

Contribution of frontostriatal function to sequence learning in Parkinson's Disease: evidence for dissociable systems

Peter F. Dominey,^{1,2,CA}
Marc Jeannerod^{1,2}

¹Vision et Motricité, Unité 94 INSERM, 69500

Bron; ²Institut des Sciences Cognitives

EP-100 - CNRS, 69008 Lyon, France

^{CA}Corresponding Author

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Abstract

THE frontostriatal system appears to play a crucial role in the organization and execution of sequential behaviour, but the precise nature of its contribution remains to be specified. From this perspective, relatively simple modifications of behavioural task parameters may invoke rather profound changes in the recruitment of appropriate neural mechanisms, including the frontostriatal system. This mini-review examines how variations in task requirements for sequence learning and related cognitive tasks can induce significant modifications in the performance of patients with Parkinson's disease. In particular, these observations are used to support a developing argument for neurophysiologically dissociable sequence learning systems in man. One of these mechanisms is sensitive to surface structure, or element-by-element sequence organization, and appears to rely on the frontostriatal system. Another sequence learning mechanism is sensitive to abstract structure, or relationships between repeating sequence elements, and appears to be largely independent of the frontostriatal system.

Introduction

A major focus of cognitive neuroscience is to associate distinct cognitive functions with their underlying neural foundations. In the domain of sequence learning, a number of neuropsychological studies have demonstrated that frontostriatal

dysfunction in Parkinson's disease (PD) leads to significant perturbations in a variety of sequence learning tasks.¹⁻⁹ Of equal interest, however, are the observations that in modified versions of some of these tasks, behaviour of patients with PD improves to that of normal subjects.^{4,10,11} We review this data from the perspective that task modifications yielding improved performance in PD can be used to identify cognitive processes that operate independently from the impaired frontostriatal system. In particular, we will review recent results that argue for the existence of two dissociable sequence learning mechanisms. One mechanism encodes sequences in terms of their surface structure, or associations between groups of elements, and relies on the intact frontostriatal system. The other encodes sequences in terms of their abstract structure, based on relations between repeating sequence elements, and appears to be largely independent of the frontostriatal system.¹²⁻¹⁴

The frontostriatal system: a functional overview

We present a brief overview of the frontostriatal role in sequence learning, in terms of a functional model (Fig. 1) that was developed based upon neuroanatomy, neurophysiology and behavioural data from human and non-human primates.¹⁵⁻¹⁷ Within this framework, PD is characterized by a progressively increasing lesion of the nigrostriatal dopamine system (see Ref. 18). Thus, cognitive functions that rely on the frontostriatal system should be impaired in PD. Indeed, this framework provides the basis for explaining several primitive cognitive functions that contribute to a sequential behaviour, including working memory, and conditional learning abilities, and their impairment in PD.

Working memory: A classic test of working memory requires the subject to see and then recall after a delay the target for a future movement.¹⁹ In the framework of Fig. 1, working memory is implemented in recurrent thalamocortical loops. The mediodorsal thalamus is disinhibited via excitatory cortico-striatal projections that stimulate inhibitory striato-nigral projections that in turn inhibit tonic, inhibitory nigrothalamic projections. The anatomy and neurophysiology of this working memory circuit have been characterized in detail for the control of oculomotor saccades to remembered targets (see Ref. 15 for review and

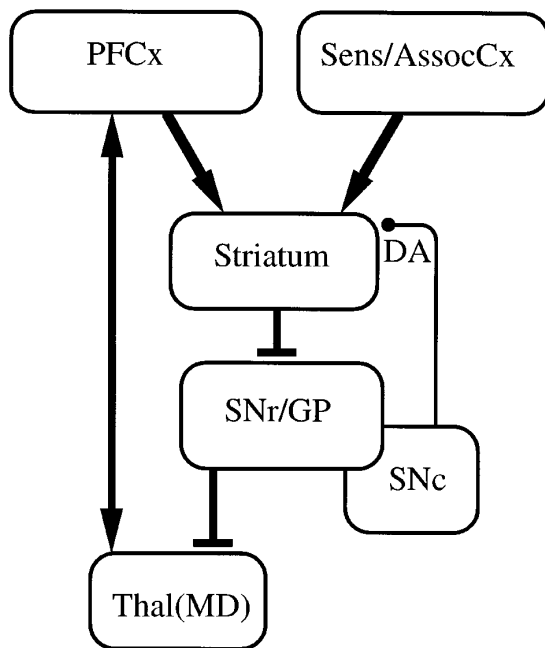


FIG. 1. Functional model of the frontostriatal system. **Working memory:** prefrontal cortex issues excitatory glutamatergic projections to striatum. Striatum in turn issues inhibitory GABAergic projections to the substantia nigra pars reticulata (SNr) and globus pallidus (GP). This corticostriatal influence on SNr/GP interrupts the tonic inhibitory effect of these nuclei on mediodorsal thalamus (MD) and other associative and motor structures (not shown). This permits a closed cortico-thalamic loop to create working memory representations via sustained short-term tonic activations. **Conditional association learning:** during conditioning, excitatory corticostriatal terminals from sensory-association cortices become strengthened via reward-related dopamine release in the striatum. **Sequence learning:** ordered sequence context representations, implemented in the recurrent working memory system, become bound to the production of the correctly ordered events via the conditional association mechanism. Modified from Ref. 17.

simulation study), and several studies of remembered saccades demonstrate significantly impaired performance in patients with PD.^{20,21}

Conditional learning: The integrity of the frontostriatal system, including the nigrostriatal dopamine system, is necessary for normal conditional learning in which visual stimuli must be discriminated and associated with an appropriate behaviour.²² In the framework of Fig. 1, this adaptive capability is provided by modifiable corticostriatal synapses that allow sensory activity in cortex to become associated with arbitrary responses via movement related neurones in the striatum.¹⁷ Such plasticity might also foster co-activation of sensory and motor related cortical areas in support of cortico-cortical adaptation.²³

The potential role of dopamine (DA) in this corticostriatal plasticity is a current focus of research. DA release in the striatum is quite closely linked to the delivery and expectation of reward during behavioural learning,²⁴ and the selective long-term

potentiation and depression effects of DA on corticostriatal synapses has been established.^{25,26} Indeed, conditional associative learning is impaired in PD patients with PD when trained in a trial-and-error protocol. However, when exposed to a 'correction' protocol in which after each error the correct response is explicitly provided, these patients' behaviour is restored to normal.¹⁰ This suggests a more specific impairment in the appropriate use of error signals in conditional learning, similar to the impaired ability to shift from incorrect behaviours in frontal and frontostriatal (PD) patients.²⁷⁻²⁹

Sequence learning: These capabilities for working memory and associative learning can provide a basis for simple sensorimotor sequence learning.^{16,17} At any point in the execution of a learned sequence the problem is always the same, that is, to correctly select the next action. Working memory, based on sensory and internal (e.g. efferent copy) inputs encodes a form of internal state, so that for each action in a behavioural sequence, there is a corresponding internal state, characterized by a unique, distributed pattern of neural activity in the frontostriatal system. The problem now remains to learn to associate each of these internal states with the production of the appropriate corresponding action. This is the role of the associative learning mechanism described above. Thus, the previous external and internal events produce a pattern of activity in the prefrontal cortex that must become associated, by trial and error learning, with the next event in the sequence. Once all the events have been learned in this manner, the sequence itself has been learned. This functional neuroanatomical view of the frontostriatal role in sequence learning and behaviour^{16,17} is supported by neuropsychological,⁷ neurophysiological^{30,31} and brain imaging data.³²⁻³⁵ Within this framework, we can address the behavioural deficits in sequential tasks in PD.

Dissociable aspects of sequential behaviour in Parkinson's disease

The serial reaction time (SRT) task is a classic measure of sequence learning³⁶ that has recently been the basis for several observations of impaired sequential behaviour in patients with PD.^{1,3,4} In the SRT task, subjects are presented with visual stimuli, and manual response times (RTs) for these stimuli are recorded. For stimuli that are presented in a repeating sequence, RTs are reduced with respect to those for stimuli appearing in a random series. The difference in RTs for random *vs* sequential elements is then used as a quantitative measure of

sequence learning. If subjects are not informed of such sequence effects, and are simply asked to respond as quickly and accurately as possible (implicit conditions), they can display significant learning with no awareness of the sequential organization.³⁷ In contrast, when patients with PD are tested in these implicit conditions they are significantly impaired, with this impairment becoming more pronounced for sequences of increasing length and complexity.^{1,3,4} A rather striking return to near normal performance can be observed, however, when the task is made explicit, that is, when the subjects are informed of the sequence that will be used in advance, or when they are allowed to learn by observation while the motor component of the task is temporarily removed.⁴ These results suggest the existence of a dissociable explicit learning system that is independent of the frontostriatal system.

A behaviourally dissociable form of sequence learning based on analogical transfer between isomorphic sequences: A sequence of visual stimuli in an SRT task might contain information or structure that is encoded at several different levels (e.g. spatial location and visual form). Indeed, distinct spatial and object sequential structures embedded in a single sensorimotor sequence can be independently learned, suggesting the existence of independent learning systems.³⁸ We have recently developed an SRT-based protocol that examines a similar dissociation between processes that treat surface and abstract structure in sensorimotor sequences.¹²⁻¹⁴ We define the surface structure of a sequence in terms of relations between elements or groups of elements and their successors, and abstract structure in terms of the relations between locations of elements that repeat within a sequence. In this context, the two sequences ABCBAC and DEFEDF share the same abstract structure, or analogical schema, 1-2-3-2-1-3 (i.e. they are isomorphic). In contrast, these two sequences have completely unrelated surface structures. For any isomorphic sequence that follows this abstract structure, note that the first three elements are unpredictable, while the fourth to sixth elements are completely predictable (i.e. they repeat the first three elements in a different order). The differences in reaction times for elements that are predictable *vs* unpredictable provides a measure of analogical schema learning. Our protocol for analogical transfer³⁹ in sequence learning (ATSL) thus tests the ability to acquire and transfer knowledge of an analogical schema or abstract structure from one isomorphic sequence to another.

The ATSL task is based on the SRT protocol³⁶ and involves a series of motor responses to single illuminated square targets on a touch-sensitive screen as quickly and accurately as possible (Fig. 2). After a target is touched it is extinguished, the reaction time (RT) is recorded and the next target is displayed. Only one target appears at a time. Targets appear in blocks of two types: random and sequence.

In order to test the learning of abstract structure, the sequence blocks were designed to contain a relatively simple abstract structure and a highly complex (and thus unlearnable) surface structure, described in detail in Fig. 2. The abstract structure follows the pattern '...ABC BCD CDE ...', where in each group of three elements, the first two elements are predictable (see BC in BCD for example) and the third is unpredictable. This repeating pattern defines the analogical schema that can be used to generate a set of isomorphic sequences.

A-B-C-B-C-D-C-D-E-D-E-F-E-F-G-F-G-H-G-H-A-H-A-B

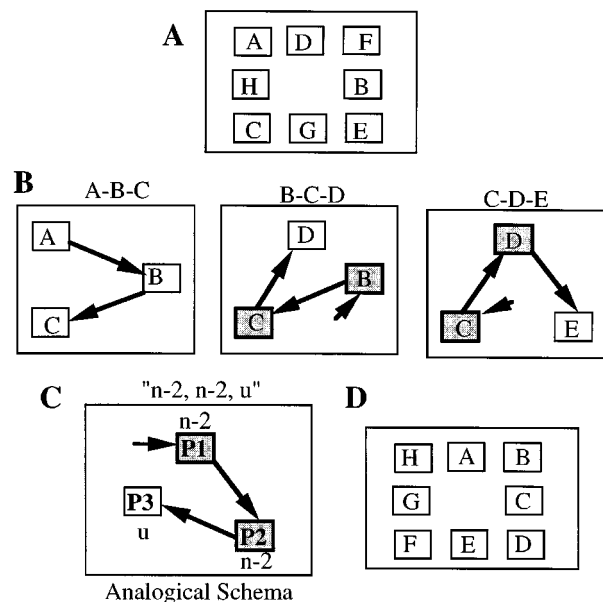


FIG. 2. Analogical transfer in sequence learning protocol. Above: 24 element sequence. (A) One mapping of letters A-H to target locations on the touch-sensitive screen. Targets are presented one at a time. Note that the letters themselves are never displayed. (B) Breakdown of sequence A-B-C-B-C-D-C-D-E into three element chunks. Note that each shaded element is predictable from the element two positions behind, labelled 'n-2'. For example, the first two elements 'B-C' in 'B-C-D' are predicted by the last two elements 'B-C' in the preceding chunk 'A-B-C'. (C) Analogical schema. The first two elements are predicted from the previous two elements (n-2), and the third element is unpredictable ('u'). These elements are referred to, respectively, by their position in the analogical schema, P1, P2 and P3. P1 and P2 are predictable and P3 is unpredictable. This analogical schema is the unit that describes the isomorphism between the sequences used in sequence blocks S1, S2 and S3 (see text). (D) An alternative mapping of A-H to the eight target locations used to generate an isomorphic sequence. Three 24-element isomorphic sequences are thus created. In one sequence block, one of these sequences is repeated 5 times for a total of 120 trials.

An experiment starts with a random block of 120 trials followed by the three sequence blocks of 120 trials each, and a final random block of 120 trials. In random blocks, 120 targets are successively presented in random order. To study the transfer of learned abstract structure between different, isomorphic sequences, three such sequences are used in the three respective sequence blocks, as described in Fig. 2. The three resulting 24-element sequences differ completely in their surface structure of the spatial targets. However, they are isomorphic in that they all share the analogical schema (Fig. 2C) that describes their common abstract structure. In each of the three isomorphic sequence blocks, one of these sequences was repeated five times for a total of 120 targets, of which 80 were predictable and 40 unpredictable by the analogical schema.

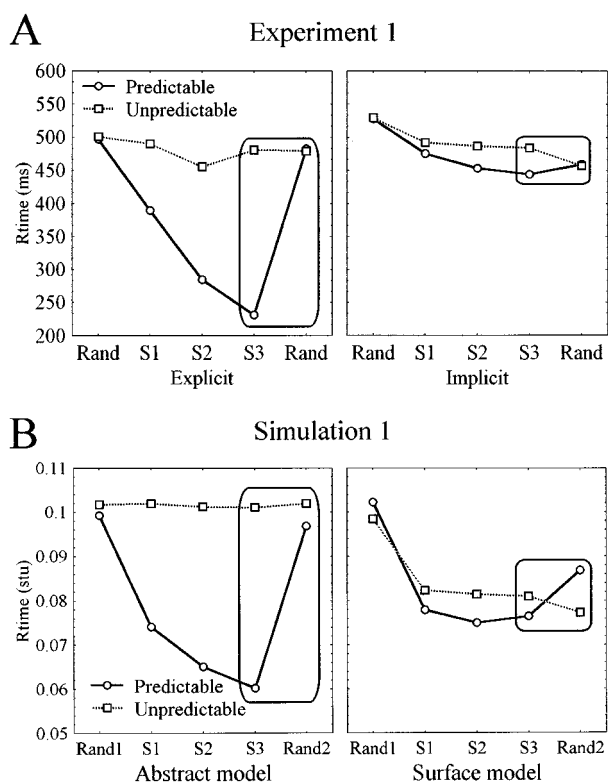


FIG. 3. Dissociable systems for analogical transfer in sequence learning. (A) Experiment 1. Mean (RTs) reaction times for predictable and unpredictable responses in the five blocks of trials for explicit and implicit groups. The first and last of the five blocks of 120 trials are random. Blocks S1, S2 and S3 are made up of three different repeating isomorphic sequences, one per block. The critical blocks for learning and transfer assessment are marked in the rounded boxes. If the abstract structure is learned then RTs for predictable elements should be reduced with respect to those for unpredictable elements in the sequence blocks. (B) Simulation 1 using abstract and surface models (five of each). Same presentation format as in (A). RT expressed in simulation time units (stu) where 1 network update cycle (time step) corresponds to 0.005 stu. See text for details.

ATSL behaviour in normal and subjects with PD: If the abstract structure alone is learned, then we would expect to see a reduction in RTs for the elements that are predictable by the abstract structure, but not for the unpredictable elements. Thus, as seen in Fig. 3A, normal subjects display significant learning and transfer of the abstract structure of the sequences, but only if they are in an explicit learning condition in which they have been briefed about the possible existence of such an abstract structure.¹²⁻¹⁴ Subjects who are simply told to respond to the stimuli as quickly and accurately as possible display no such learning nor transfer. The observations that subjects with PD are impaired in implicit sequence learning^{1,3,4} suggests that the frontostriatal system is a necessary component for implicit learning. In contrast, in the explicit ATSL task, patients with PD display significant learning and transfer of the abstract structure,¹²⁻¹⁴ consistent with the argument that the frontostriatal system is not a necessary component for learning abstract structure in the explicit ATSL task.

Transfer of the analogical schema: As stated above, learning of the abstract structure is indicated by the RT reduction for predictable *vs* unpredictable elements. If knowledge of the abstract structure indeed transfers between the three sequences, then this difference should increase across the three sequence blocks as a result of the transfer. Note that this learning index should increase, despite the fact the different sequence blocks do not use the same sequence. The reason for this increase is that although the sequences differ in their surface structure they are isomorphic and share the same abstract structure that can thus be transferred from one sequence block to the next. Indeed, as seen in Fig. 4 for both Parkinson and control groups this was the case: there was a significant positive transfer between the three isomorphic sequences, with no group interaction.¹⁴

Rule *vs* specific sequence learning: One might argue that subjects are simply learning the surface structures for these different sequences, rather than their common abstract structure. In this case, learning effects could only be seen after a new sequence had been presented at least once in its entirety. Thus, if learning is already evident in a new 24-element sequence before that sequence has been completely presented for the first time, the learning can only be due to a rule acquired and transferred from previous training. To address directly whether a transferable rule or individual sequences were being learned, we analysed RTs for the first 24 elements of sequence block SEQ3, i.e.

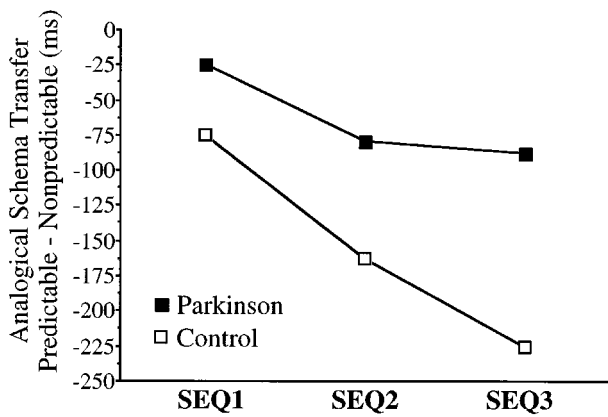


FIG. 4. Analogical schema transfer. The level of analogical schema transfer is displayed as the progressive increase in the difference between predictable minus unpredictable RTs. For both the control and PD groups, this measure becomes increasingly significant in the progression from SEQ1 to SEQ3, indicating a significant level of analogical transfer in both groups. From Ref. 14.

the first presentation of the previously unseen sequence of block SEQ3. Even during this very first presentation of the new sequence, its predictable structure was already being exploited, with a specific difference between predictable and unpredictable responses, and no significant difference in PD *vs* control groups in the use of the learned rule during this first repetition of the 24 element sequence in SEQ3.¹⁴

Converging evidence for dissociable sequence learning system

These results argue that learning abstract structure in ATSL is functionally dissociable from learning surface structure (see Ref. 40). Particular differences between these processes can be seen for both PD and control groups in terms of the distribution of reaction times for elements within sequence blocks, the dependence of learning on sequence length, and characteristics of performance transfer to new sequences. Finally, theoretical evidence from simulation studies is used to support the argument for dissociable systems.

Distribution of reaction times within the sequence blocks: If the surface structure of a sequence is learned, the RTs should be uniformly reduced for all sequence elements. In the ATSL task, however, reduced RTs are seen only for predictable but not for unpredictable elements, even though both are contained in sequence blocks.¹²⁻¹⁴ That is, only the elements that are predicted by the abstract structure display a learning effect. This supports

the view that an abstract structure that is not specific to any one of these sequences is being learned, and not the surface structures themselves. Curran and Keele³² performed a similar analysis of RT distribution in an SRT task using a repeating surface structure and confirmed that RTs for sequence elements are uniformly reduced with respect to those for random elements, supporting their contention that the entire structure of the sequence was being learned. We can consider that in general if a single given sequence is successively repeated then the sequence itself, i.e. the surface structure, will be learned, whereas if a number of isomorphic sequences are presented then the rule common to all, i.e. the abstract structure, will be learned.

The lack of dependence on sequence length: Motor sequence performance is dependent upon several parameters of the sequence, including its length.^{1,3,4,41} Length dependence in the SRT task was demonstrated by Pascuale-Leone *et al.*⁴ in normal controls and subjects with PD. RT reduction was inversely related to sequence length in control and subjects with PD, and for the longer sequences, patients with PD were particularly impaired. In contrast, even using a sequence with a length twice that of the longest used by Pascuale-Leone *et al.*⁴ we observed significant unpredictable-predictable RT differences for control and subjects with PD, respectively, which represent a notable departure from the length dependencies observed in surface structure SRT tasks in PD.^{1,3,4}

Transfer to isomorphic sequences: The most profound evidence for distinct learning mechanisms for surface *vs* abstract structure is the significant positive transfer to different but isomorphic sequences for both PD and control groups. This is in contrast to the negative transfer results of Robertson and Flowers,⁴² who observed that while subjects with PD were able to demonstrate explicit sequence learning, when asked to change from one sequence to the next, they tended to continue with the old sequence. A related form of negative transfer was observed by Benecke *et al.*⁴³ in making the transition from one movement to another in a sequence, and is related to the more general impairment in set-shifting observed in PD.²⁷⁻²⁹

In contrast, our observation of positive transfer results from the fact that it was not a set of different sequences that was learned, but instead, an abstract structure was learned that was common to all of these sequences. The observed transfer was in fact positive, since from the perspective of the rule in question, all three sequences are the same.

Given these observations, we can speculate, however, that while the learning of abstract structure is relatively independent of frontostriatal integrity, the ability to shift between appropriate abstract structures in a context-dependent fashion would continue to rely on the frontostriatal system.⁴⁴

Theoretical support for dissociable forms of learning: The data reviewed argue that there is a behavioural and neurophysiological separation between the treatment of surface and abstract sequential structure. Theoretical support for this argument can also be drawn from recent neural network simulation studies. A number of sequence learning models are based on the principle of an internal state or context mechanism that maintains a representation of the history of previous events, and allows the prediction of future events.^{16,17,44-46} These systems are able to resolve surface structure ambiguities, as in determining the successor to B in the sequence ABCBAC. However, in order to represent the abstract structure common to the two isomorphic sequences ABCBAC and DEFEDF these systems are insufficient. That is, they cannot represent the abstract structure u, u, u, n-2, n-4, n-3 that is common to these two sequences, where 'u' indicates unpredictable and 'n-3' indicates a (predictable) repeat of the element 3 places behind, etc. Instead, the capacity to represent this kind of abstract relation requires the capacity to recognize the structure of repeating elements, and to let this information be the source of the context. In support of the proposal that surface and abstract structure learning rely on dissociable systems, our recent simulation results have demonstrated that a recurrent neural network based on the frontostriatal system can learn surface structures in SRT task. Each element in the surface structure is embedded in a form of sequential context. The recurrent network is ideal for representing this recurrent context and thus for learning the surface structure. However, it could not learn abstract structures and thus failed in the ATSL task (Fig. 3B) due to an incapacity to represent positional relations between repeating elements.^{12,13} That is, because the model was incapable of detecting repetitions and thus encoding a sequence ABCBAC in terms of its abstract structure 'u, u, u, n-2, n-4, n-3' it could not transfer such knowledge between isomorphic sequences.

To address this problem, we augmented the model with a short term memory (STM) of the previous 4-7 elements. During each response, the current element could then be compared with elements in the STM. This permits sequences to be

represented in terms of their abstract structure of repeated elements such as 'u, u, u, n-2, n-4, n-3' for ABCBAC. Thus, the original (surface) model can predict specific elements given a learned context, e.g. given the surface structure context ABCBA, the model can predict that the next element is C. Likewise, the updated, abstract model can predict that a certain repetition will occur given a learned context. For example, given the abstract context 'u, u, u, n-2, n-4', the updated model can predict that the next abstract structure element is 'n-3'. The n-3rd element can then be extracted from the STM where it is temporarily stored, thus yielding a reduced RT for this response. When augmented with this ability to represent abstract structure in terms of relations between repeating elements, the model performed abstract as well as explicit human subjects, providing further evidence for the ATSL a dissociation between processes for learning surface and abstract structure.^{12,13}

Conclusion

While the frontostriatal system appears to play an essential role in important aspects of sequential learning,^{1,3,4} it has been clearly demonstrated that more explicit and abstract sequence learning appears to rely much less on the frontostriatal system.^{4,14} In particular, we have reviewed recent experimental and simulation data that argue for the existence of at least two dissociable sequence learning systems. One of these systems, that relies heavily on the intact frontostriatal system, operates at the level of surface structure or associative relations between sequence elements and their successors, and provides the basis for implicit learning as revealed in SRT tasks. A second system, relatively independent of frontostriatal intervention, operates at a different representational level, in terms of an abstract structure that can describe an ensemble of isomorphic sequences. We suggest that this system provides the basis for a primitive form of analogical transfer in the problem solving domain of sequence learning.¹²⁻¹⁴ More generally, one can appreciate the existence of this kind of system as it addresses a class of problems in which the complexity of representing an unbounded data set in the environment can be greatly reduced based on a systematic recording, here in terms of the abstract structure.^{47,48}

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