Willingham et al., 1989). We have applied the same approach to examine the effects of drugs, toxic chemicals (e.g., Fountain, Raffaele, and Annau, 1986), and brain lesions on neurobehavioral systems involved in organizing sequential behavior.

Recently, the sequence production paradigm has been used to examine and characterize long-lasting cognitive deficits resulting from adolescent exposure to nicotine and other psychoactive drugs. This work employs a rat adolescent drug exposure protocol that has been used to characterize the effects of adolescent drug exposure on a broad range of biological and behavioral processes including genetic expression, apoptosis (programmed cell death), synaptogenesis, cell replication, receptor expression in neurotransmitter systems, and the functional programming of simple behavioral responses. Animal adolescent exposure protocols have been used to study the effects of a variety of drugs including nicotine, alcohol, and cocaine, to name but three common drugs threats for adolescents (Kelley and Rowan, 2004; Kelley and Middaugh, 1999; Sircar and Sircar, 2005). One particularly important link to sequential learning research is that early exposure to nicotine in mice, using this exposure procedure, has demonstrated alterations in serotonergic, dopaminergic, noradrenergic, and, most importantly, cholinergic systems (Kelley and Middaugh, 1999; Trauth, Seidler, McCook, and Slotkin, 1999). What the sequence production paradigm brings to the table is a rat cognition paradigm tightly modeled after paradigms for studying high-level cognitive functions in humans. Initial studies show that our paradigm detects cognitive dysfunction in adult rats that over a month earlier received adolescent exposure to nicotine. To our knowledge, this is the first evidence that long-term, low-level adolescent nicotine exposure significantly impairs higher cognitive functioning in adulthood. Numerous studies have established adolescence as a critical developmental period during which unique pharmacological sensitivity is exhibited. This line of research promises to extend our understanding of both the development of higher cognitive processes and the neurobiological basis of these processes in the rat brain.
Our recent work has shown that sequential learning is likely subserved by at least three dissociable brain and behavioral systems that are recruited concurrently in sequential learning tasks (Fountain, 2006). When rats learn serial patterns with phrasing cues and a violation element, learning about chunk boundary elements is impaired under physiological manipulations such as the NMDA receptor antagonist, MK-801 (Fountain and Rowan, 2000), the anticholinergic drug, atropine, and hippocampal lesions, but not by medial frontal cortex lesions. In addition, learning about violation elements in serial patterns is profoundly impaired by MK-801 and atropine, but not by hippocampal lesions or medial frontal cortex lesions. Learning about within-chunk elements is resistant to disruption by all these manipulations and may reflect learning by internal representations of motor or cognitive rules. The sequence production paradigm is a rich and flexible methodology for studying the complex interactions of the multiple psychological and neural processes that mediate the organization of sequential behavior.

REFERENCES


