On The Neural Mechanisms of Sequence Learning

Tim Curran
Department of Psychology
10900 Euclid Avenue
Case Western Reserve University
Cleveland, Ohio 44106-7123
U.S.A.

tec3@po.cwru.edu

PSYCHE, 2(12), August 1995
http://psyche.cs.monash.edu.au/v2/psyche-2-12-curran.html

KEYWORDS: Implicit Learning, Sequence Learning, Serial Reaction Time, Basal Ganglia, Motor Cortex, Prefrontal Cortex.

Abstract

Nissen and Bullemer's (1987) serial reaction time task (SRT) has proven to be a useful model task for exploring implicit sequence learning. Neuropsychological research indicates that SRT learning may depend on the integrity of the basal ganglia, but not on medial temporal and diencephalic structures that are crucial for explicit learning. Recent neuroimaging research demonstrates that motor cortical areas (primary motor cortex, premotor cortex, supplementary motor cortex), prefrontal, and parietal cortex also may be involved. This paper reviews this neuropsychological and neuroimaging research, but finds it lacking specific links between structure and function. In order to promote better functional hypotheses, the second part of the paper examines the function of these brain areas (basal ganglia, motor cortical areas, prefrontal cortex, parietal cortex) from a broader perspective. Neuroimaging and neuropsychological research with human subjects, as well as neurophysiological and lesion research with animals, suggests a number component operations that these brain mechanisms may contribute to learning in the SRT task.

1. SRT Learning

Introduction and Background

1.1 Nissen and Bullemer (1987) introduced a serial reaction time (SRT) task to study sequence learning via performance improvement. Reaction time (RT) improvements, despite little measurable explicit knowledge of the sequence, suggested that learning occurred without awareness of the sequence. The disappearance of these RT improvements when subjects were distracted by a concurrent tone-counting task suggested that learning was dependent upon attention. The ability of amnesics patients with Korsakoff's syndrome to show such RT improvements has been interpreted as suggesting that this learning did not depend on the brain structures that are critically involved in explicit learning, and also that SRT learning does not require explicit knowledge. Thus, Nissen and Bullemer (1987) not only introduced a influential paradigm for the study of sequence learning, but also helped define the major questions that students of sequence learning continue to debate and explore: awareness (e.g., Shanks & St. John, 1994), attention (e.g., Cohen, Ivry, & Keele; Curran & Keele, 1993; Stadler, 1995) and underlying neural mechanisms. The present paper provides a critical review of research relevant to the latter question: What are the neural mechanisms of sequence learning? First, neuropsychological and neuroimaging experiments using the SRT task will be reviewed. This research suggests certain neural mechanisms that are involved in spatial sequence learning, but has yet to precisely identify the function(s) that these mechanisms may contribute. With these candidate brain mechanisms in mind, the second part of the paper considers evidence from other domains that may help specify their functional roles in sequence learning.

1.2

1.2 The SRT task provides a simple model for the study of serial learning processes that underlie of a variety of human behaviors from motor coordination to language. Serial learning has been investigated from perspectives ranging from the motor control tradition (Rosenbaum, 1987) to the verbal learning tradition (Jensen & Rohwer, 1965). Much of this previous work on serial learning has been done under intentional learning conditions. The present review concentrates on research related to implicit sequence learning for two primary reasons. First, many of the real-world sequential behaviors that we learn, from walking to grammatical speaking, appear to be learned unintentionally and often without explicit awareness of the requisite sequential regularities. Second, knowledge of the underlying neural mechanisms of implicit sequence learning-- and how they differ from the brain mechanisms that are known to normally support explicit learning and memory-- might provide evidence that is relevant to debates over the separability of implicit and explicit learning. Most of the evidence on the neural mechanisms of implicit sequence learning has used the SRT task. Other evidence from related domains such as artificial grammar learning (Knowlton, Ramus, & Squire, 1992; Knowlton & Squire, 1994) and other forms of "procedural learning" (for reviews see Gabrieli, 1994; Willingham, 1992) is not reviewed.

Methodological Issues

1.3 On each trial of the SRT task, a visual stimulus (typically an x-mark or asterisk) is presented at one of three or four spatially distinct locations. The subject has an equal

number of corresponding response keys and presses the correct key as quickly as possible on each trial. The visual signal disappears upon the subject's response then another signal appears over a different position after a short response-stimulus interval (RSI is typically 200-500 ms, longer RSIs may preclude learning, Frensch & Miner, 1994). Unbeknownst to subjects, often the visual signal follow a specific repeating sequence. For example, Nissen & Bullemer (1987) used 4 spatial positions, and designating the positions as 1 to 4 from left to right, their sequence was 4-2-3-1-3-2-4-3-2-1 (hereafter called the N&B sequence). The visual signal moves from position 4 to 2 to 3 etc. The beginning and end of the sequence are not designated in any way, so the end of the sequence cycles directly back to the beginning. A typical block of trials contains 6 to 10 cycles of the repeating sequence.

1.4 Sequence learning cannot be assessed by merely measuring the reaction time (RT) improvement across trials, because RT tends to improve as subjects become practiced with nonsequential aspects of the task-- such as becoming more proficient with the stimulus-response mapping. Therefore, learning is typically measured as the RT difference between a block of trials that follows the repeating sequence and an adjacent control block that does not follow the sequence. The most commonly used control block presents stimuli at pseudorandom locations with the constraint that the same position is not immediately repeated (the to-be-learned sequence typically does not have immediate repetitions either). Here I will refer to sequential blocks as "S" and pseudorandom blocks as "R". Thus, an experimental design with 4 sequential blocks followed by two random blocks will be abbreviated as: S-S-S-S-R-R or 4S-2R. The RT difference between adjacent random and sequence blocks that serves as the primary performance measure of SRT learning similarly can be denoted R-S (R minus S).

1.5 Bullemer & Nissen (1987) also developed a variant of the SRT task to assess explicit knowledge of the sequence. The Generate Task is a cued-recall task in which subjects are shown a visual signal, then are asked to explicitly predict which stimulus will appear next. Unlike the SRT task, subjects are encouraged to respond slowly and accurately because accuracy is the primary dependent measure. The Generate Task is often given after the SRT task with stimuli occurring in the same sequence as in the SRT. Accurate generation performance is taken to reflect explicit knowledge of the sequence. College students have shown significant R-S learning differences in the SRT task, despite inaccurate generation performance (Cohen, Ivry, & Keele, 1990; Willingham, Nissen, & Bullemer, 1989). Thus, it has been inferred that SRT learning is implicit, though such inferences have not gone unchallenged (e.g., Perruchet & Amorim, 1992; Shanks & St. John, 1994).

1.6 Much of the review that follows is somewhat critical of the methodology that has been used to investigate the neural mechanisms of sequence learning. There are three issues that are especially important for interpreting results from these studies. First, insofar as we are interested in implicit sequence learning, one must consider the possibility that various effects or between-group differences might be attributable to explicit knowledge. Though SRT learning may not require explicit knowledge, explicit knowledge clearly enhances SRT learning (Curran & Keele, 1993; Perruchet & Amorim,

1992; Willingham et al., 1989). The proper method for assessing explicit knowledge is not agreed upon (e.g., Cohen & Curran, 1993; Perruchet & Amorim, 1992; Shanks & St. John, 1994; Willingham, Greenley, & Bardona, 1993), but available methods allow some interpretive leverage.

1.7 Second, interpretation of group differences is often complicated by differences in overall reaction time. The primary performance measure of sequence learning is the RT difference between responses occurring to sequentially determined events versus pseudorandomly occurring events (R-S). Such RT differences scores can be inflated by increases in overall RT (Chapman, Chapman, Curran, & Miller, 1994), so RT differences cannot be unambiguously compared between a faster group (e.g., control subjects) and a slower group (e.g., patients with Huntington's disease or Korsakoff's syndrome). Realizing this problem, investigators have sometimes expressed sequence learning as the proportion of the RT difference over the baseline RT ([R-S]/R) or used logarithmic transformations. These methods are based on an implicit assumption that the regression of R-S on R is linear with an intercept of zero-- an assumption that may be false (see Chapman et al., 1994 for a more thorough discussion). Thus, conclusions such as, "Group X showed greater learning than Group Y", cannot be unequivocally accepted when X and Y differ on baseline RT-- even when RTs are transformed.

1.8 A final issue that deserves considerable attention when interpreting studies of sequence learning concerns the structure of the to-be-learned sequence and the manner in which it differs from the non-sequential control condition. Most studies compare RT to sequential stimuli (S) versus RT to pseudorandom stimuli (R). A number of researchers have correctly argued that, depending on the structure of the to-be-learned sequence, pseudorandom trials may not be the proper control for the assessment of sequence learning (Jackson & Jackson, 1992; Reed & Johnson, 1994; Shanks & St. John, 1994). Consider the N&B sequence which has been most commonly used in neuropsychological investigations : 4-2-3-1-3-2-4-3-2-1. This sequence differs from pseudorandom trials in a number of ways that may enable learning of nonsequential information. First, some positions occur more frequently than others (1 & 4 occur twice; 2 & 3 occur three times). On average, each position occurs equally often in a pseudorandom condition, so RTs to a block of sequential trials could be faster than those to pseduorandom trials merely because the subject has learned that 2 and 3 are more likely to occur than 1 and 4. Such learning of relative frequency may be interesting in its own right (e.g., Hasher & Zacks, 1984), but this is not the kind of sequential learning that is claimed to be the object of study with the SRT paradigm.

1.9 Second, differences in first-order probabilities confound the comparison of Nissen & Bullemer's sequence to pseudorandom trials. Though the sequence does not contain uniquely predictive pairwise associations, the sequence contains pairwise associations that are probabilistically predictive (Jackson & Jackson, 1992; Stadler, 1992). For example, 3 is followed by 2 more than by 1; or, 4 is followed by 2 or 3 but never by 1. For pseudorandom trials, these pairwise probabilities should, on average, be equivalent (each position is equally likely to be followed by any other position). Therefore, a subject who learns which positions are most likely to be followed by which others may show

faster RT for sequence trials than to pseudorandom trials without learning any information that is truly sequential. By "truly sequential" I mean information that involves learning the relationship between multiple stimuli rather than simple pairwise associations between adjacent stimuli.

1.10 Each of the issues -- explicit knowledge, baseline RT differences, and sequence structure -- will be considered in interpreting the experiments that are reviewed. It will become apparent that few experiments pass the criteria for unambiguous interpretation on each of these issues, and indeed, unambiguous criteria for assessing explicit knowledge do not exist. Dwelling on these issues does not entail a call for the dismissal of any experiment, but merely represents a prod toward interpretive caution. Fortunately, more recent neuropsychological studies of sequence learning are methodologically cleaner than their predecessors but have generally reached similar conclusions.

Theoretical Foundations

1.11 To understand the mapping between cognitive abilities (e.g., sequence learning) and neural mechanisms, it is useful to start with a theory of the underlying mental processes. Indeed, Marr (1982) considered implementational theories that specify neural mechanisms as subordinate to computational and algorithmic theories. From other perspectives (e.g., Kosslyn, 1994) understanding behavior at the cognitive and neural levels can proceed in a more interactive fashion. Given the current lack of coherent cognitive theories of sequence learning, consideration of the underlying neural mechanisms cannot be completely guided by computational and/or algorithmic theories. However, I will present a cursory review of the sorts of processes that behavioral research has implicated in sequence learning.

1.12 Two recurrent connectionist models have been successfully applied to SRT learning (Cleeremans & McClelland, 1991; Cleeremans, 1993a, 1993b; Keele & Jennings, 1992). Though details differ, both models exemplify how learning might be accomplished by high-level associations between some combination of previous stimuli and the next stimulus and/or response. For example, in learning the sequence 1-2-1-4-2-3-4-1-3-2-4-3, these networks might learn that 1-2-1 is followed by 4, 2-1-4 is followed by 2, etc. More generally, the hidden-unit representation of each stimulus is shaded by the identity of all preceding stimuli with remote stimuli exerting a lesser influence than immediately prior stimuli (see Cleeremans, 1993b, for an excellent discussion of the representations developed by such recurrent networks). In general, a mechanism that learns only pairwise associations between adjacent stimuli is computationally insufficient to underlie all sequence learning. This has been made clear by numerous demonstrations of SRT learning of sequences that do not contain predictive pairwise associations (Cleeremans & McClelland, 1991; Cohen et al., 1990; Reed & Johnson, 1994; Stadler, 1993), so brain systems that are know to learn only pairwise associations are not sufficient.

1.13 The notions of hierarchic representation and chunking have also been invoked to play a role in sequence learning. The basic idea is that a sequence such as 1-2-3-2-13 can be chunked as 1-2-3, 2-3-1 or 1-2, 3-2, 3-1. Hierarchic representation posits the further

idea that sequences are represented at multiple levels such as entire sequences (1-2-3-2-13), chunks (1-2-3, 2-3-1) and individual elements within these chunks. Compelling evidence for such hierarchic coding has been obtained in studies of explicit sequence learning (e.g., Gordon & Meyer, 1987; Povel & Collard, 1982; Restle & Burnside, 1972), but the evidence for hierarchic coding in implicit SRT learning is merely suggestive. Keele and his colleagues (Cohen et al., 1990, Curran & Keele, 1993; Keele & Curran, in press; Keele & Jennings, 1992; also see Servan-Schreiber & Anderson, 1990) have suggested that sequences can be hierarchically represented when learning proceeds without distraction. This idea primarily comes from research showing that learning of complex sequences (those for which first-order associations are ambiguous and insufficient for learning) is more drastically impaired by distraction than simpler sequences with some predictive first-order information (Cohen et al., 1990; Curran & Keele, 1993). Recurrent network simulations have suggested that learning of these complex sequences benefits from chunking (Keele & Jennings, 1992). Other research has shown that the standard distraction task that is used in SRT research (tone counting) seems to impair learning by disrupting the ability to parse sequences into consistent chunks (Stadler, 1995).

1.14 Another question that is particularly useful for guiding the search on the neural underpinnings of sequence learning concerns the extent to which SRT learning is best characterized as the learning of stimulus sequences, responses sequences, or stimulus-response sequences. Behavioral research with the SRT task has clearly shown that sequence learning cannot be purely explained at the level of motor execution. Learning can transfer across different effectors (e.g., Keele, Jennings, Jones, Caulton, & Cohen, 1995; Stadler, 1989) and learning can be demonstrated in cases where stimulus sequences have been decoupled from response sequences (Howard, Muter, Howard, 1992; Mayr, 1994). Thus, the neural mechanisms of sequence learning are unlikely to be exclusively localized to the motor systems of the brain. However, response-based systems that operate at a higher-level than specific effectors are likely to be involved. Keele et al. (1995) found nearly perfect transfer across effectors when the response modality remained the same (key pressing with three fingers versus one finger) but transfer was less complete across different response modalities (key pressing to verbal responses). Thus, learning may have a response-specific component but not an effector-specific component, and the existence of manual-verbal transfer (even if incomplete) makes a purely response-based mechanism unlikely -- as do demonstrations of learning that is completely response-independent (Howard et al., 1992; Mayr, 1994).).

1.15 A final theoretical question concerns the distinction between implicit and explicit sequence learning. As previously mentioned, the ability of subjects to show SRT learning without awareness is currently debated (see Shanks & St. John, 1994). However, even if one assumes (as I do here) that SRT learning can be implicit, the theoretical relevance of this distinction for understanding the neurocognitive mechanisms of sequence learning remains unclear. Unlike research on implicit memory (for review see Roediger and McDermott, 1993) -- which is primarily driven by the search for functional dissociations between implicit memory and a vast body of research on explicit memory -- we know very little about explicit learning in the SRT task. Rather than searching for experimental

variables that might differentially effect implicit versus explicit sequence learning -- to establish functional dissociations -- SRT researchers have typically adopted the strategy of trying to investigate implicit learning under conditions in which the effects of explicit knowledge are undetectable. As mentioned in regard to hierarchic coding, we do know something about explicit sequence learning, but this comes from paradigms that are quite different from the SRT task (e.g., Gordon & Meyer, 1987; Povel & Collard, 1982; Restle & Burnside, 1972). Comparisons between implicit and explicit learning within the same task are sorely needed, but there are a few hints about how implicit and explicit leering may functionally differ that I will briefly review.

1.16 First, Willingham et al. (1989) found that subjects with explicit sequence knowledge are more likely to show anticipatory responding on the SRT task than subjects with little or no explicit knowledge. That is, explicit knowledge may allow subjects to anticipate the identity of a forthcoming stimulus before it actually appears. Implicit knowledge, in contrast, may only reflect a kind of priming whereby processing of a stimulus and/or response is facilitated by prior knowledge but this prior knowledge is not sufficient for actual anticipation. Only two experiments have actually included a group of subjects in an explicit learning condition. Curran and Keele (1993, Experiment 1) showed that subjects who explicit learned a sequence showed a large reaction time advantage over subjects who learned implicitly. However, this advantage disappeared when both groups were transferred to a condition with distraction. Thus, whatever is responsible for the advantage of explicit over implicit sequence learning (e.g., anticipation) depends upon freedom from distraction. Frensch and Miner (1994, Experiment 1) also directly compared subjects who learned implicitly against those who learned explicitly. Implicit learning was found when the response-stimulus intervals (RSI) were brief (500 ms) but not when they were longer (1500 ms). Though explicit learning was also inversely related to RSI, it was still significant after the longer intervals. Thus, implicit SRT learning seems to demand short RSIs but explicit learning can proceed at longer RSIs. Frensch and Miner suggest that implicit sequence learning depends upon the co-activation of stimuli in short-term memory in order for them to become associated, and this activation might not persist across long RSIs. One might speculate that all of these characteristics of explicit SRT learning-- anticipation, sensitivity to distraction, robustness to longer RSIs-- are related to some sort of working memory contribution. An active rehearsal process may be necessary for maintaining activation of information across longer time periods during learning. After learning, such a control process can generate the identity of the next event to guide anticipatory responding, but this capacity for anticipation might be disabled by distraction (for a formal model that embodies similar ideas see Cleeremans, 1993a).

1.17 In summary, our theoretical understanding of SRT learning is incomplete, but some general principles have been elucidated. It is clear that two types of mechanisms would be insufficient for implicit sequence learning (and almost certainly insufficient for explicit sequence learning as well). First, a purely response-based mechanisms is insufficient because learning can be response-independent. Second, a mechanism that can only form pairwise associations between adjacent stimuli/responses is insufficient. The underlying representations need to associate multiple stimuli, and likely mechanisms for

establishing such higher-order associations include recurrent networks, chunking, and/or hierarchic representation. Implicit and explicit SRT learning have not been well differentiated, but the available evidence suggests that only explicit learning can lead to anticipatory responding, explicit learning can span longer RSIs than implicit learning, and explicit learning is more drastically affected by distraction than implicit learning.

2. Review of SRT Research on Neural Mechanisms

SRT Learning in Patients with Explicit Memory Deficits

2.1 A number of experiments have examined the sequence learning abilities of patients with explicit memory deficits. Profound impairments in explicit learning and memory have been reported in patients with organic amnesia (e.g., Mayes, 1988; Parkin & Leng, 1993) and Alzheimer's disease (e.g., Albert & Moss, 1992; Huppert, 1991; Kopelman, 1992). Whether such patients can learn in the SRT task has been of interest for 2 primary reasons. First, spared SRT learning in patients with explicit learning impairments suggests that SRT learning may not depend on the brain regions that are crucial for explicit learning. Amnesic patients typically have damage to medial temporal lobe regions, including he hippocampus, or to the diencephalon (Parkin & Leng, 1993; Squire, Amaral, & Press, 1990) whereas Alzheimer's disease has more widespread effects which include neurofibrillary tangles and neuritic plaques in limbic, temporal and posterior association cortex, and frontal regions which are involved in explicit learning and memory (Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991). Second, given that these patients have explicit memory deficits, spared learning might be taken as evidence that SRT learning is truly implicit. This inference is not universally accepted. For example, Shanks & St. John (1994) have suggested that amnesic performance may be irrelevant to the question of whether learning is unconscious. Because tests of explicit knowledge are given after learning, an amnesics inability to explicitly remember the sequence tells us little about his or her awareness of the sequence during learning. That is, the amnesic might have been aware of the sequence during learning, but may have forgotten. The present review will generally consider the performance of such patients as providing information about possible neural mechanisms rather than about awareness. Because studies of SRT learning under pharmacologically induced amnesia do not isolate effects on particular neural mechanisms, and are more typically thought relevant to issues of awareness, these studies are not considered (e.g., Knopman, 1991b; Nissen, Knopman, & Schacter, 1987) 2.2 Consideration of the neural mechanisms of sequence learning began with Nissen & Bullemer's (1987) experiment with 6 Korsakoff's patients. Each block contained 100 trials with their 10-element sequence in a design in which 4 sequence blocks were followed by 4 pseudorandom blocks (hereafter, "4S-4R"). Both Korsakoff's patients and control subjects were significantly faster for sequence blocks than pseudorandom blocks. Korsakoff's were marginally slower than controls, and the group by condition interaction suggests that the learning effect was greater for controls than Korsakoff's patients. The difference between groups could reflect explicit knowledge since all of the control subjects but none of Korsakoff's patients reported noticing a sequence. Nissen and Bullemer examined learning for each element of the sequence by comparing RT to each element with RTs to the same position within

pseudorandom blocks. Chunking patterns were inferred by examining the patterns of RT differences for each element, and both groups displayed similar chunking. Although the significance tests were not reported for each sequence element, it appears that subjects from both groups were learning more than relative frequencies. Whether anything more than pairwise probabilities were learned, especially for Korsakoff's patients, remains unclear.

2.3 Nissen, Willingham, & Hartman (1989) extended Nissen and Bullemer's result in an experiment that included a delayed-retention measure. Seven Korsakoff's patients, 8 alcoholic controls, and 7 healthy elderly participated in 2 sessions, separated by one week. The design of each session was 4S-1R. Korsakoff's were significantly slower overall. In the first session, all groups were significantly faster for sequential than random trials. All groups showed similar retention of sequence knowledge across the week delay, as inferred from similar RTs in the last sequence block of the first session and the first sequence block of the second session. Similar to Nissen & Bullemer (1987), the Korsakoff's patients were less likely to report explicit knowledge of the sequence. If such differences in reported explicit knowledge influenced SRT performance, one would expect the patients to show less SRT learning, but they did not. Unlike Nissen and Bullemer (1987), Nissen et al (1989) found no differences in sequence learning between patients and controls. However, this equivalence must be interpreted cautiously since the Korsakoff patients were significantly slower, and therefore their random minus sequence differences may be artifactually inflated.

2.4 The research with Korsakoff's patients from Nissen's lab (Nissen & Bullemer, 1987; Nissen et al., 1989) is generally accepted to demonstrate that implicit sequence learning does not depend on the diencephalic brain mechanisms that are damaged by Korsakoff's syndrome. This conclusion is limited by the slower reaction time of Korsakoff's patients and the exclusive use of the N&B sequence. As previously discussed, sequence learning must be generally controlled by a mechanism that learns more than pairwise associations, but learning of the N&B sequence might reflect pairwise learning. This issue is particularly important in studies of human amnesia because many theories of medial temporal lobe function have emphasized the role of these brain areas for learning higher-order associations between multiple stimuli. For example, it has been suggested that the hippocampus is involved in chunking (Wicklegren, 1979), configural learning (Sutherland & Rudy, 1989), relational learning (Cohen & Eichenbaum, 1993), or stimulus-stimulus re-representation (Gluck & Myers, 1993; Myers & Gluck, 1994). Particularly relevant to sequence learning are findings that rats with hippocampal lesions can learn simple pairwise associations, but cannot solve conditional learning problems in which a cue given at time t, predicts different consequences depending on a preceding cue that was presented at time t-1 (Leaton & Borszcz, 1990; Ross, Orr, Holland, & Berger, 1984; but for contradicting results see, Jarrard & Davidson, 1991; Skinner et al., 1994). Such research suggests that the hippocampus may be necessary for learning higher-order associations that are mediated by more than a simple pairwise contingency between two stimuli.

2.5 According to such theories Korsakoff's patients may have learned the N&B sequence

because (a) their hippocampus and related medial temporal structures are intact and the diencephalon is not part of the functional circuit that is addressed by these theories, or (b) the N&B sequence was learnable by their residual pairwise learning capabilities (Knowlton, Gluck, & Squire [1994] have confirmed that amnesics can learn first-order probabilities in a non-sequential paradigm). These possibilities have recently been addressed by Reber and Squire (1994) who studied a group of nine amnesic patients with mixed etiologies (including 6 with diencephalic damage and 2 with hippocampal damage). In the first session of Experiment 1, amnesic and control subjects showed a similar reaction time slope across four 100-trial blocks with the N&B sequence. In a second session, subjects were given 10 training blocks with a different sequence that was structurally identical to a N&B sequence. After a retention interval that was filled with various tests of explicit knowledge, the amnesic patients showed a reaction time difference between a random and sequence blocks that was not significantly different from that of control subjects. Tests of explicit knowledge were able to detect explicit knowledge in control subjects but not in amnesic patients. A second experiment used a design that was similar to the second session of Experiment 1, but it used a sequence for which pairwise associations are insufficient for learning (2-3-4-2-1-4-1-3-1-2-4-3...). Overall reaction times were similar for amnesic and control subjects. As in Experiment 1, control and amnesics subjects did not show significantly different amounts of learning. This experiment provides the clearest evidence to-date that amnesic patients show normal SRT learning with a sequence that demands more than pairwise associations. However, it should be noted that the amnesic patients consistently showed nonsignificant trends that were suggestive of less learning than controls. These slight differences might reflect some contribution of explicit knowledge (which was thoroughly assessed with multiple measures) in control subjects who showed consistently greater levels of explicit knowledge than amnesic subjects.

2.6 Reber and Squire's (1994) finding that amnesic patients can learn relationships among multiple stimuli appears to be at odds with the theories stressing the importance of the medial temporal lobe (and especially the hippocampus) for complex associative learning. There are many possible reasons for this discrepancy. Many of these theories (e.g., Cohen & Eichenbaum, 1993; Gluck & Myers, 1993; Sutherland & Rudy, 1989) have been focused toward explaining the results of animal lesion studies and have not been well tested in human amnesics. Given that debates over the merits of these theories often center on lesion specificity (e.g., Eichenbaum, Otto, & Cohen, 1994), it should not be surprising that a group of amnesic subjects with heterogeneous lesions sites (often concentrated in the diencephalon rather than hippocampus) failed to show corroborative results. It is unclear if Reber and Squire's patients with diencephalic versus hippocampal lesions showed similar patterns. Given that the majority of the amnesic patients had diencephalic damage, it is possible that these results do not extend equally amnesic patients with different areas of brain damage, but Cleeremans (1993b) also reported successful sequence learning in a single amnesic with medial temporal lobe damage resulting from herpes encephalitis. Future research will be needed to determine if the present results reflect a deficiency in these theories or an anatomical discrepancy. For the present purposes, the weight of the evidence suggests that the brain areas damaged in amnesia do not significantly contribute to sequence learning.

2.7 A few studies have investigated sequence learning in patients with Alzheimer's disease (AD). Knopman & Nissen (1987) used N&B's sequence in a 4S-1R design with 100 trials per block. Overall, AD patients were nearly twice as slow as controls, but the groups showed a similar R-S RT difference of about 100 ms. Most of the controls reported noticing a repeating sequence compared to only 1 of 28 AD patients. Thus, interpretation is clouded by differences in explicit knowledge that are likely to inflate the SRT learning measure of control subjects, and extremely slow RTs that are likely to inflate the SRT learning measure of the AD patients.

2.8 A later study investigated retention of sequence knowledge by including a second session after 1-2 weeks: Session 1, 4S-1R; Session 2, 2S-1R (Knopman, 1991a). The session 1 results were very similar to those of Knopman and Nissen (1987) -- AD patients were much slower than controls, but showed a similar R-S learning effect. When RTs were log-transformed to alleviate between-group differences in variability, the AD showed less learning than controls. In an attempt to measure retention in a manner that would be unconfounded with group differences in initial learning, 8 AD patients and 14 controls were selected who showed a R-S difference greater than 50 ms in the first session. The RT difference between the last block of session 1 and the first block of session 2 served as the measure of retention. The groups were not significantly different when sequence retention was measured with either raw or log-transformed RTs. The controls were only marginally better than AD patients on a test of explicit knowledge (the generate task) given at the end of the second session.

2.9 Grafman et al. (1990) tested a large group of inpatients with AD (n3D42) on the N&B sequence. AD subjects completed 7, 100-trial blocks (2R-4S-1R) and showed a R-S difference of over 150 ms. Control subjects were not used, so it is unclear if this learning effect and baseline RTs were "normal". The range of mean RTs (about 500 - 800 ms) was somewhat lower than the AD patients in previous studies (about 750 - 1000 ms, Knopman, 1991a; Knopman & Nissen, 1987), but probably above the range of age-matched controls.

2.10 Ferraro, Balota, & Connor (1993) replicated the Knopman and Nissen (1987) experiment with two subgroups of AD patients, as well as a group of non-demented Parkinson's patients that will be discussed later. Ferraro et al. used a dementia rating scale to differentiate between mildly and very mildly demented AD patients. No differences were detected between very mildly demented AD patients and elderly controls in either baseline RT or R-S learning (RTs were log-transformed). In contrast, the mildly demented group was much slower and showed little or no R-S learning. Explicit knowledge was not assessed, but this does not undermine the conclusion that Alzheimer's dementia impaired sequence learning. 2.1.11 In summary, experiments with subjects who have explicit learning and memory deficits have shown rather variable SRT learning, but some useful conclusions might be drawn. Experiments with Korsakoff's patients and other medial temporal lobe amnesics have shown relatively normal SRT learning. Therefore, implicit sequence learning probably does not depend on the diencephalic and medial temporal structures that are crucial for explicit learning and memory. Alzheimer's

patients have given more variable results. This variability may reflect the diffuse and heterogeneous pattern of neuropathology that is associated with Alzheimer's disease. Given amnesics' normal sequence learning, it might be inferred that sequence learning deficits in some Alzheimer's patients are attributable to the abnormal functioning of brain areas other than the diencephalon and medial temporal lobes.

SRT Learning in Patients with Striatal Disfunction

2.11 A number of investigators have studied the sequence learning ability of patients with Huntington's (HD) or Parkinson's (PD) diseases. Because these progressive diseases are prominently associated with striatal disfunction, these studies are considered to test the general proposal that skill learning depends on the integrity of the striatum (e.g., Gabrieli, 1994; Mishkin & Appenzeller, 1987; Squire, 1992). Knopman & Nissen (1991) were the first to report a sequence learning deficit in HD patients. The HD sample included subjects with a range of disease durations and medications. Subjects were given 4 blocks of SRT trials (100 trials/block) with the N&B sequence followed by a block of pseudorandom trials (4S-1R). The RT difference between the last sequential block and the pseudorandom block was greater for controls than for HD patients. Furthermore, every control subject, but only 9 of 13 HD subjects, were faster in the sequence than random block. Therefore, it might be inferred that HD subjects showed less sequence learning than control subjects. This conclusion is subject to a few qualifications. First, HD subjects were slower overall than controls, so comparison of RT differences between groups may be compromised by scale effects. However, since slow performance tends to inflate reaction time differences (Chapman et al., 1994), it is unlikely that slower RTs artifactually decreased the HD learning effects in comparison to control subjects. Second, the control group tended to exhibit more explicit knowledge of the sequence as measured by performance on the generation task and subjective reports, so differences between groups might reflect differences in explicit knowledge. Another notable caveat is the fact that HD and controls showed similar retention of their sequence knowledge after a 20-60 minute delay.

2.12 Fortunately, Knopman and Nissen's results have been extended by an experiment that addressed some of these concerns (Willingham & Koroshetz, 1993). A mostly medicated group of patients in the early stages of HD completed 10 blocks of 60 trials with a 12-element sequence (2-3-1-4-3-2-4-1-3-4-2-1) followed by a pseudorandom block (10S-1R). Since each position is equally likely to be followed by each other position within this sequence, learning must transcend pairwise associations. The RT difference between the final sequence block and the random block was significantly larger for controls than HD subjects, and not significantly different than zero for HD patients (D.B. Willingham, personal communication, September 22, 1994). In contrast to Knopman and Nissen's (1989) experiment, there was little indication that between group differences in SRT learning could be attributed to differences in explicit knowledge. No differences were detected between the groups on the generation task. Of all subjects, only one control claimed awareness of a repeating sequence but this subject could not describe any of the sequence. Thus, Willingham and Koroshetz (1993) more convincingly demonstrated an implicit sequence learning deficit in patients with HD.

2.13 A few recent studies with PD patients have been able to assess the consequences of basal ganglia disfunction without baseline RT differences. Ferraro et al. (1993) performed an experiment virtually identical to Knopman and Nissen (1989), but without the delayed retention block. PD patients were nondemented and most were taking medication. Control subjects showed a R-S difference of 88 ms whereas nondemented PD patients showed a difference of 51 ms. The significant block (random vs. sequence) by group (control vs. PD) interaction confirmed that controls showed significantly greater sequence learning than PD subjects. Unfortunately, the possibility of between group differences in explicit knowledge was not addressed by Ferraro et al., but their was no reason to suspect any such differences since the nondemented PD patients were similar to NC subjects on a variety of cognitive tasks.

2.14 Similar results were obtained by (Pascual-Leone et al., 1993) who investigated SRT learning in patients with PD and others with cerebellar lesions. All PD patients were taking medication, but were tested both on and off medication. The only effects of medication state appeared to be slower overall reaction time without medication. In Experiment 1 subjects completed 6 blocks of 100 trials (1R-4S-1R) with the N&B sequence. PD patients were not significantly slower than controls, but RT difference between the final random and sequence blocks was smaller for PD subjects. Explicit knowledge was not assessed in this first experiment, but was assessed in later experiments. Experiment 2 examined the effects of list length by using sequences of length 8, 10, and 12. Both PD and control subjects showed an inverse relationship between sequence learning and sequence length. However, PD patients showed less learning than controls at each sequence length . Some of these differences may be attributable to differences in explicit knowledge because, when queried, control subjects were more likely to state that they noticed a repeating sequence.

2.15 In Experiment 3 (Pascual-Leon et al., 1993) subjects were explicitly taught the 10-element Nissen and Bullemer sequence until they were able to verbally reproduce it without error. After subjects demonstrated perfect explicit knowledge of the sequence, they were given 40 cycles of the sequence in the SRT task and informed that the stimuli would follow the previously learned sequence. Both PD and control subjects could use this explicit knowledge to decrease response times to 50% of baseline across 40 cycles of the sequence. However, PD patients showed a significantly slower rate of RT improvement than control subjects, so their ability to use this explicit knowledge to improve performance developed more slowly than for controls. As a whole, Pascual-Leon et al (1993) found that PD patients showed significant, but below normal, sequential learning. Whether differences reflect implicit or explicit knowledge is unclear. However, Experiment 3 demonstrated that PD patients were somewhat poorer at utilizing sequential knowledge to improve SRT performance even when sequential knowledge was explicit.

2.16 Pascual-Leone et al. also tested 15 patients with cerebellar degeneration who failed to show SRT learning. Interpretation of these results is complicated by extremely variable RTs and explicit learning deficits in Experiment 3. Further research on the role of the

cerebellum in sequence learning is needed, given its importance in associative conditioning (Thompson, 1986; Thompson, 1990) and timing (Ivry & Keele, 1989; Keele & Ivry, 1990; LlinE1s & Welsh, 1993).

2.17 A recent study has overcome the limitations of its predecessors-- baseline RT differences, uncertainties about explicit knowledge, and the use of sequences that can lead to RT improvements without true sequential learning -- and found no evidence of sequence learning in 11 non-medicated PD patients (Jackson, Jackson, Harrison, Henderson, & Kennard, 1995). Jackson et al. used an 11-element sequence, 12431421343, and a matched control condition rather than a pseudorandom condition. A critical transfer block (T) included one presentation of six different 11-element sequences. Each of these sequences were statistically equivalent to the learned sequence--that is, each had 0-order and first-order transitional probabilities that were equivalent to the practiced sequence. Therefore, any RT differences between the transfer block and surrounding sequence blocks must reflect sequential knowledge (at least second-order associations). Subjects completed 10 blocks of trials with 66 trials per block: 2R-6S-1T-1S. Baseline RTs were equivalent for PD and control subjects, but only the control subjects showed a significant difference between the sequence and transfer blocks. Numerically, the reaction time difference was 74 ms for controls and 9 ms for PD patients. Generation task performance was also more accurate than controls, reflecting differences in explicit knowledge. However, removal of subjects with generation performance indicative of explicit knowledge increased the random minus sequence mean for controls but brought that for PD patients closer to zero. Therefore, Jackson et al.'s study provides the clearest evidence to-date for an implicit sequence learning deficit in patients with basal ganglia disfunction.

2.18 In summary, considering all the experiments with HD and PD patients together, one can confidently conclude that these patients show impaired sequence learning. It is may be telling that the two studies which most convincingly dismissed any effects of explicit knowledge found no significant learning in patient with basal ganglia disfunction (Jackson et al., 1995; Willingham & Koroshetz, 1993) . The studies in which explicit knowledge appeared to differ between groups (Knopman & Nissen, 1991; Pascual-Leone et al., 1993, Exp 2) or explicit knowledge was not assessed (Ferraro et al., 1993; Pascual-Leone et al., 1993, Exp 1) showed some evidence for learning in PD and HD patients, but less than for controls. Another key difference between these studies is that learning of pairwise associations was not possible in the experiments in which basal ganglia disfunction abolished learning (Jackson et al., 1995; Willingham & Koroshetz, 1993) , but non-sequential learning was possible in the cases where the patients showed some learning of the 10-element N&B sequence (Ferraro et al., 1993; Knopman & Nissen, 1991; Pascual-Leone et al., 1993) . It is also notable that PD patients even had difficulty in using explicit knowledge to guide SRT performance (Pascual-Leone et al., 1993 , Exp 3). This latter finding suggests that the basal ganglia may be critical for the using sequential information to guide performance even in conditions where the basal ganglia is not critical for learning per se.

Neuroimaging Experiments using the SRT Task

2.19 A couple of modern neuroimaging techniques-- Transcranial Magnetic Stimulation (TMS, Pascual-Leon, Grafman, & Hallet, 1994) and Positron Emission Tomography (PET, Grafton, Hazeltine, & Ivry, in press) -- have recently been applied to sequence learning in the SRT task.

2.20 Pascual-Leon et al., (1994) used TMS to relate changes in the size and amplitude of motor cortex output maps to SRT learning. Subjects were given 12 blocks of 120 trials with a 10-element sequence-- presumably the N&B sequence was used because Willingham et al. (1989) was used as a methodological reference. In an critical methodological departure from most SRT experiments, Pascual-Leon's subjects were asked if they noticed a repeating sequence after each block. This procedural change likely induces subjects to look for regularities and become aware of the sequence (Stadler, 1994). During the early blocks of learning the motor cortex maps expanded in size and amplitude, but declined back to baseline levels after more extensive practice. All five subjects were able to report the entire sequence at some point between blocks 6 and 9. Pascual-Leone report that motor-map expansion continued until the subject demonstrated full explicit knowledge. After that point, the motor maps returned to baseline. The motor map increases are interpreted as reflecting a motor cortex contribution to implicit learning whereas the return to baseline reflects a transfer to an explicit state that is presumably controlled by other brain mechanisms. Stadler (1994) noted that Pascual-Leone's RTs were very fast-- well before explicit knowledge had supposedly formed. In fact, the motor maps continued to grow when reaction times were under 100 ms. As previously discussed, such fast RTs are typically seen as indicative of anticipatory responding based on explicit knowledge (Willingham et al., 1989). Therefore, this motor cortex expansion likely continued after subjects had actually acquired explicit knowledge.

2.21 Grafton et al. (in press) recently completed a PET study in which regional cerebral blood flow (rCBF) changes were measured while subjects learned sequences with or without distraction. Grafton et al. used a 6-element sequence with 2 unique and 2 ambiguous pairwise associations (1-3-2-4-2-3 or 1-4-3-2-3-4) which subjects can learn when distracted (Cohen et al., 1990; Curran & Keele, 1993; Frensch, Buchner, & Lin, 1994). Subjects completed a 17-block phase (84 trials per block) while performing a concurrent distraction task (tone-counting), followed by another 17-block phase without distraction. Subjects were given a different sequence in the two phases, with sequence and pseudorandom blocks arranged as 7R-8S-2R within each phase. Behaviorally, subjects showed R-S differences of about 50 ms when distracted and over 150 ms when not distracted. Verbal reports suggested that subjects were predominantly unaware of the sequence when distracted but were predominantly aware in the nondistracted phase. Thus, Grafton et al. interpret rCBF changes during phase 1 as related to implicit learning under distraction, and phase 2 activity as related to explicit learning. Based on a review of the behavioral literature that has suggested a dissociation between implicit and explicit sequence learning, Grafton et al. predicted that distinct brain areas would underlie the two different forms of learning.

2.22 Within each phase PET scans were taken during the 2nd, 3rd, and final random blocks, and during the 1st, 4th, and 7th sequence blocks. Grafton et al. focused on areas

that showed monotonic increases or decreases in rCBF across the three sequence blocks that were scanned. Because activity changes across these blocks could be unrelated to sequence learning (for example, subjects might be learning something related to the distraction task), areas that showed increases or decreases across the 3 random blocks were excluded from the analysis of sequence learning. A number of areas showed rCBF increases across the sequence blocks, but the areas associated with dual-task learning did not overlap those associated with explicit learning.

2.23 Grafton et al. emphasize the changes in contralateral "motor effector areas" (left sensorimotor, left supplementary motor, left parietal, and bilateral putamen) that were associated with implicit learning under distraction. Thus, it is suggested that movement-dedicated brain areas contralateral to the response hand underlie implicit sequence learning when subjects are distracted. This interpretation is consistent with Pascual-Leone et al.'s (1994) TMS study. The replication of motor cortex changes across two experiments with different experimental procedures and imaging techniques lends added credence to the possibility of a motor cortex contribution to implicit sequence learning. Pascual-Leone et al. (1994) could observe changes only in motor cortex because TMS can only be applied to circumscribed areas of the cortical surface. Additional areas observed by Grafton et al.-- the supplementary motor cortex, putamen, and inferior parietal cortex-- may reflect a more extensive network involved in SRT learning. Grafton et al. note that these areas are components of a motor-circuit implicated in voluntary movement control (e.g., Alexander, Crutcher, & DeLong, 1990) .

2.24 During explicit learning, Grafton emphasize right prefrontal and bilateral parietal changes. Right dorsolateral prefrontal cortex and parietal cortex have been implicated as subserving spatial working memory (Goldman-Rakic, 1988; Goldman-Rakic, 1990; Jonides, Smith, Koeppe, Awh, Minoshima, & Mintun, 1993) and/or spatial attention (Corbetta, Miezen, Dobmeyer, Shulman, & Peterson, 1991; Jackson, Marrocco, & Posner, 1994; Mesulam, 1990; Posner & Peterson, 1990). In summary, recent neuroimaging research has lead the search for the neural mechanisms of SRT learning beyond the basal ganglia. In addition to findings of learning-related basal ganglia activity that is consistent with the previously reviewed neuropsychological evidence, these studies have implicated the prefrontal cortex, parietal cortex, and motor cortical areas including primary motor cortex, premotor cortex, and supplementary motor areas.

3. Evidence from other Domains

3.1 The foregoing review has identified certain brain areas that are likely involved in spatial sequence learning. These include the basal ganglia, motor cortical areas (premotor cortex, supplementary motor cortex, and primary motor cortex), prefrontal cortex, and parietal cortex. Conversely, it appears that the diencephalic and medial temporal regions which are damaged in amnesic patients do not play a major role. Next, I will consider evidence from other domains that may lead to more specific hypotheses concerning the particular functions or computations that each of these areas contribute to sequence learning. This endeavor might be approached from two different angles. First, we might consider evidence from other, nominally similar, "skill learning" or "procedural learning"

tasks such as the Tower of Honoi (e.g., Tower of Toronto, Saint-Cyr, Taylor, & Lang, 1988), the pursuit-rotor task (e.g., Heindel, Salmon, Shults, Walicke, & Butters, 1989), adaptation-level tasks with weight judgments (e.g., Heindel, Salmon, & Butters, 1991), or mirror reading (Martone, Butters, Payne, Becker, & Sax, 1984). Often such tasks are lumped together, along with the SRT task, to consider hypotheses such as Mishkin's hypothesis that habit learning depends upon the basal ganglia (Mishkin, Malamut, & Bachevalier, 1984; Mishkin & Petri, 1984; Mishkin & Appenzeller, 1987). Given our insufficient empirical and theoretical understanding of the relation ship between these tasks, this approach runs the risk of mixing apples and oranges. A second approach is to consider research from other domains that suggest more precise functional roles for these candidate brain areas. Working from this perspective, I will review evidence which is suggestive of component processes that may depend on these candidate brain regions and may contribute to sequence learning.

Basal Ganglia

3.2 Researchers investigating the effects of basal ganglia disfunction on implicit learning have suggested a number of possible functions that the basal ganglia may contribute to SRT learning. First, PD and HD may interrupt the processing loop between the caudate and prefrontal cortex (Ferraro et al., 1993; Jackson et al., 1995; Knopman & Nissen, 1991; Pascual-Leone et al., 1993; Willingham & Koroshetz, 1993). Notably, PD patients in Jackson et al.'s (1995) study who showed no signs of frontal pathology were more likely to show sequence learning than those with poor performance on tests indicative of frontal pathology. The possibility of a prefrontal contributions to sequence learning will be considered in more detail later. Second, the basal ganglia may be crucially involved with attentional mechanisms upon which sequence learning may depend (Knopman & Nissen, 1991; Willingham & Koroshetz, 1993). Attention-related problems have been previously described in patients with striatal dysfunction (e.g., Brown & Marsden, 1991), and a number of authors have suggested that attentional mechanisms are critical in sequence learning, though the nature of this attentional contribution is still debated (Cohen et al., 1990; Curran & Keele, 1993; Nissen & Bullemer, 1987; Reed & Johnson, 1994; Stadler, 1995). Finally, some have suggested that the basal ganglia may not be intimately involved with learning per se, but may be crucial for the proper execution of motor programs that are required for sequential knowledge to enhance performance. By this view, sequential learning and memory may be independent of the basal ganglia, but the ability to utilize sequential knowledge to enhance SRT performance may depend on the basal ganglia (Jackson et al., 1995; Knopman & Nissen, 1991; see also Gabrieli, 1994). These alternatives are not mutually exclusive. Depending on your view of how attentional mechanisms contribute to sequence learning, some of these hypotheses would be complimentary. For example, from the view that attentional mechanisms influence the organization of sequence knowledge (Keele & Curran, in press; Keele & Jennings, 1992; Stadler, 1995), this would be consistent with possible prefrontal contributions --mediated by the basal ganglia-- that are outlined below.

3.3 Unfortunately, the existing data do not allow us to differentiate between these alternative functions that the basal ganglia may contribute to sequence learning. More

fine-grained dissociations are sorely needed. Only two studies have manipulated independent variables that might provide some insight to the specific role of the basal ganglia. Pascual-Leone et al. (1993) manipulated sequence length, but this did not differentially effect PD and control subjects. Willingham & Koroshetz (1993) showed that their HD patients could learn new perceptual-motor mappings as well as control subjects despite their impaired sequence learning, but this does not clarify the nature of their sequence learning deficit. Another approach has been the examination of correlations between sequence learning and performance on other cognitive or motor tasks, but none of these correlations have been significant (Ferraro et al., 1993; Knopman & Nissen, 1991; Willingham & Koroshetz, 1993).

3.4 Mishkin's hypothesis that habit learning depends upon the basal ganglia (Mishkin et al., 1984; Mishkin & Petri, 1984; Mishkin & Appenzeller, 1987) is often discussed in relation to the sequence learning research with PD and HD patients. It is important to remember what Mishkin actually meant by a habit-- "It is noncognitive: it is founded not on knowledge or even on memories (in the sense of independent mental entities) but on automatic connections between a stimulus and a response" (Mishkin & Appenzeller, 1987, p. 89) . It is well documented that sequence learning involves more than "automatic connections between and stimulus and a response" (Cleeremans & McClelland, 1991; Cohen et al., 1990; Reed & Johnson, 1994; Stadler, 1993). Mishkin's habit learning system could learn sequences with unique pairwise associations (e.g., 1-3-2-5-4, Cohen et al., 1990), but would not be able to learn sequences in which pairwise associations are ambiguous and higher-order representations are needed.

3.5 Subsequent research has supported the hypothesized striatal contribution to learning of consistent s-r pairings. Two experiments have found a double dissociation between striatal and hippocampal lesions on two versions of an eight arm radial maze task (McDonald & White, 1993; Packard, Hirsh, & White, 1989) . Hippocampal, but not striatal, lesions impaired learning in a win-shift task. Striatal , but not hippocampal, lesions impaired learning in a win-stay task. Win-stay performance is typically thought to merely depend on the acquisition of a simple stimulus-response association that drives the animal to approach a consistently baited arm. Win-shift learning depends on associating each arm of the maze with extramaze stimuli (e.g., learning a "cognitive map", Nadel, 1992) in order to discriminate visited from unvisited arms. A qualitatively similar double dissociation between the effects of hippocampal and striatal lesions was found in a water maze task (Packard & McGaugh, 1992). Rats were trained to escape from a water tank by discriminating between a secure platform that could be mounted for escape and an insecure platform that could not be mounted. In a spatial version of this task, the platforms were consistently in particular quadrants of the tank. In a pattern version, the platforms had consistently different visual patterns. Hippocampal lesions impaired spatial discrimination but not pattern discrimination whereas striatal lesions had the opposite affect. Again, pattern discrimination learning simple involved a simple stimulus response association that directed rats to a particular stimulus whereas rats needed to associate multiple extratank cues to discriminate the safe from unsafe locations.

3.6 If the striatum only contributes to the learning of consistent s-r associations, it alone cannot support sequence learning in studies which have demonstrated learning of non-unique associations. Furthermore-- unlike rats with striatal lesions who could learn to associate multiple stimuli (McDonald & White, 1993; Packard et al., 1989; Packard & McGaugh, 1992)-- we know that the learning of non-unique associations is impaired in patients with PD (Jackson et al., 1995 and HD (Willingham & Koroshetz, 1993). One might posit a model by which all sequence learning ultimately depends upon such s-r associations but the functional stimulus input to the s-r mechanism is different from the nominal stimulus that appears on the computer screen. For example, multiple stimuli might be combined into higher order units such as chunks (Wicklegren, 1979), configural cues (Sutherland & Rudy, 1989), or distributed representati ons that capture stimulus-stimulus regularities (Gluck & Myers, 1993; Myers & Gluck, 1994). These higher order units may become the functional stimulus for striatal s-r learning. Interestingly, Gluck & Myers (1993; Myers & Gluck, 1994) have attributed the learning of these higher-order units to the hippocampus, and they have specified how the hippocampus may provide these higher order representations as input to s-r learning mechanisms in other brain regions such as the cerebellum. Reber and Squire's (1994) research with amnesic patients suggests that learning of second-order associations does not depend on the integrity of the medial temporal lobe and diencephalon. However, a model in which a separate mechanism-- other than medial temporal or diencephalic-- learns higher-order associations that are input to a striatal s-r mechanism would be consistent with the existing SRT learning data, but not entirely consistent with the double dissociations in maze learning (McDonald & White, 1993; Packard et al., 1989; Packard & McGaugh, 1992).

3.7 If the basal ganglia only learns s-r associations, its function is peripheral to and dependent upon other mechanisms that actually learn the sequences because more than s-r associations are typically learned. However, other research suggests that the basal ganglia is more directly involved in sequential processing. One line of research examined stereotyped grooming sequences in rats and found that striatal lesions produced deficits in the coordination of grooming sequences without affecting the ability to implement the component movements (Berridge & Whishaw, 1992). Similarly, striatal neurons were differentially responsive to the same movement depending on whether or not the movement was part of a grooming sequence (Aldridge, Berridge, Herman, & Zimmer, 1993). Ablation of the cerebellum, motor cortex, or entire neocortex does not disrupt the coordination of grooming sequences (Berridge & Whishaw, 1992), so this sequential information is likely represented in the striatum. However, Berridge and Whishaw (1992) note that sequential control may be more cortically dependent in primates, especially for learned rather than instinctual behaviors.

3.8 Electrophysiological studies in lower primates have found that neuronal activity in the basal ganglia is correlated with sequential behavior. Kermadi, Jurquet, Arzi, & Joseph (1993) had monkeys view a sequence of three visuospatial targets then press the targets in the same order after a delay. Many stimulus-responsive caudate neurons were selective, not for particular spatial positions, but for particular positions that were preceded by a

specific target/response (e.g., neurons would fire to 2 in 1-2, but not 3-2). Conversely, response-locked neurons respond to particular responses in a way that depended upon the next response (e.g., neurons would fire to 2 in 2-1, but not 2-3). Therefore the stimulus-locked neurons are sensitive to previous context, and the response-locked neurons are sensitive to future context. Such sensitivity to temporally adjacent events is a requisite property of a sequential learning or control mechanism, but it is notable that only first-order context-effects of this sort were observed.

3.9 In humans, research on PD and HD patients has revealed deficits in sequential-control tasks requiring sequences of arm movements (Agostino, Berardelli, Formica, Accornero, & Manfredi, 1992) or hand postures (Harrington & Haaland, 1991). A couple of studies have been especially useful for suggesting specific functions of the basal ganglia that are relevant to sequence learning. Robertson & Flowers (1990) had subjects memorize two key-press sequences (e.g., 2-4-1-5 & 5-1-4-2). PD patients learned and performed these sequences as accurately as controls, but made more errors when required to spontaneously shift from one sequence to the other. These errors were predominantly intrusions from the other sequence. This deficit was characterized as a difficulty in selecting and maintaining the appropriate motor set.

3.10 Jennings (in press) had subjects memorize two sequences (e.g., t 3D 1-3-2 x 3D 3-1-2) in a cueing paradigm. Subjects were given a cue (x or t) to prepare a response sequence before the actual target sequence (x or t) was displayed for execution. Cues were neutral, valid (75%), or invalid (25%) predictors of the actual target sequence. PD and control subjects showed similar RT costs and benefits of cueing, but it appeared as if the PD patients were only using the cue to prepare the first key-press whereas controls prepared the entire sequence in advance. This interpretation was supported by a second experiment with two sequences differing only on the second element (e.g., x3D1-2-4, t3D1-3-4). Controls showed the cost of preparing the wrong sequence because they had prepared the second keypress in advance; however-- consistent with the idea that PD patients could only prepare the first response-- PD patients showed no costs to invalid cues. A final experiment demonstrated that PD patients failed to show normal sequences length effects on RT which is again consistent with PD patients only preparing a single response.

3.11 These studies illuminate two, possibly related, deficits that may be relevant to SRT learning and performance: maintaining and switching set (Robertson & Flowers, 1990; see also Benecke et al., 1987; Jackson et al., 1994) and the advance preparation of multiple responses (Jennings , in press). If sequences are represented as hierarchically organized chunks (e.g., Keele & Curran, in press; Keele & Jennings, 1992), the ability to smoothly switch between chunks while suppressing intrusion from competing chunks would be crucial. Furthermore, the inability to prepare more than a single response would limit a PD patient's ability to use such chunks to speed RTs. There is one critical respect in which these studies are similar-- both document an inability to USE sequential information in a normal manner in cases where the patients clearly, and explicitly, learned the sequences. By analogy, it is quite possible that the PD and HD patients show "learning" deficits in the SRT task have actually learned "what" the sequence is, but lack

the ability to use this knowledge to facilitate SRT performance. Corroborative evidence comes from the finding that PD patients were somewhat poorer than controls at utilizing explicit sequential knowledge to improve SRT performance (Pascual-Leone et al., 1993).

3.12 Before leaving the discussion basal ganglia, it is important to consider evidence suggesting that behavioral impairments shown by patients with HD or PD (such as seen in the SRT tasks) do not necessarily reflect a deficit that is specific to the basal ganglia. A PET study compared joystick movements in patients with Parkinson's disease to control subjects (Playford, Jenkins, Passingham, Nutt, Frackowiak, & Brooks, 1992). When resting activity was subtracted from either a repetitive movement task or a free selection task, important rCBF difference between PD and control subjects emerged. PD patients showed less activity than controls in the putamen, thalamus, SMA, anterior cingulate, and dorsolateral prefrontal cortex. Putamen, thalamus, and SMA activity were below normal in both the repetitive and free selection tasks, whereas the other deficits were primarily associated with free selection. Activity in primary sensorimotor, lateral premotor, and parietal cortex was normal. Thus, PD patients showed abnormal activity extending beyond the basal ganglia-- throughout key components of the "motor" and "prefrontal" basal ganglia-thalamocortical circuits (Alexander et al., 1990). In light of this finding, evidence that PD patients show abnormal SRT learning does not necessarily implicate the basal ganglia per se.

3.13 A further experiment investigated the relationship between akinesia and rCBF changes during Playford et al.'s (1992) free selection task by examining rCBF changes when PD patients were off versus on medication that relieves akinesia (apomorphine: a dopamine agonist; Jenkins, Fernandez, Playford, Lees, Frackowiak, Passingham et al., 1992). Each subject was tested in three kinetic/medication states: (1) an akinetic state, off medication; (2) akinetic, on; and (3) kinetic, on. Results of the first 2 conditions replicated Playford et al. with little direct effects of apomorphine on rCBF. In condition 3, when sufficient time had passed for apomorphine to relieve akinesia, SMA activity selectively increased. Thus, it was suggested that SMA is crucially involved with the generation of self-initiated movements, and that SMA disfunction underlies akinesia associated with PD.

3.14 These neuroimaging experiments suggest caution in attributing the functional impairments of PD specifically to the basal ganglia. Areas outside the basal ganglia (SMA, thalamus, anterior cingulate, prefrontal cortex) that have shown decreased PET activity when PD patients perform other motor tasks (Jenkins et al., 1992; Playford et al., 1992), have also been implicated in a PET study of SRT learning (Grafton, Hazeltine, & Ivry, in press). Furthermore, Jackson et al . (1995) noted a relationship between prefrontal impairments and SRT learning in their PD patients. Most likely these results suggest that these different areas function as an integrated network that may not be simply divided into functionally independent components (Alexander, DeLong, & Crutcher, 1992; Kalaska & Crammond, 1992).

3.15 In summary, there is good evidence that basal ganglia is involved in both learning and sequential control. Available evidence suggests that the striatum is necessary for

learning certain s-r associations, but it may not be required when more complex representations are needed (McDonald & White, 1993; Packard et al., 1989; Packard & McGaugh, 1992). Considerable evidence suggests that more than pairwise associations are learned in the SRT paradigm by normal subjects (Cleeremans & McClelland, 1991; Cohen et al., 1990; Reed & Johnson, 1994; Stadler, 1993), amnesic patients (Reber & Squire, 1994), Parkinson's patients (Jackson et al., 1995), and Huntington's patients (Willingham & Koroshetz, 1993); so the basal ganglia alone is unlikely to support SRT learning. Other evidence suggests a more central role of the basal ganglia in sequential control. Various theories have been advanced to specify the basal ganglia's function in sequential control. A number of researchers have endorsed variants of the idea that the basal ganglia performs a set switching or selection function: switching from sensory-guided to externally-guided control (Aldridge et al., 1993); or selection and maintenance of behaviorally relevant cortical signals (Jackson et al., 1994; Robertson and Flowers, 1990). Such a selection and maintenance function is clearly required if sequences are learned through chunking or hierarchic representation (Keele and Curran, in press; Keele and Jennings, 1992). Current work in Keele's laboratory (personal communication) is exploring the hypothesis that basal ganglia damage impairs, not the ability to learn and perform sequences, but the fluent transition between one portion of a sequence and the next as the representation of one chunk must be suppressed as the next is activated.

Primary (M1), Premotor (PMC), and Supplementary (SMA) Motor Cortex:

Motor Cortex Activity and Effector Independence

3.16 The two extant neuroimaging studies of SRT learning (Grafton et al., in press; Pascual-Leon et al., 1994) have reported learning related changes in motor cortex. As noted by Stadler (1994), these finding appear to contradict research showing that SRT learning can transfer across effectors (e.g., Keele et al., 1995; Stadler, 1989), and that learning can occur when conditions are observational rather than response-driven (Howard, Mutter, & Howard, 1992; Mayr, 1994). A review of motor cortex function makes it apparent that learning-dependent changes in motor cortex activity would be expected even if sequences were represented in a effector-independent form.

3.17 First, it should be emphasized that muscle-independent response selection exists throughout cortical and subcortical motor areas including M1 (Alexander & Crutcher, 1990a, 1990b; Crutcher & Alexander, 1990). Nonetheless, even if the motor cortex activity was completely effector-dependent, learning-related activity changes in these areas may merely reflect a secondary influence of sequential knowledge stored in other brain areas rather than a direct reflection of the learned representation itself. In this context, evidence will be discussed which shows how motor cortex activity (M1, PMC , SMA) is influenced by advanced information about an ensuing response. The basic hypothesis is that activity in these motor cortex areas reflects both movement preparation and execution, therefore cortical activity will be increased when sequential knowledge is available (Sequence 3D execution + preparation) compared to a pseudorandom condition (R) without sequential knowledge (R 3D execution).

3.18 Georgopoulos (1994) reviewed studies from his lab that have explored the directionally selective coding properties of neuronal populations in primary motor cortex. Primary motor cortex neurons not only code the direction of movement during performance, but "plan" the direction of an impending movement 160-180 ms before movement initiation (Georgopoulos, Kalaska, Caminiti, & Massey, 1984). In other experiments monkeys were given a visual cue that specified the direction of an upcoming response, but had to wait for a delay before executing the response. The M1 population response "held" a reliable specification of the direction during the delay. This was true both when the visual cue remained visible as well as when it disappeared and the monkey remembered the response location (Smyrins, Taira, Ashe, & Georgopoulos, 1994). Interestingly, the directional signal was stronger in the memory than nonmemory condition. It is quite likely that learning-related activity in primary motor cortex in studies of sequence learning is related to these preparatory "planning" and "holding" functions.

3.19 Similar preparatory activity has been recorded in neurons throughout all areas of the "cortical/basal ganglionic motor circuit" (Alexander et al., 1992). Movement-selective preparatory neuronal firing rates in PMC have been directly correlated with RT changes arising from directional precueing (Riehle & Requin, 1989) and from learning of conditional associations (Mitz, Godschalk, & Wise, 1991). Importantly, PMC neurons were only response-selective when the response was guided by learned s-r associations, not when the same response was accidentally made to the same stimulus before learning (Mitz et al., 1991). Alexander & Crutcher (1990b) discovered a large percentage of M1, SMA, and putamen neurons that were selective for the direction of the forthcoming movement during a preparatory phase.

3.20 In summary, all of the major motor cortical areas show activity that is related to response preparation. This preparatory activity would be more prominent in sequential than nonsequential conditions of previous neuroimaging studies of sequence learning (Grafton et al., in press; Pascual-Leone et al., 1994) even if these areas did not contribute to learning per se.

Functional Differences between Motor Areas

3.21 In their PET study of sequence learning Grafton et al. (in press) found that PMC activity was observed during explicit SRT learning, but SMA activity was associated with implicit learning. The finding that SMA activity related to implicit learning but PMC activity related to explicit learning seems somewhat paradoxical when other relevant research is considered. Both SMA and PMC are hypothesized to be involved in movement selection. However, it has been hypothesized that the PMC makes a greater contribution when movements are directed by external cues, whereas the SMA makes a greater contribution when external cues are unavailable (Goldberg , 1985; Passingham, 1993).

3.22 Deiber, Passingham, Colebatch, Friston, Nixon, & Frackowiak (1991) report a PET

study in which subjects moved a joystick upon hearing a tone, but the basis for selecting the movement was varied. In the fixed condition, the same movement was repeated throughout the scan. In the selection conditions movements were: (1) freely selected by subjects; (2) performed in a pre-memorized sequence; or (3) specified by tones that were arbitrarily paired with different movements. Compared to the fixed condition, all selection tasks increased activation in the parietal cortex. The sequential and free-selection tasks both activated the lateral premotor areas. However, the supplementary motor cortex, anterior cingulate, and prefrontal areas only showed increases associated with free-selection but not with the pre-learned sequence. Thus, self-initiated motor control was associated with parietal, prefrontal, cingulate, premotor, and supplementary motor cortex activity, whereas memory-guided movement was only associated with parietal and premotor activity. Similarly, Mushiake, Inase, & Tanji (1991) recorded from M1, SMA, and PMC while monkeys performed visually-guided (VG) versus memory-guided (MG) sequential movements. In M1 preparatory firing was equivalent in the VG and MG conditions. SMA firing was more prevalent in the MG condition, but PMC activity was more prevalent in the VG conditions. Mushiake et al. stress the fact that this separation between memory-triggered activity in SMA and visually-triggered activity in PMC is only relative, and does not support a strict functional dichotomy between these two areas (see also (Tanji, 1994).

3.23 A subtype of neurons recorded by Mushiake et al. (1991) are of particular interest. During memory guided performance, "sequence specific" neurons showed firing increases that were specifically related to the initiation of a particular of movement sequence . For example, firing would increase prior to the first press of 1-3-2, but not 1-2-3 or 1-4-2. These sequence specific neurons were more prevalent in SMA than PMC, and seem very similar to response-locked neurons in the basal ganglia that were also sensitive to future actions (Kermadi et al., 1993).

3.24 Studies of neuropsychological patients with SMA or PMC lesions have also provided evidence relevant to movement selection and sequential control. Gaymard, Pierrot-Deseilligny, and Rivand (1990) tested two patients with left SMA lesions on visually-guided saccades, antisaccades, memory-guided saccades, and memory-guided saccade sequences. Patients performed similarly to controls for visually-guided saccades and antisaccades, one patient was impaired on memory-guided saccades, and both were impaired on saccade sequences. Both were less accurate on 3-saccade than 2-saccade sequences, and errors of sequential order were most common. Thus, Gaymond et al. argued that spatial memory was preserved after SMA lesions, but memory for sequential order was impaired. Halsband and Freund (1990) found that patients with PMC lesions could learn to associate visual, auditory, or tactile stimuli with visuospatial locations, but were impaired in learning to associate these same stimuli with prelearned arm movements. The patients were able to discriminate between the sensory stimuli and able to perform the required movements from memory, but had great difficult in the selection of the appropriate movement from sensory cues. Taken together these experiments are consistent with the notion that PMC is involved in the selection of responses that are associated with exogenous cues (Halsband & Freund, 1990), but the SMA is involved in response selection in the absence of these cues (Gaymard et al., 1990).

3.25 In summary, the SMA and PMC seem to be involved in response selection with PMC being more related to the selection of responses based on exogenous cues and the SMA being more related to the selection of responses based on endogenous information. Grafton et al.'s results seem to run against this relative functional specialization. Explicit learning (PMC in Grafton et al.) appears to elicit relatively more internally-guided responses whereas implicit learning (SMA in Grafton et al.) is more visually guided as evidenced by the fact that explicit knowledge leads to pre-stimulus, anticipatory responding more so than implicit learning (Willingham et al., 1989). Though the distinct functional contributions of the SMA versus the PMC to SRT learning remain unclear, the research reviewed above clearly suggests that these areas share a role in response selection based on external or internal information. These areas might contribute to sequence learning by serving as an interface between response-independent sequential representations and task-specific responses. That is, the SMA and PMC may draw on learned sequential representations to select upcoming responses.

Dorsolateral Prefrontal Cortex (DLPFC)

3.26 Neurophysiological studies of prefrontal function have often used spatial delayed response tasks in which monkeys are given a cue to hold in memory across a delay. After the delay the monkey chooses the cued location with a button press, reaching movement, or saccade. Prefrontal neurons often show sustained firing during the delay period that is selective for particular stimulus locations or responses. Convergent evidence has come from delayed response deficits following DLPFC lesions. Goldman-Rakic (Funahashi, Bruce, & Goldman-Rakic, 1989; Goldman-Rakic, 1987; Goldman-Rakic, 1988; Goldman-Rakic, 1990; Wilson, Scalaidhe, & Goldman-Rakic, 1993) has interpreted these findings as indicative of a contribution of DLPFC to spatial working memory (e.g., Baddeley, 1986). Passingham (1993) concludes that the DLPFC is involved in generating actions that are specified by cues in memory or by arbitrary decisions.

3.27 Fuster (1990; 1993; 1994) -- taking the middle-ground between Goldman-Rakic's focus on working memory and Passingham's focus on action generation-- argues that the prefrontal cortex holds the super-ordinate position in a perception-action hierarchy whose lower branches include lower level sensory, association, and motor mechanisms. Fuster emphasizes evidence for two complimentary cell types in the prefrontal cortex which seem to (1) maintain memory for a cue and (2) plan or predict a forthcoming action. It is clear that any of these characterizations of prefrontal function could play a role in SRT learning, but some research has more specifically documented sequential aspects of prefrontal function.

3.28 A number of neuropsychological investigations of the effects of frontal lobe lesions on human memory have suggested that memory for temporal order is disproportionately disrupted compared to recognition memory (Kesner, Hopkins, & Fineman, 1994; Milner, Corsi, & Leonard, 1991; Milner, Petrides, & Smith, 1985; Shimamura, Janowski, & Squire, 1990). When memory for visuospatial locations was specifically examined, lesions of right, but not left, prefrontal cortex impair memory for the sequential order of

locations but not recognition memory for those locations (Kesner et al., 1994). This is consistent with Grafton et al.'s finding of right, prefrontal activation during explicit sequence learning. Sequencing-related deficits have also been well documented when patients with frontal lobe lesions are asked to learn and perform sequences of hand gestures (Canavan, Passingham, Marsden, Quinn, Wyke, & Polkey, 1989; Jason, 1985, 1986). To-date there have been no studies of the effects of frontal lobe lesions on implicit sequence learning tasks, but as previously mentioned, it appears that Parkinson's patients who show neuropsychological symptoms of frontal pathology are especially poor SRT learners compared to patients without frontal symptoms (Jackson et al., 1995).

3.29 Research on nonhuman primates has also suggested that prefrontal cortex contributes to sequential learning. Petrides (1991) examined the effects of mid-dorsolateral (bilateral areas 46/9, M-DLPFC) versus posterior dorsolateral (bilateral areas 8/6, P-DLPFC) prefrontal lesions on recency discrimination in monkeys. Monkeys were presented with a series of 3 to 5 objects, one at a time. Upon presentation of each object, the monkey displaced that object for a reward. At the end of the series, the monkey was shown two of the objects from the series and was rewarded for choosing the object that had occurred earlier in the series. M-DLPFC monkeys were drastically impaired on this task, but P-DLPFC monkeys performed like non-lesioned controls. All groups showed normal recognition memory. This pattern is analogous to results previously described in humans with prefrontal lesions, especially those of Kesner et al. (1994) who used a similar force-choice test with short lists of spatial stimuli. Petrides (1991) notes that the same M-DLPFC monkeys normally learned such sequences when a single fixed sequence was repeatedly presented. Thus, M-DLPFC cortex seems especially crucial for learning sequences which change from trial to trial. A similar susceptibility to inter-trial interference is often noted in humans with prefrontal lesion and has inspired the hypothesis that prefrontal cortex acts to inhibit extraneous information (Shimamura, 1994).

3.30 In summary, the prefrontal cortex has been associated with a number of functions that could contribute to sequence learning : working memory, action planning, memory for temporal order, and inhibition of extraneous information. Keele and Jennings (1992) suggest that high-level plans operate as super-ordinate nodes in the hierarchic representation of SRT sequences. Keele and Jennings' (1992) proposal also provides a mechanism by which extraneous information is inhibited. In their model, the ambiguity of first-order association is overcome through hierarchic representation. By representing a sequence such as 1-3-2-1-2-3 as a hierarchy of two chunks (1-3-2 and 1-2-3) a prefrontal planning mechanism would also serve to inhibit extraneous information. That is, when the prefrontal plan specifies that first chunk, the inconsistent information from the second chunk is inhibited from interfering with sequential behavior.

3.31 It is important to remember that direct evidence for a prefrontal contribution to SRT learning has only been obtained during the explicit lear ning condition of Grafton et al.'s (in press) PET study. Conversely, the basal ganglia (bilateral putamen) was only active during implicit learning. The previous discussions of possible prefrontal and basal ganglia contributions to sequence learning have each emphasized possible roles in

hierarchic representation and/or hierarchic control of action. A speculation that arises from these considerations is that the basal ganglia and prefrontal contribute similar functions to implicit and explicit sequence learning respectively. The basal ganglia contributes to implicit sequence learning through maintaining and switching between different sequence chunks. The basal ganglia might accomplish this function in a relatively reflexive way that depends upon stimulus input (and therefore primes responses rather than anticipating). The prefrontal cortex may play a similar role in explicit sequence learning, by maintaining high-level plans that draw on learned representations to guide behavior. In addition, the prefrontal cortex can use this information to guide behavior in the absence of stimulus input, and therefore is able to actively anticipate the next response in a learned sequence.

Parietal Cortex

3.32 Parietal cortex has been implicated in the visuospatial perception (Felleman & Van Essen, 1991; Ungerleider & Mishkin, 1982) and attention (Corbetta, Miezin, Shulman, & Petersen, 1993; Mesulam, 1990; Posner & Peterson, 1990). Furthermore, through its interaction with previously discussed areas such as prefrontal cortex, premotor cortex, supplementary motor areas, and the basal ganglia, parietal cortex is thought to contribute to the control of action that is guided by visuospatial information (Fuster, 1993; Goldman-Rakic, 1990; Goodale, 1993; Passingham, 1993). The only direct evidence for a parietal contribution to SRT learning comes from the PET study of Grafton et al. (in press). Parietal activity was associated with both implicit learning under distraction and explicit learning without distraction. However, the possibility of parietal involvement has been more widely hypothesized because of the spatial nature of the task.

3.33 Mayr (1994) suggests that parietal cortex may be involved in the learning of visuospatial sequences via the mechanisms of attentional orienting (see also Posner & Rothbart, 1991). Mayr's subjects pressed keys that arbitrarily corresponded to the identity of geometric shapes. The shapes appeared in one of four different locations, but location was irrelevant to response selection. Unknown to the subjects, the geometric shapes-- and hence the order of responses-- occurred in one particular sequential order whereas the locations of the shapes occurred in a different and uncorrelated sequence. By occasionally reverting to random order either in shapes or in locations, Mayr was able to show that subjects had acquired sequential knowledge not only of the upcoming shape (or response) but also of its locations, despite the fact that position was non-determining of response. Similar results occurred both for learning in a nondistracted situation in which several subjects became aware of the sequences and in a tone-distracted study. Most importantly, these results show that learning of the spatial positions occurred when they were dissociated from responses, so the sequential representation was stimulus-bound, but response independent. Mayr suggests that the sequential advantage may reflect learning by the parietal mechanisms of spatial attention and orienting. That is, reaction time may increase when the attentional system has acquired knowledge that allows in to orient to stimuli in advance. The actual role of eye movements has not been systematically explored in SRT learning, but Mayr's ideas may be generalized by the suggestion that a basic visuospatial representation of sequential knowledge in parietal

cortex can guide multiple response systems including the eyes, fingers, voice, etc. (e.g., Keele & Curran, in press).

3.34 The distinction between parietally-based perceptual mechanisms and frontal control mechanisms is supported by studies of ideomotor apraxia in which movement is intact and fluent, but inaccurate (Gonzalez & Heilman, 1985; Heilman, Rothi, & Valenstein, 1982). These patients are impaired at making gestures such as a salute. Heilman and colleagues found such apraxic syndromes to occur in subtly different forms following lesions either of posterior parietal cortex or premotor cortex. Patients were asked to produced gestures or to observe pairs of gestures-- one correctly performed and one poorly performed-- and indicate the correct gesture. Patients with frontal damage showed accurate gesture recognition despite their production problems. Patients with parietal damage performed poorly on both recognition and production. This dissociation suggests that perceptual representations of gestures-- which are examples of movement sequences-- is parietally-based, but frontal mechanisms are necessary for sequence production. Similarly, parietal cortex may be responsible for a kind of stimulus-based sequence learning, like that observed by Mayr (1994), while PMC and/or SMA use this information to prepare the appropriate responses.

3.35 The distinction between perceptually-based parietal mechanisms and response-based motor systems may not be entirely clear cut. Recent theories of parietal function emphasize its role in motor planning (Anderson, 1994) and the control of action (Goodale, 1993). For instance, Anderson and colleagues have studied the activity of inferior parietal neurons during the delay period of memory-guided saccade tasks. These studies have suggested that delay-period firing is sensitive to a neurons motor field rather than its stimulus receptive field (Gnat & Anderson, 1988). Furthermore, this response-related activity has been observed in some neurons for both visual and auditory stimuli (Bracewell, Barash, & Andersen, 1991). Thus, a parietal contribution to sequence learning is not necessarily indicative of a purely visuospatial representation. However, the well documented response-independence of SRT learning (Cohen et al., 1990; Howard et al., 1992; Keele et al., 1995 Mayr, 1994; Stadler, 1989) suggests a primarily perceptually-based representation that underlies visuospatial SRT learning.

3.36 In summary, the parietal lobe contributes to visuospatial perception, attention, and memory. Parietal mechanisms may contribute to sequence learning through the mechanisms that control attentional selection of spatial locations. The parietal lobe may also provide a basic visuospatial representation of sequence information that is tapped by frontal mechanisms to influence behavior.

4. Summary and Conclusions

4.1 Neuropsychological research suggests that implicit sequence learning in the SRT task is spared in patients with organic amnesia, so implicit SRT learning does not appear to depend on the medial temporal and diencephalic brain regions that are critical for explicit memory. Conversely, patients with Huntington's or Parkinson's diseases have consistently shown SRT impairments, so the basal ganglia seem to be critically involved in SRT

learning. Recent neuroimaging research has also documented basal ganglia activity in SRT learning, as well as activity in motor cortical areas (M1, PMC , SMA), prefrontal, and parietal cortex. Unfortunately the functional contribution of these areas to sequence learning remains unclear. Research from other domains suggests component functions that are likely related to sequence learning.

4.2 I have suggested that implicit SRT learning results in representations that are not entirely response-dependent. Given the typically spatial nature of the SRT task, these representations are likely to draw on parietal mechanisms of visuospatial perception and attention. By analogy sequences presented in other modalities would be represented in other cortical areas (e.g., auditory cortex for tonal sequences; for further discussion of this point see Keele and Curran, in press).

4.3 I have further argued that motor cortical areas draw on these learned representations in order to select and prepare the appropriate responses in advance. Supplementary motor areas (SMA) and premotor cortex (PMC) may use learned information (possibly represented in parietal cortex) as well as available stimulus information to specify the location of the ensuing response. Primary motor cortex (M1) may use this information to prepare the particular effectors that will execute the response.

4.4 If sequences are hierarchically represented in different chunks, the basal ganglia may allow the smooth selection among sequence chunks. Both the basal ganglia and prefrontal cortex may act at the interface between parietal sequence representations and the specification of motor responses. These mechanisms could play similar roles in hierarchically controlling the selection of appropriate sequence chunks at different points within the sequence. The prefrontal cortex may provide a more powerful form of hierarchic control over motor cortical areas that gives rise to anticipatory responding, whereas the basal ganglia may only prime appropriate responses. These ideas are highly speculative, but hopefully they can inspire future research.

Acknowledgments

Many of the ideas expressed in this paper have been inspired by discussions with Steve Keele, who has been instrumental in shaping my views about sequence learning. I would also like to thank Georgina Jackson, Steve Jackson, Peggy Jennings, Dan Willingham, and an anonymous reviewer for helpful comments on previous versions of this paper.

References

Agostino, R., Berardelli, A., Formica, A., Accornero, N., & Manfredi, M. (1992). Sequential arm movements in patients with Parkinson's disease, Huntington's disease and dystonia. *Brain, 115,* 1481-1495.

Albert, M. S., & Moss, M. B. (1992). The assessment of memory disorders in patients

with Alzheimer's disease. In L. R. Squire & N. Butters (Eds.), *Neuropsychology of memory*. (pp. 211-219). New York: The Guilford Press.

Aldridge, J. W., Berridge, K. C., Herman, M., & Zimmer, L. (1993). Neuronal coding of serial order: Syntax of grooming in the neostriatum. *Psychological Science, 4*, 391-395.

Alexander, G. E., & Crutcher, M. D. (1990a). Neuronal representations of the target (goal) of visually guided arm movements in three motor areas of the monkey. *Journal of Neurophysiology, 64*, 164-178.

Alexander, G. E., & Crutcher, M. D. (1990b). Preparation for movement: Neuronal representations of intended direction in three motor areas of the monkey. *Journal of Neurophysiology, 64*, 133-150.

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia thalamo-cortical circuits: Parallel substrates for motor control, oculomotor, "prefrontal" and "limbic" functions. *Progress in Brain Research, 85*, 119-146.

Alexander, G. E., DeLong, M. R., & Crutcher, M. D. (1992). Do cortical and basal ganglionic motor areas use "motor programs" to control movement? *Behavioral and Brain Sciences, 15*, 656-.

Anderson, R. A. (1994). Coordinate transformations and motor planning in posterior parietal cortex. In M. S. Gazzaniga (Eds.), *The cognitive neurosciences.* (pp. 519-532). Cambridge: MIT Press.

Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R., & Van Hoesen, G. W. (1991). The topographical and neuroanatomic distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cerebral Cortex, 1*, 103-116.

Baddeley, A. (1986). *Working Memory*. Oxford: Claredon Press.

Benecke, R., Rothwell, J. C., Dick, J. P. R., Day, B. L., & Marsden, C. D. (1987).

Disturbance of sequential movements in patients with Parkinson's disease. *Bran, 110*, 361-379.

Berridge, K. C., & Whishaw, I. Q. (1992). Cortex, striatum, and cerebellum: Control of serial order in a grooming sequence. *Experimental Brain Research, 90,* 275-290.

Bracewell, M., Barash, S., P., M., & Andersen, R. A. (1991). Neurons in the macaque lateral intraparietal cortex (LIP) appear to encode the next intended saccade. *Neuroscience Abstracts, 17,* 1282.

Brown, R. G., & Marsden, C. D. (1991). Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. *Brain, 114,* 215-231.

Canavan, A. G. M., Passingham, R. E., Marsden, C. D., Quinn, N., Wyke, M., & Polkey, C. E. (1989). Sequencing ability in Parkinsonians, patients with frontal lobe lesions and patients who have undergone unilateral temporal lobectomies. *Neuropsychologia, 27,* 787-798.

Chapman, L. J., Chapman, J. P., Curran, T., & Miller, M. B. (1994). Do children and the elderly show heightened semantic priming? How to answer the question. *Developmental Review, 14,* 159-185.

Cleeremans, A. (1993a). Attention and awareness in sequence learning. In *Proceedings of the 15th Annual Conference of the Cognitive Science Society.* Hillsdale, NJ: Erlbaum.

Cleeremans, A. (1993b). *Mechanisms of implicit learning: Connectionist models of sequence processing.* Cambridge, MA:: MIT Press.

Cleeremans, A., & McClelland, J. L. (1991). Learning the structure of event sequences. *Journal of Experimental Psychology: General, 120(3),* 235-253.

Cohen, A., & Curran, T. (1993). On tasks, knowledge, correlations, and dissociations: Comment on Perruchet and Amorim. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 19,* 1431-1437.

Cohen, A., Ivry, R. I., & Keele, S. W. (1990). Attention and structure in sequence learning. *Journal of Experimental Psychology: Learning, Memory, and, Cognition, 16,* 17-30.

Cohen, N. J., & Eichenbaum, H. (1993). *Memory, amnesia, and the hippocampal system.* Cambridge: MIT Press.

Corbetta, M., Miezen, F. M., Dobmeyer, S., Shulman, G. L., & Peterson, S. E. (1991). Selective and divided attention during visual discriminations of shape, color, and speed: Functional anatomy by positron emission tomography. *Journal of Neuroscience, 11*, 2383-2402.

Corbetta, M., Miezin, F. M., Shulman, G. L., & Petersen, S. E. (1993). A PET study of visuospatial attention. *Journal of Neuroscience, 13*, 1202-1226.

Crutcher, M. D., & Alexander, G. E. (1990). Movement-related neuronal activity selectively coding either direction or muscle pattern in three motor areas of the monkey. *Journal of Neurophysiology, 64,* 151-163.

Curran, T., & Keele, S. W. (1993). Attentional and nonattentional forms of sequence learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 19*, 189-202.

Deiber, M.-P., Passingham, R. E., Colebatch, J. G., Friston, K. J., Nixon, P. D., & Frackowiak, R. S. J. (1991). Cortical areas and the selection of movement: A study with positron emission tomography. *Experimental Brain Research, 84*, 393-402.

Eichenbaum, H., Otto, T., & Cohen, N. J. (1994). Two functional components of the hippocampal memory system. *Behavioral and Brain Sciences, 17,* 449-518.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex, 1*, 1-47.

Ferraro, F. R., Balota, D. A., & Connor, L. T. (1993). Implicit memory and the formation of new associations in nondemented Parkinson's disease individuals and individuals with senile dementia of the Alzheimer type: A serial reaction time (SRT) investigation. *Brain and Cognition, 21,* 163-180.

Frensch, P. A., Buchner, A., & Lin, J. (1994). Implicit learning of unique and ambiguous serial transactions in the presence and absence of a distractor task. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20,* 567-584.

Frensch, P. A., & Miner, C. S. (1994). Effects of presentation rate and individual differences in short-term memory capacity on an indirect measure of serial learning. *Memory and Cognition,* 95-110.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology, 61*, 331-349.

Fuster, J. M. (1990). Behavioral electrophysiology of the prefrontal cortex of the primate. In H. B. M. Uylings, C. G. Van Eden, J. P. C. De Bruin, M. A. Corner, & M. G. P. Feenstra (Eds.), *Progress in Brain Research* (pp. 313-324). Amsterdam: Elsevier.

Fuster, J. M. (1993). Frontal lobes. Current Opinion in Neurobiology, 3, 160-165. Fuster, J. M. (1994). *Memory in the cerebral cortex: An empirical approach to neural networks in the human and nonhuman primate.* Cambridge: MIT Press.

Gabrieli, J. (1994). Contributions of the basal ganglia to skill learning and working memory in humans. In J. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Information processing in the basal ganglia.* (pp. 277-294). Cambridge, MA: MIT Press.

Gaymard, B., Pierrot-Deseilligny, C., & Rivand, S. (1990). Impairment of sequences of memory-guided saccades after supplementary motor area lesions. *Annals of Neurology, 28,* 622-626.

Georgopoulos, A. P. (1994). Motor cortex and cognitive processing. In M. S. Gazzaniga (Eds.), *The cognitive neurosciences* (pp. 507-517). Cambridge: MIT Press.

Georgopoulos, A. P., Kalaska, J. F., Caminiti, R., & Massey, J. T. (1984). The representation of movement direction in the motor cortex. In G. M. Edelman, W. M. Cowan, & W. E. Gall (Eds.), *Dynamic aspects of neocortical function* (pp. 5-524). New York: Wiley.

Gluck, M. A., & Myers, C. E. (1993). Hippocampal mediation of stimulus representation: A computational theory. *Hippocampus, 3,* 491-516.

Gnat, J. W., & Anderson, R. A. (1988). Memory related motor planning activity in posterior parietal cortex of macaque. *Experimental Brain Research, 70,* 216-220.

Goldberg, G. (1985). Supplementary motor area structure and function: Review and hypotheses. *Behavioral and Brain Sciences, 8,* 567-616.

Goldman-Rakic, P. S. (Ed.). (1987). *Circuitry of primate prefrontal cortex and regulation of behavior by representational memory.* American Psychological Society.

Goldman-Rakic, P. S. (1988). Topography of cognition: Parallel distributed networks in primate association cortex. *Annual Review of Neuroscience, 11,* 137-156.

Goldman-Rakic, P. S. (1990). Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. In H. B. M. Uylings, C. G. Van Eden, J. P. C. De Bruin, M. A. Corner, & M. G. P. Feenstra (Eds.), *Progress in Brain Research* (pp. 325-336). Amsterdam: Elsevier.

Gonzalez, L. J., & Heilman, K. M. (1985). Ideomotor apraxia: Gestural discrimination, comprehension and memory. In E. A. Roy (Eds.), *Neuropsychological studies of apraxia* (pp. 65-74). New York:: North Holland Publishers.

Goodale, M. A. (1993). Visual pathways supporting perception and action in the primate cerebral cortex. *Current Opinion in Neurobiology, 3,* 578-585.

Gordon, P. C., & Meyer, D. E. (1987). Hierarchic representation of spoken syllable order. In A. Allport, D. MacKay, W. Prinz, & E. Scheerer (Eds.), *Language perception and production.* (pp. 445-462). Orlando: Academic Press.

Grafman, J., Weingartner, H., Newhouse, P. A., Thompson, K., Lalonde, F., Litvan, I., Molchan, S., & Sunderland, T. (1990). Implicit learning in patients with Alzheimer's disease. *Pharmacopsychiatry, 23,* 94-1.

Grafton, S. T., Hazeltine, E., & Ivry, R. (in press). Functional mapping of sequence learning in normal humans. *Journal of Cognitive Neuroscience.* Halsband, U., & Freund, H.-J. (1990). Premotor cortex and conditional motor learning in man. *Brain, 113,* 207-222.

Harrington, D. L., & Haaland, K. Y. (1991). Sequencing in Parkinson's disease. *Brain, 114,* 99-115.

Hasher, L., & Zacks, R. T. (1984). Automatic processing of fundamental information: The case of frequency of occurrence. *American Psychologist, 39,* 1372-1388.

Heilman, K. M., Rothi, L. J., & Valenstein, E. (1982). Two forms of ideomotor apraxia. *Neurology, 32,* 342-346.

Heindel, W. C., Salmon, D. P., & Butters, N. (1991). The biasing of weight judgments in Alzheimer's and Huntington's disease: A priming or programming phenomenon? *Journal of Clinical and Experimental Neuropsychology, 13,* 189-203.

Heindel, W. C., Salmon, D. P., Shults, C. W., Walicke, P. A., & Butters, N. (1989). Neuropsychological evidence for multiple implicit memory systems: A comparison of Alzheimer's, Huntington's, and Parkinson's Disease. *Journal of Neuroscience, 9,* 582-587.

Howard, J. H., Mutter, S. A., & Howard, D. V. (1992). Serial pattern learning by event observation. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18,* 1029-1039.

Huppert, F. A. (1991). Age-related changes in memory: learning and remembering new information. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology* (pp. 123-147). Elsevier Science Publishers.

Ivry, R. I., & Keele, S. W. (1989). Timing functions of the cerebellum. *Journal of Cognitive Neuroscience, 1,* 134-150.

Jackson, G.M., & Jackson, S.R. (1992). *Sequence structure and sequential learning: The evidence from aging reconsidered.* (Technical Report No. 92-9). Institute of Cognitive and Decision Sciences, University of Oregon.

Jackson, G. M., Jackson, S. R., Harrison, J., Henderson, L., & Kennard, C. (1995). Serial reaction time learning and Parkinson's disease: Evidence for a procedural learning deficit. *Neuropsychologia, 33,* 577-593.

Jackson, S. R., Marrocco, R., & Posner, M. I. (1994). Network of anatomical areas controlling visuospatial attention. *Neural Networks, 7,* 925-944.

Jarrard, L. E., & Davidson, T. L. (1991). On the hippocampus and learned conditional responding: Effects of aspiration versus ibotentate lesions. *Hippocampus, 1,* 107-117.

Jason, G. W. (1985). Manual sequence learning after focal cortical lesions.

Neuropsychologia, 23, 483-496. Jason, G. W. (1986). Performance of manual copying tasks after focal cortical lesions. *Neuropsychologia, 24,* 181-191.

Jenkins, I. H., Fernandez, W., Playford, E. D., Lees, A. J., Frackowiak, R. S. J., Passingham, R. E., & Brooks, D. J. (1992). Impaired activation of the supplementary motor are in Parkinson's disease is reversed when akinesia is treated with apomorphine. *Annals of Neurology, 32,* 749-757.

Jennings, P. J. (in press). Evidence of incomplete motor programming in Parkinson's disease. *Journal of Motor Behavior.* Jensen, A. R., & Rohwer, W. D. (1965). What is learned in serial learning? *Journal of Verbal Learning and Verbal Behavior, 4,* 62-75.

Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S., & Mintun, M. A. (1993). Spatial working memory in humans as revealed by PET. *Nature, 363,* 623-625.

Kalaska, J. F., & Crammond, D. J. (1992). Cerebral cortical mechanisms of reaching movements. *Science, 255,* 1517-1523.

Keele, S. W., & Curran, T. (in press). On the modularity of sequence learning systems in humans. In E. Covey (Eds.), *Neural representation of temporal patterns.* Plenum. Keele, S. W., &

Ivry, R. (1990). Does the cerebellum provide a common computation for diverse tasks: A timing hypothesis. In A. D. (Ed.) (Eds.), *The Development and Neural Bases of Higher Cognitive Function.* Annals of the NY Academy Sciences

Keele, S. W., Jennings, P., Jones, S., Caulton, D., & Cohen, A. (1995). On the modularity of sequence representation. *Journal of Motor Behavior, 27,* 17-30.

Keele, S. W., & Jennings, P. J. (1992). Attention in the representation of sequence: *Experiment and theory. Human Movement Studies, 11,* 125-138.

Kermadi, I., Jurquet, Y., Arzi, M., & Joseph, J. P. (1993). Neural activity in the caudate nucleus of monkeys during spatial sequencing. *Experimental Brain Research, 94,* 352-356.

Kesner, R. P., Hopkins, R. O., & Fineman, B. (1994). Item and order dissociation in humans with prefrontal cortex damage. *Neuropsychologia, 32,* 881-891.

Knopman, D. (1991a). Long-term retention of implicitly acquired learning in patients with Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology, 13,* 880-894.

Knopman, D. (1991b). Unaware learning versus preserved learning in pharmacologic amnesia: Similarities and differences. *Journal of Experimental Psychology: Learning, Memory, and Cognition., 17(5),* 17-1029.

Knopman, D., & Nissen, M. J. (1991). Procedural learning is impaired in Huntington's disease: Evidence from the serial reaction time task. *Neuropsychologia, 29,* 245-254.

Knopman, D. S., & Nissen, M. J. (1987). Implicit learning in patients with probable Alzheimer's disease. *Neurology, 37,* 784-788.

Knowlton, B. J., Gluck, M. A., & Squire, L. R. (1994). Probabilistic classification learning in amnesia. *Learning & Memory, 1,* 106-120.

Knowlton, B. J., Ramus, S. J., & Squire, L. R. (1992). Intact artificial grammar learning in amnesia: Dissociation of classification learning and explicit memory for specific instances. *Psychological Science, 3,* 172-179.

Knowlton, B. J., & Squire, L. J. (1994). The information acquired during artificial grammar learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20,* 79-91.

Kopelman, M. D. (1992). The "new" and the "old": Components of the anterograde and retrograde memory loss in Korsakoff and Alzheimer patients. In L. R. Squire & N. Butters (Eds.), *Neuropsychology of memory.* (pp. 130-146). New York: The Guilford Press.

Kosslyn, S. M. (1994). *Image and brain.* Cambridge, MA: MIT Press.

Leaton, R. N., & Borszcz, G. S. (1990). Hippocampal lesions and temporally chained conditioned stimuli in a conditioned suppression paradigm. *Psychobiology, 18,* 81-88.

LlinE1s, R., & Welsh, J. P. (1993). On the cerebellum and motor learning. *Current Opinion in Neurobiology, 3,* 958-965.

Marr, D. (1982). *Vision: A computational investigation into the human representation and processing of visual information.* New York: Freeman.

Martone, M., Butters, N., Payne, M., Becker, J. T., & Sax, D. S. (1984). Dissociations between skill learning and verbal recognition in amnesia and dementia. *Archives of Neurology, 41,* 965-970.

Mayes, A. R. (1988). *Human organic memory disorders.* Cambridge: Cambridge University Press.

Mayr, U. (1994). *Spatial attention and implicit sequence learning: Evidence for independent learning of spatial and nonspatial sequences.* (Technical Rept No. 94-13). Institute of Cognitive and Decision Sciences, University of Oregon, Eugene, Oregon, USA.

McDonald, R. J., & White, N. M. (1993). A triple dissociation of memory systems: Hippocampus, amygdala, and dorsal striatum. *Behavioral Neuroscience, 107,* 3-22.

Mesulam, M.-M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology, 28,* 597-613.

Milner, B., Corsi, P., & Leonard, G. (1991). Frontal-lobe contribution to recency judgments. *Neuropsychologia, 29,* 6-618.

Milner, B., Petrides, M., & Smith, M. L. (1985). Frontal lobes and the temporal organization of memory. *Human Neurobiology, 4,* 137-142.

Mishkin, M., Malamut, B., & Bachevalier, J. (1984). Memories and habits: Two neural systems. In G. Lynch, J. McGaugh, & N. Weinberger (Eds.), *Neurobiology of learning and memory* (pp. 65-77). New York: Guilford Press.

Mishkin, M., & Petri, H. L. (1984). Memories and habits: Some implications for the analysis of learning and retention. In L. R. Squire & N. Butters (Eds.), *Neuropsychology of Memory* (pp. 287-296). New York: Guilford Press.

Mishkin, M., & Appenzeller, T. (1987). The anatomy of memory. *Scientific American., 256(6),* 80-89.

Mitz, A. R., Godschalk, M., & Wise, S. P. (1991). Learning-dependent neuronal activity in the premotor cortex: Activity during the acquisition of conditional motor associations. *Journal of Neuroscience, 11,* 1855-1872.

Mushiake, H., Inase, M., & Tanji, J. (1991). Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. *Journal of Neurophysiology, 66,* 705-718.

Myers, C. E., & Gluck, M. A. (1994). Context, conditioning, and hippocampal rerepresentation in animal learning. *Behavioral Neuroscience, 108,* 835-847.

Nadel, L. (1992). Multiple memory systems: What and why. *Journal of Cognitive Neuroscience, 4,* 179-188.

Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology, 19,* 1-32.

Nissen, M. J., Knopman, D. S., & Schacter, D. L. (1987). Neurochemical dissociation of memory systems. *Neurology, 37,* 789-794.

Nissen, M. J., Willingham, D., & Hartman, M. (1989). Explicit and implicit remembering: When is learning preserved in amnesia. *Neuropsychologia, 27,* 341-352.

Packard, M. G., Hirsh, R., & White, N. M. (1989). Differential effects of fornix and caudate lesions on two radial maze tasks: Evidence for multiple memory systems. *Journal of Neuroscience, 9,* 1465-1472.

Packard, M. G., & McGaugh, J. L. (1992). Double dissociation of fornix and caudate nucleus lesions on acquisition of two water maze tasks: Further evidence for multiple memory systems. *Behavioral Neuroscience, 106,* 439-446.

Parkin, A. J., & Leng, N. R. C. (1993). *Neuropsychology of the amnesic syndrome.* Hillsdale, NJ: Lawrence Erlbaum Associates.

Pascual-Leon, A., Grafman, J., & Hallet, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science, 263,* 1287-1289.

Pascual-Leone, A., Grafman, J., Clark, K., Stewart, M., Massaquoi, S., Lou, J.-S., & Hallett, M. (1993). Procedural learning in Parkinson's disease and cerebellar degeneration. *Annals of Neurology, 34,* 594-602.

Passingham, R. E. (1993). *The frontal lobes and voluntary action.* Oxford: Oxford University Press.

Perruchet, P., & Amorim, M. (1992). Conscious knowledge and changes in performance in sequence learning: Evidence against dissociation. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18,* 785-800.

Petrides, M. (1991). Functional specialization within the dorsolateral frontal cortex for serial order memory. *Proceedings of the Royal Society of London [Biology], B 246,* 299-306.

Playford, E. D., Jenkins, I. H., Passingham, R. E., Nutt, J., Frackowiak, R. S. J., & Brooks, D. J. (1992). Impaired mesial frontal and putamen activation in Parkinson's disease: A positron emission tomography study. *Annals of Neurology, 32,* 151-161.

Posner, M. I., & Peterson, S. E. (1990). The attention system of the human brain. Annual Review of Neuroscience, 13, 25-42. Posner, M. I., & Rothbart, M. K. (1991). Attentional mechanisms and conscious experience. In D. Milner & M. Rugg (Eds.), *The Neuropsychology of Consciousness.* (pp. 91-111). San Diego: Academic Press.

Povel, D. J., & Collard, R. (1982). Structural factors in patterned finger tapping. *Acta Psychologica, 52,* 107-123.

Reber, P. J., & Squire, L. R. (1994). Parallel Brain Systems for Learning with and without Awareness. *Learning & Memory, 1,* 217-229

Reed, J., & Johnson, P. (1994). Assessing implicit learning with indirect tests: Determining what is learned about sequence structure. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20,* 585-594.

Restle, F., & Burnside, B. L. (1972). Tracking of serial patterns. *Journal of Experimental Psychology, 118,* 219-235.

Riehle, A., & Requin, J. (1989). Monkey primary motor and premotor cortex: Single-cell activity related to prior information about direction and extent of an intended movement. *Journal of Neurophysiology, 61,* 534-549.

Robertson, C., & Flowers, K. A. (1990). Motor set in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 53,* 583-592.

Roediger, H. L., & McDermott, K. B. (1993). Implicit memory in normal human subjects. In H. Spinnler & F. Boller (Eds.), *Handbook of neuropsychology* (pp. 63-131). Amsterdam: Elsevier.

Rosenbaum, D. A. (1987). Successive approximations to a model of human motor programming. In G. Bower (Eds.), *The psychology of learning and motivation* New York: Academic Press.

Ross, R. T., Orr, W. B., Holland, P. C., & Berger, T. W. (1984). Hippocampectomy disrupts acquisition and retention of learned conditional responding. *Behavioral Neuroscience, 98,* 211-225.

Saint-Cyr, J. A., Taylor, A. E., & Lang, A. E. (1988). Procedural learning and neostriatal dysfunction in man. *Brain, 111,* 941-959.

Servan-Schreiber, E., & Anderson, J. R. (1990). Learning artificial grammars with competitive chunking. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 16,* 592-608.

Shanks, D. R., & St. John, M. F. (1994). Characteristics of dissociable human learning systems. *Behavioral and Brain Sciences, 17,* 367-447.

Shimamura, A. P. (1994). Memory and frontal lobe function. In M. S. Gazzaniga (Eds.), *The cognitive neurosciences* (pp. 803-814). Cambridge: MIT Press.

Shimamura, A. P., Janowski, J. S., & Squire, L. R. (1990). Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients. *Neuropsychologia, 28,* 803-813.

Skinner, D. M., Martin, G. M., Harley, C., Kolb, B., Pridgar, A., Bechara, A., & van der Kooy, D. (1994). Acquisition of conditional discriminations in hippocampal lesioned and decorticated rats: Evidence for learning that is separate from both simple classical conditioning and configural learning. *Behavioral Neuroscience, 1994*, 911-926.

Smyrins, N., Taira, M., Ashe, J., & Georgopoulos, A. P. (1994). Motor cortical activity in a memorized delay task. *Experimental Brain Research, 92,* 139-151.

Squire, L. R. (1992). Memory and the hippocampus: A synthesis of findings with rats, monkeys, and humans. *Psychological Review, 99,* 195-231.

Squire, L. R., Amaral, D. G., & Press, G. A. (1990). Magnetic resonance imaging of the hippocampal formation and mammilary nuclei distinguish medial temporal lobe and diencephalic amnesia. *The Journal of Neuroscience, 10,* 3106-3117.

Stadler, M. A. (1989). On the learning of complex procedural knowledge. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 15,* 1061-1069.

Stadler, M. A. (1992). Statistical structure and implicit serial learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18,* 318-327.

Stadler, M. A. (1993). Implicit serial learning: Questions inspired by Hebb (1961). *Memory & Cognition, 21,* 819-827.

Stadler, M. A. (1994). Explicit and implicit learning and maps of cortical motor output. *Science, 265,* 1600.

Stadler, M. A. (1995). Role of attention in implicit learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 21,* 674-685.

Sutherland, R. J., & Rudy, J. W. (1989). Configural association theory: The role of the hippocampal formation in learning, memory, and amnesia. *Psychobiology, 17,* 129-144.

Tanji, J. (1994). The supplementary motor area in the cerebral cortex. *Neuroscience Research, 19,* 251-268.

Thompson, R. F. (1986). The neurobiology of learning and memory. *Science, 233,* 941-947.

Thompson, R. F. (1990). Neural mechanisms of classical conditioning in mammals. *Philosophical Transaction of the Royal Society of London, B 329,* 161-170.

Ungerleider, W., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingel, M. A. Goodale, & R. J. W. Mansfield (Eds.), *The Analysis of Visual Behavior.* (pp. 549-586). Cambridge, MA: MIT Press.

Wicklegren, W. A. (1979). Chunking and consolidation: A theoretical synthesis of semantic networks, configuring in conditioning, S-R versus cognitive learning, normal forgetting, the amnesic syndrome, and the hippocampal arousal system. *Psychological Review, 86,* 44-60.

Willingham, D. B. (1992). Systems of motor skill. In L. R. Squire & N. Butters (Eds.), *Neuropsychology of memory.* (pp. 166-178). New York: The Guilford Press.

Willingham, D. B., Greenley, D. B., & Bardona, A. M. (1993). Dissociation in a serial response time task using a recognition measure: Comment on Perruchet and Amorim (1992). *Journal of Experimental Psychology: Learning, Memory, and Cognition, 19,* 1424-1430.

Willingham, D. B., & Koroshetz, W. J. (1993). Evidence for dissociable motor skills in Huntington's disease patients. *Psychobiology, 21,* 173-182.

Willingham, D. B., Nissen, M. J., & Bullemer, P. (1989). On the development of procedural knowledge. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 15(6),* 1047-1060.

Wilson, F. A. W., Scalaidhe, S. P. O., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing in primate prefrontal cortex. *Science, 260,* 1955-1958.