The study of sequence learning in individuals with schizophrenia: A critical review of the literature

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The serial reaction time task (SRTT) has been used extensively to study implicit sequence learning. A number of studies have used the SRTT to examine sequence learning in schizophrenia patients. Despite these studies, it remains unclear whether sequence learning is impaired in patients, whether antipsychotic medications affect sequence learning, and what types of sequential information patients might have difficulty learning. Methodological limitations have made it difficult to obtain good answers to these questions. Methodological innovations from the general SRTT literature that have not yet been adopted in the schizophrenia literature could provide better answers.

Schizophrenia is associated with numerous cognitive deficits (Reichenberg & Harvey, 2007). Many of the cognitive deficits may stem from an impaired ability to consciously process context information – such as specific prior stimuli, a sequence of prior stimuli, task instructions, or goals – in order to perform task-appropriate behaviour (Barch & Ceaser, 2012; Hemsley, 2005). Conscious processing of context is correlated with working memory and intelligence (MacDonald, Goghari, et al., 2005). It is also correlated with activity in the prefrontal cortex, and prefrontal cortex dysfunction in schizophrenia patients may account for the context-processing deficit in these individuals (MacDonald, Carter, et al., 2005).

Schizophrenia patients clearly have a problem with explicit (i.e., conscious, intentional) processing of context. It is natural to ask, then, whether patients also have a problem with implicit (i.e., non-conscious, non-intentional) processing of context. Work in cognitive psychology has supported the distinction between explicit and implicit modes of processing. The distinction has spurred considerable research to try to establish whether implicit modes of processing are spared or impaired in patients. The results of these efforts have been mixed (Gold, Hahn, Strauss, & Waltz, 2009).

A number of tasks have been employed to study implicit processing. A popular task, in both the general and schizophrenia literatures, and arguably the most relevant to context processing is the serial reaction time task (SRTT).

The SRTT
The SRTT has been used extensively to study explicit and implicit sequence learning. On each trial of the standard SRTT, a target appears at one of a number of possible

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locations on a monitor and the key corresponding to the location of the target is pressed. The sequence of target locations may be deterministic (i.e., the sequence repeats after a number of trials) or probabilistic (i.e., given previous target locations, some locations are more probable successors than other locations). In the explicit version of the standard SRTT, subjects are instructed to try to learn the structure of the sequence.

In the implicit version of the standard SRTT, subjects are not informed about the structure of the sequence. Sequence learning is inferred when the repeating sequence of target locations elicits shorter reaction times (RTs) than does a random or newly introduced sequence of target locations (for deterministic sequences), or when given previous target locations, more probable succeeding locations elicit shorter RTs than do less probable succeeding locations (for probabilistic sequences). The implicitness of sequence learning is established by assessing the awareness of the sequence. Sequence learning that is explicit would lead to an awareness of the sequence. Thus, a lack of awareness of the sequence would suggest that sequence learning was implicit.

Variants of the standard SRTT have also been developed. For example, individuals might respond to the identity of the target rather than its location, or responses might be vocal rather than manual.

The results of SRTT studies suggest that explicit and implicit sequence learning involve distinct mechanisms. First, explicit sequence learning is correlated with working memory and intelligence whereas implicit sequence learning is not (Gebauer & Mackintosh, 2007; Kaufman et al., 2010; Unsworth & Engle, 2005). Second, explicit sequence learning is not correlated with implicit sequence learning (Marvel, Schwartz, Howard, & Howard, 2005; Pedersen et al., 2008). Third, sequence knowledge acquired explicitly is represented differently than sequence knowledge acquired implicitly (Knee, Thomason, Ashe, & Willingham, 2007). Fourth, sequence knowledge acquired explicitly can be used in a controlled and flexible manner, whereas sequence knowledge acquired implicitly cannot (Jimenez, Vaquero, & Lupianez, 2006). Finally, it has been proposed that explicit sequence learning involves the anterior striatum and the prefrontal cortex, whereas implicit sequence learning involves the dorsolateral striatum and the primary motor cortex (Ashe, Lungu, Basford, & Lu, 2006; Penhune & Steele, 2012).

If explicit and implicit sequence learning are impaired and spared, respectively, in schizophrenia patients, then this would suggest that patients do not have a general context-processing deficit and that deficits in context processing may be limited to situations that require explicit processing of context and the use of working memory and the prefrontal cortex. The goal of this paper is to critically review SRTT studies in the schizophrenia literature to determine whether explicit sequence learning is impaired in patients and, more importantly, whether implicit sequence learning is spared.

**Search method**

The following method was used to identify SRTT studies involving schizophrenia patients. The title, abstract, and keyword sections of articles in the PsychINFO database were searched using the Boolean phrase *schizophrenia and (sequence or serial or SRT or implicit or procedural)*. The search was limited to English, peer-reviewed journals and to articles published between 1987 and 2012. The SRTT was introduced in 1987 (Nissen & Bullemer, 1987). The search produced 840 titles for review. Each title was read and if there was any hint in the title that the SRTT might have been used, then the
abstract was read. If there was any hint in the abstract that the SRTT might have been used, then the article was read. This strategy yielded 16 studies. The reference section of each study and the list of citations provided by PsychINFO for each study were examined. This produced two additional studies. Two of the 18 studies were subsequently excluded. One study did not have a healthy control group (Kern et al., 1998) and the magnitude of sequence learning could not be determined in a second study because there was no random sequence (Perry, Light, Davis, & Braff, 2000). A similar search of the Medline database produced no additional studies. Thus 16 studies are reviewed in this paper.

**Explicit sequence learning**

Four of the 16 studies examined explicit sequence learning. Studies using the standard SRTT (Karatekin, White, & Bingham, 2009; Pedersen et al., 2008) or a variant of the standard SRTT (Marvel et al., 2005; Posada, Franck, Georgieff, & Jeannerod, 2001) have all shown that, relative to healthy controls, explicit sequence learning is impaired in schizophrenia patients. Also, patients are impaired at using sequence knowledge to anticipate subsequent events even after they have memorized the sequence (Dominey & Georgieff, 1997; Posada et al., 2001). These results are consistent with the view that patients have a problem with explicit processing of context.

**Implicit sequence learning**

Fourteen of the 16 studies compared implicit sequence learning in schizophrenia patients to that in healthy controls. Twelve studies used the standard SRTT and two studies used a variant of the standard SRTT. The former studies will be reviewed first, followed by the latter studies.

Seven studies using the standard SRTT suggest that implicit sequence learning is impaired in patients (Exner, Boucsein, Degner, & Irle, 2006; Exner, Weniger, Schmidt-Samoa, & Irle, 2006; Green, Kern, Williams, McGurk, & Kee, 1997; Kumari et al., 2002; Marvel et al., 2007; Pedersen et al., 2008; Schwartz, Howard, Howard, Hovagimian, & Deutsch, 2005), whereas five studies suggest that implicit sequence learning is normal in patients (Foerde et al., 2008; Karatekin et al., 2009; Purdon, Waldie, Woodward, Wilman, & Tibbo, 2011; Reiss et al., 2006; Zedkova, Woodward, Harding, Tibbo, & Purdon, 2006). A consistent difference between the two sets of studies is the method of target offset in the SRTT. Every study that found impaired sequence learning in patients used a response-triggered offset where a response to the onset of the target immediately leads to the offset of the target. In contrast, every study that found normal sequence learning in patients used a time-triggered offset where the offset of the target occurs after a fixed amount of time has elapsed since its onset.

It is conceivable that controls acquire more sequence knowledge than do patients, but a time-triggered offset masks the difference in sequence knowledge. Sequence knowledge allows one to orient attention to the next location in the sequence and prepare the corresponding response in advance of the target’s presentation at that location (Marcus, Karatekin, & Markiewicz, 2006; Remillard, 2003). The result is a short RT when the target appears at the anticipated location. Thus anticipatory orienting of attention enhances the expression of sequence knowledge. A time-triggered offset might interfere with this process. For example, the individual responds to the current
location of the target, orients to the next location in the sequence, and then orients back to the current location of the target as it offsets. Offsets can capture attention (e.g., Pratt & McAuliffe, 2001; Welsh & Pratt, 2008). Alternatively, the individual responds to the current location of the target and the continued presence of the target makes it difficult for the individual to orient to the next location in the sequence. It is more difficult to orient to a spatial location in the presence of a fixated stimulus than in the absence of such a stimulus (e.g., Huestegge & Koch, 2010; Pratt, Lajonchere, & Abrams, 2006). Relative to a situation that does not interfere with the expression of sequence knowledge, a situation that does interfere with the expression of sequence knowledge would produce a greater lengthening of RTs in individuals with greater sequence knowledge. Thus controls may have had greater sequence knowledge than patients in the studies that found normal sequence learning in patients, but the time-triggered offset masked the difference in sequence knowledge.

It is also conceivable that controls and patients acquire equivalent sequence knowledge, and a time-triggered offset allows the equivalency to be revealed. There is evidence that patients have greater difficulty disengaging attention from an attended location than do controls (e.g., Chirio et al., 2010; Mushquash, Fawcett, & Klein, 2012). Thus anticipatory orienting of attention to the next target location in the sequence could be delayed in patients relative to controls. It is therefore possible that studies using a response-triggered offset were observing group differences in the expression of sequence knowledge and not differences in sequence knowledge. Studies using a time-triggered offset might have equated the expression of sequence knowledge in controls and patients, and permitted group equivalency in sequence knowledge to be revealed.

The five studies that used a time-triggered offset also used a deterministic sequence and the RT difference between random and sequence trials across those studies ranged from 22 to 45 ms in controls (mean 33 ms) and from 17 to 66 ms in patients (mean 33 ms). Four of the seven studies that used a response-triggered offset also used a deterministic sequence and the RT difference between random and sequence trials across those studies ranged from 53 to 90 ms in controls (mean 69 ms) and from 2 to 53 ms in patients (mean 30 ms; Exner, Boucsein, et al., 2006; Exner, Weniger, et al., 2006; Green et al., 1997; Pedersen et al., 2008). Thus RT differences for controls were smaller in studies employing a time-triggered offset than in studies employing a response-triggered offset, with little difference across the two sets of studies in the RT differences for patients. This is consistent with the idea that time-triggered offsets interfere with the expression of sequence knowledge more so in controls than in patients.

It is important that investigators formally examine (1) whether a time-triggered offset affects the expression of sequence knowledge in controls and patients, and (2) whether patients have difficulty expressing sequence knowledge because of delayed anticipatory orienting of attention. Abrahamse, van der Lubbe, and Verwey (2009) provide one approach for determining whether different variations of the SRTT produce differences in the expression of sequence knowledge (see also Deroost, Coomans, & Soetens, 2009). This approach could be used to determine whether response versus time-triggered offsets produce differences in the expression of sequence knowledge. Manipulation of the time interval between the response to the target’s current location and the target’s next appearance (response-stimulus interval, RSI) in a SRTT employing a response-triggered offset could be used to determine whether patients have difficulty expressing sequence knowledge because of delayed anticipatory orienting. The delayed anticipatory orienting hypothesis would predict a greater expression of sequence knowledge with increasing
RSI. Until issues regarding the expression of sequence knowledge are resolved, it will be difficult to establish with any confidence whether sequence learning in the SRTT is impaired in patients.

Two studies have sidestepped the interpretive ambiguity associated with presenting targets spatially by having participants respond to the identity of centrally presented targets with corresponding key presses. One study suggests that sequence learning is normal in patients (Stevens et al., 2002), and the other study suggests that sequence learning is impaired in patients (Marvel et al., 2005). Stevens et al. trained participants for one session and found that the RT difference between sequence and random trials in patients was similar to that in controls. Marvel et al. trained participants for six sessions. Whereas the RT difference between sequence and random trials in patients was similar to that in controls, the response accuracy difference between sequence and random trials was greater in controls than in patients. Marvel et al. suggested that response accuracy might be a more sensitive measure of group differences in sequence learning than RT when targets are presented centrally. Thus Stevens et al. might have found impaired sequence learning in patients had they analysed response accuracy and extended training beyond one session. More work is required to establish whether sequence learning is impaired in patients when targets are presented centrally. This version of the SRTT certainly deserves more attention. Group differences in the expression of sequence knowledge could be less of an issue with the central version of the SRTT than with the spatial version of the SRTT.

One might argue that patients have difficulty learning stimulus-response mappings and that this difficulty could interfere with sequence learning or with the expression of sequence knowledge in the central version of the SRTT. This seems unlikely for two reasons. First, Marvel et al. (2005) found that the decrease in RT with practice in patients was similar to that in controls. This suggests that patients were learning the stimulus-response mappings at a rate comparable to that of controls. Second, increasing the difficulty of stimulus-response mappings does not negatively affect sequence learning (Deroost & Soetens, 2006; Schwarb & Schumacher, 2010). Nonetheless, it would be useful to determine whether sequence learning is impaired in patients when there is no visual stimulus that needs to be mapped onto a response. This could be achieved by using vibrotactile stimulation of the response fingers as the stimulus (e.g., Abrahamse et al., 2009).

The effect of antipsychotic medication on implicit sequence learning

Five of the six studies that found normal sequence learning in patients used a sample in which all of the patients were taking only atypical neuroleptics (Foerde et al., 2008; Karatekin et al., 2009; Reiss et al., 2006; Stevens et al., 2002) or no medication at all (Purdon et al., 2011). Patient medications, when reported, were olanzapine (Stevens et al., 2002) and predominantly risperidone (Foerde et al., 2008). In contrast, some of the studies that found impaired sequence learning in patients used a sample in which a substantial number of patients were taking typical neuroleptics. There is evidence that typical neuroleptics can impair sequence learning (Kumari et al., 1997; Stevens et al., 2002). However, two relatively large studies that found impaired sequence learning in patients used a sample in which all (Pedersen et al., 2008) or the vast majority (89%; Marvel et al., 2007) of the patients were taking only atypical neuroleptics. Patient medications, when reported, were predominantly quetiapine and clozapine (Pedersen et al., 2008). Also, Zedkova et al. (2006) found normal sequence learning in a sample of
patients where 30% were taking typical neuroleptics. Thus treatment with typical neuroleptics does not completely account for impaired sequence learning in patients.

Table 1 lists three pairs of studies. Each study used a response-triggered offset and found impaired sequence learning in patients. Studies within a pair were methodologically similar. Despite the fact that all patients in the first study of the first pair were taking only atypical neuroleptics and the vast majority of patients in the second study were taking typical neuroleptics, the per cent reduction in sequence learning in patients relative to controls increased only slightly from 31% to 41% across the two studies. The second pair of studies reveals a similar pattern. It is also noteworthy that the magnitude of sequence learning in patients was not statistically different from zero in both studies. Finally, across the two studies in the third pair, the percentage of patients taking typical neuroleptics increased from 21% to 38% and the per cent reduction in sequence learning in patients relative to controls decreased from 56% to 51%. Thus, cross-study comparisons suggest that, relative to atypical neuroleptics, typical neuroleptics do not substantively increase the magnitude of the sequence learning impairment in patients.

Five of the six studies that found normal sequence learning in patients reported mean drug dosages of 0, 287, 330, 422, and 425 mg/day chlorpromazine equivalent (see Table 2). Six of the eight studies that found impaired sequence learning in patients reported mean dosages of 410, 416, 510, 531, 581, and 955 mg/day chlorpromazine equivalent. Although the former dosages tend to be smaller than the latter dosages, there is

1 Dopamine D2 receptor blockade has been posited as the reason that typical neuroleptics interfere with sequence learning (Kumari et al., 1997; Stevens et al., 2002). Risperidone is an atypical neuroleptic with a D2 receptor affinity profile comparable to that of typical neuroleptics like haloperidol (Horacek et al., 2006). Also, a randomized double-blind study reported that the magnitude of sequence learning in patients receiving risperidone was equivalent to that in patients receiving haloperidol (Kern et al., 1998). Thus in the context of sequence learning, risperidone acts like a typical neuroleptic. It is noteworthy then that Foerde et al. (2008) found normal sequence learning in a sample of patients where 60% were taking risperidone.
some overlap. Thus drug dosage does not completely account for impaired sequence learning in patients.

There is also no evidence that drug dosage is negatively correlated with sequence learning. Studies that have examined the correlation between dosage and sequence learning have consistently found nonsignificant correlations (see Table 2). The large variability in dosage across patients in these studies, as indicated by the standard deviations, suggests that the nonsignificant correlations are probably not the result of restriction of range. Alternatively, the relationship between dosage and sequence learning

<table>
<thead>
<tr>
<th>Study</th>
<th>SL</th>
<th>SRTT</th>
<th>MTO</th>
<th>Dos (^d)</th>
<th>rDos (^e)</th>
<th>Dur (^f)</th>
<th>rDur (^g)</th>
<th>rSym (^h)</th>
<th>Aware (^i)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green et al. (1997)</td>
<td>I</td>
<td>S</td>
<td>R</td>
<td>–</td>
<td>–</td>
<td>19.7</td>
<td>ns</td>
<td>ns</td>
<td>–</td>
</tr>
<tr>
<td>Kumari et al. (2002)</td>
<td>I</td>
<td>S</td>
<td>R</td>
<td>410</td>
<td>–</td>
<td>10.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Schwartz et al. (2003)</td>
<td>I</td>
<td>S</td>
<td>R</td>
<td>955</td>
<td>ns</td>
<td>18.5</td>
<td>ns</td>
<td>ns</td>
<td>C-Y, P-Y, C = P</td>
</tr>
<tr>
<td>Exner, Weniger, et al. (2006)</td>
<td>I</td>
<td>S</td>
<td>R</td>
<td>416</td>
<td>ns</td>
<td>0.0</td>
<td>–</td>
<td>ns</td>
<td>C-N, P-N, C = P</td>
</tr>
<tr>
<td>Marvel et al. (2007)</td>
<td>I</td>
<td>S</td>
<td>R</td>
<td>531</td>
<td>ns</td>
<td>11.9</td>
<td>ns</td>
<td>ns</td>
<td>C-N, P-Y, C &lt; P</td>
</tr>
<tr>
<td>Pedersen et al. (2008)</td>
<td>I</td>
<td>S</td>
<td>R</td>
<td>581</td>
<td>ns</td>
<td>4.0</td>
<td>ns</td>
<td>ns</td>
<td>C-Y, P-Y, C = P</td>
</tr>
<tr>
<td>Reiss et al. (2006)</td>
<td>N</td>
<td>S</td>
<td>T</td>
<td>330</td>
<td>ns</td>
<td>11.5</td>
<td>–</td>
<td>ns</td>
<td>C = P (^j)</td>
</tr>
<tr>
<td>Zedkova et al. (2006)</td>
<td>N</td>
<td>S</td>
<td>T</td>
<td>422(^k)</td>
<td>–</td>
<td>11.5</td>
<td>–</td>
<td>ns</td>
<td>–</td>
</tr>
<tr>
<td>Foerde et al. (2008)</td>
<td>N</td>
<td>S</td>
<td>T</td>
<td>287</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Karatekin et al. (2009)</td>
<td>N</td>
<td>S</td>
<td>T</td>
<td>–</td>
<td>–</td>
<td>2.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Purdon et al. (2011)</td>
<td>N</td>
<td>S</td>
<td>T</td>
<td>–</td>
<td>0.0</td>
<td>–</td>
<td>ns</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Stevens et al. (2002)</td>
<td>N</td>
<td>V</td>
<td>R/T(^m)</td>
<td>425</td>
<td>ns</td>
<td>4.1</td>
<td>–</td>
<td>ns</td>
<td>–</td>
</tr>
</tbody>
</table>

Note. Dashes indicate that the information was not available.

\(^a\)SL = Sequence learning in schizophrenia patients (I = impaired, N = normal).

\(^b\)SRTT = Type of serial reaction time task (S = standard, V = variant).

\(^c\)MTO = Method of target offset (R = response-triggered, T = time-triggered).

\(^d\)Dos = Mean drug dosage (in mg/day chlorpromazine equivalent).

\(^e\)rDos = Correlation between drug dosage and sequence learning (ns = not significant).

\(^f\)Dur = Mean illness duration in years (0.0 = first-episode).

\(^g\)rDur = Correlation between illness duration and sequence learning (ns = not significant).

\(^h\)rSym = Correlation between symptom severity and sequence learning (ns = not significant).

\(^i\)Was there any evidence of awareness of the sequence in controls (C) and patients (P; Y = yes, N = no) and what was the difference in the level of awareness (C > P, control greater than patient; C < P, control less than patient; C = P, control equal patient)?

\(^j\)The authors did not report whether there was significant awareness in controls and patients.

\(^k\)Raw dosages were converted to chlorpromazine equivalents using the ratios in Woods (2003).

\(^l\)The authors used multiple measures of awareness with one indicating C < P and another indicating C > P.

\(^m\)Reaction times (RTs) <700 ms produced a response-triggered offset and RTs >700 ms produced a time-triggered offset.
might be nonlinear, thereby reducing the ability to detect a significant correlation. Stevens et al. (2002) visually inspected their data and found no evidence of a nonlinear relationship between dosage and sequence learning. The nonsignificant correlations could reflect inadequate power because of small sample sizes. Unfortunately, only two studies reported the magnitude of the correlation and so it is difficult to get a general sense of the magnitude. The magnitudes, when reported, were small \(- r = -0.051\) (Exner, Boucsein, et al., 2006) and \(r = -0.22\) (Stevens et al., 2002). Finally, a randomized double-blind study by Kern et al. (1998) found no difference in sequence learning between a group of patients receiving 6 mg/day risperidone (300 mg/day chlorpromazine equivalent; Woods, 2003) and a group of patients receiving 15 mg/day haloperidol (750 mg/day chlorpromazine equivalent).

Studies by Stevens et al. (2002) and Kumari et al. (1997) are often cited as evidence that typical neuroleptics can impair sequence learning. However, the studies do have limitations. Stevens et al. found that sequence learning was impaired in patients receiving only typical neuroleptics relative to patients receiving only atypical neuroleptics. However, patients were not randomly assigned to medication condition. Also, the typical group probably experienced a greater number of time-triggered offsets than did the atypical group because (1) RTs < 700 ms produced a response-triggered offset and RTs > 700 ms produced a time-triggered offset; and (2) the typical group had a greater mean RT and standard deviation than did the atypical group. Thus the method of target offset was likely not equivalent across the two groups. Finally, error rate increased with training in the typical group, but not in the atypical group suggesting that the former, but not the latter, was having progressively more trouble performing the SRTT as training progressed. This could have reflected possible group differences in motivation or attention span.

Kumari et al. (1997) found significant sequence learning in normal individuals taking a placebo and nonsignificant sequence learning in normal individuals taking a typical neuroleptic. However, the magnitude of sequence learning did not differ significantly across the two groups. Thus the results were mixed. Also, overall RT decreased with training in the placebo group and increased with training in the typical group suggesting that the latter, but not the former, was having progressively more trouble performing the SRTT as training progressed. This is the only study to observe an increase in overall RT with training in medicated individuals. All SRTT studies of medicated schizophrenia patients that have reported RT as a function of training have observed a decrease in overall RT with training. Kumari et al. noted that individuals in the typical group tended to experience side effects (e.g., the need for frequent urination). Thus general discomfort in the typical group may have led to reduced motivation or attention span relative to the placebo group. Finally, Kumari et al. did not establish whether the nonsignificant sequence learning in the typical group was due to impaired sequence learning or to an impairment in the expression of sequence knowledge. This could have been established by allowing the typical neuroleptic to wear off and then testing for sequence knowledge in both groups. Equivalent sequence knowledge in both groups in the test phase would have suggested that the typical neuroleptic impaired the expression of sequence knowledge. Conversely, greater sequence knowledge in the placebo group than in the typical group in the test phase would have suggested that the typical neuroleptic impaired sequence learning.

More research is required to better understand the impact of different neuroleptics and drug dosages on sequence learning. Ideally, patients and controls should be randomly assigned to different neuroleptics and drug dosages, and the effects of drug type and drug.
dosage on sequence learning and the expression of sequence knowledge assessed. Also, using animal models of sequence learning could further our understanding of drug effects on sequence learning and the expression of sequence knowledge. Animal versions of the SRTT have been developed for rodents (Schwarting, 2009) and nonhuman primates (Heimbauer, Conway, Christiansen, Beran, & Owren, 2012).

The effect of illness duration and symptom severity on implicit sequence learning

Seven of the eight studies that found impaired sequence learning in patients reported mean illness durations of 0 (first-episode), 1.5, 4.0, 10.5, 11.9, 18.5, and 19.7 years (see Table 2). Five of the six studies that found normal sequence learning in patients reported mean illness durations of 0, 2.0, 4.1, 11.5, and 11.5 years. Given the large overlap in the two sets of durations, it is clear that illness duration does not account for impaired sequence learning in patients. Also, studies that have examined the correlation between illness duration and sequence learning have consistently found nonsignificant correlations (see Table 2). Unfortunately, the magnitudes of the correlations were not reported.

Eleven studies examined the correlations between the severity of various symptoms and sequence learning (see Table 2). The 11 studies each examined three correlations for a total of 33 correlations. Of the 33 correlations, 31 were not significant and two were significant. Thus there is no evidence of a relationship between symptom severity and sequence learning. The magnitudes of 29 of the 33 correlations were not reported. Exner, Boucsein, et al. (2006) found that patients were impaired at sequence learning during the acute phase of the disorder and unimpaired after symptoms had largely remitted. Thus the presence of symptoms, regardless of severity, may dictate whether sequence learning is impaired in patients. Consistent with this view is evidence that sequence learning may be normal in unaffected siblings of patients (Woodward, Tibbo, & Purdon, 2007). However, that study used a time-triggered offset and so it is not clear whether sequence learning was truly normal because of the absence of symptoms or sequence learning was truly impaired and the impairment masked by the method of target offset. More research is required to establish whether sequence learning in patients is affected by the presence of symptoms.

It is worth noting here that the study of unaffected relatives of patients could be informative. If sequence learning is impaired in unaffected relatives, then this would suggest that impaired sequence learning is a core deficit of schizophrenia. Conversely, if sequence learning is normal in unaffected relatives and impaired in patients, then this would suggest that impaired sequence learning in patients is the result of disease progression or medication.

Sequence awareness

Six of the eight studies that found impaired sequence learning in patients assessed awareness of the sequence following the SRTT (see Table 2). In no case was the level of awareness significantly greater in controls than in patients. Patients developed some awareness of the sequence in four of the studies, whereas controls developed some awareness in two of the studies. Thus the greater sequence learning in controls than in patients cannot be explained by greater sequence awareness in controls than in patients.

Two studies have examined the correlation between sequence awareness and sequence learning (Exner, Boucsein, et al., 2006; Marvel et al., 2007). In both studies,
the correlation was not significant for controls, but was significant and positive for patients. This suggests that patients may be more likely than controls to engage the explicit sequence learning system or to use explicit sequence knowledge while performing the SRTT.

What types of sequential information do patients have difficulty learning?

If sequence learning is impaired in patients, the method that studies have used to assess sequence learning makes it very difficult to determine the specific types of information that patients have difficulty learning. All studies assessed sequence learning in patients and controls by comparing RT performance on sequenced (S) trials to that on pseudorandom (R) trials. Unfortunately, the structure of S trials differed from the structure of R trials in numerous ways, making it difficult to know precisely what information patients had difficulty learning. For example, Green et al. (1997) presented participants with the repeating sequence 4-2-3-1-3-2-4-3-2-1 (where numbers represent target locations) over the course of four, 100-trial blocks. The fifth block was pseudorandom with the constraints that each location did not repeat on consecutive trials and that locations 1, 2, 3, and 4 appeared 20, 30, 30, and 20 times, respectively, to match the relative frequencies in the repeating sequence. The structure of S trials differed from that of R trials with respect to Lag 1, Lag 2-1, and Lag 2-x conditional probabilities, and with respect to reversal proportion and full-coverage proportion. Each type of information is discussed next.

A Lag 1 probability is the probability of event \( E \) occurring on trial \( t \), given the occurrence of event \( A_1 \) on trial \( t - 1 \) (i.e., \( p[E|A_1] \)). For example, in Green et al. (1997), \( p(2|3) = .67 \) and \( p(4|3) = 0 \) on S trials, whereas \( p(2|3) = .45 \) and \( p(4|3) = .27 \) on R trials.\(^2\) A Lag 2-1 probability is the probability of event \( E \) occurring on trial \( t \), given the occurrence of events \( A_2 \) and \( A_1 \) on trials \( t - 2 \) and \( t - 1 \), respectively (i.e., \( p[E|A_2A_1] \)). For example, \( p(3|2-4) = 1.00 \) and \( p(2|2-4) = 0 \) on S trials, whereas \( p(3|2-4) = .43 \) and \( p(2|2-4) = .36 \) on R trials. Finally, a Lag 2-x probability is the probability of event \( E \) occurring on trial \( t \), given the occurrence of event \( A_2 \) on trial \( t - 2 \) (i.e., \( p[E|A_2x] \) where \( x \) is a placeholder). For example, \( p(2|1-x) = 1.00 \) and \( p(3|1-x) = 0 \) on S trials, whereas \( p(2|1-x) = .30 \) and \( p(3|1-x) = .29 \) on R trials.

A reversal is a three-element sequence in which the first and third elements are equal, but different from the second element (e.g., 1-2-1). A full-coverage run is a four-element sequence that covers all target locations (e.g., 4-2-1-3). In Green et al. (1997), the proportions of S trials that formed the last element of a reversal and a full-coverage run were .10 and .50 respectively. The respective proportions for R trials were .30 and .23.

People can learn Lag 1, Lag 2-1, and Lag 2-x probabilities (e.g., Remillard, 2008; Remillard & Clark, 2001). There is also evidence that people can learn the frequencies of reversals and full-coverage runs (Howard et al., 2004; Pronk & Visser, 2010; Reed & Johnson, 1994). Both controls and patients in Green et al. (1997) produced shorter RTs on S trials than on R trials, but the difference was greater for the controls than for the patients. Because learning any of the five types of information could have contributed to the shorter RTs on S trials than on R trials in controls, one cannot know what information patients had difficulty learning.

\(^2\)I generated 100, 100-trial pseudorandom blocks with the same two constraints imposed by Green et al. (1997) and then determined Lag 1, Lag 2-1, and Lag 2-x conditional probabilities over the 10,000 trials. The 10,000 trials were also used to determine reversal proportion and full-coverage proportion.
A number of studies that followed Green et al. (1997) employed a repeating second-order conditional sequence (e.g., 1-2-1-4-2-3-4-1-3-2-4-3) where each location occurs three times and each location is followed by every other location once. These studies, unfortunately, used pseudorandom sequences to test for sequence learning. Consequently, reversal proportion was considerably smaller and full-coverage proportion considerably greater on S trials than on R trials. Also, the structure of S trials differed from that of R trials with respect to Lag 2-1 and Lag 2-x probabilities.

Some studies have used a probabilistic sequence rather than a deterministic sequence. For example, Marvel et al. (2007) used the four quadrants of a 2 × 2 grid as target locations and constructed a sequence using three rules – a horizontal movement of the target is followed by a vertical movement, a vertical movement is followed by a diagonal movement, and a diagonal movement is followed by a horizontal movement. However, the location of the target on every fourth trial was random with the constraint that the location did not repeat on consecutive trials. If a random target location followed the rule set it was considered an S trial, otherwise it was an R trial. The R – S difference in RT was greater for controls than for patients. Unfortunately, it is not clear what information patients had difficulty learning because there were numerous types of information that controls could have learned that could have contributed to the R – S difference in RT. Controls could have learned the rule set or they could have learned Lag 2-1 probabilities because the two were confounded. For example, the sequence 1-4-2 (diagonal followed by horizontal) followed the rule set and \( p(2|1-4) = .84 \), whereas the sequence 1-4-3 (diagonal followed by vertical) did not follow the rule set and \( p(3|1-4) = .09 \). Alternatively, controls could have learned about the low reversal or full-coverage frequencies. The reversal and full-coverage proportions were .08 and .17 over all trials, but .50 and .50 on R trials respectively. Schwartz et al. (2003) also used a probabilistic sequence. In that study, learning Lag 2-1 probabilities, Lag 2-x probabilities, or about the low reversal frequency could have contributed to the R – S difference in RT in controls.

Finally, people have a learning-independent bias to respond more slowly and less accurately to the third element of a reversal than to that of a non-reversal (Anastasopoulou & Harvey, 1999; Curran, Smith, DiFranco, & Daggy, 2001; Howard et al., 2004; Vaquero, Jimenez, & Lupianez, 2006). In all of the patient studies of sequence learning, the reversal proportion on S trials was smaller than that on R trials. Thus the learning-independent bias is one more factor that could have contributed to the shorter RTs on S trials than on R trials in controls.

All patient studies of sequence learning to date have been unable to precisely determine what information patients have difficulty learning. This is because a learning-independent bias and learning any of a number of different types of information could have contributed to the shorter RTs on S trials than on R trials in controls. When using a deterministic sequence, R trials should be replaced with trials that are structurally equivalent to S trials except for the specific type of information under investigation. For example, S trials might be created using the training sequence S1 (1-2-1-4-3-2-4-1-3-4-2-3) and R trials replaced with the test sequence S2 (3-2-3-4-1-2-4-3-1-4-2-1). S1 and S2 differ only with respect to Lag 2-1 and Lag 2-x probabilities. S1 and S2 have identical Lag 1 probabilities, reversal proportions, and full-coverage proportions. Thus shorter RTs on S1 than on S2 would suggest that participants learned the Lag 2-1 or Lag 2-x probabilities in S1 (for an example of this approach, see Vaquero et al., 2006; Experiment 2). It is difficult to isolate a single type of information (e.g., Lag 2-1 probability) with deterministic sequences. Probabilistic sequences such as those employed by Remillard (2008) and Remillard and Clark (2001) permit the isolation of a single type of information.
A final note

The distinction between sequence learning (i.e., the acquisition of sequence knowledge) and the expression of sequence knowledge has long been recognized in the general SRTT literature. The distinction has not yet been made in the schizophrenia literature. Likewise, the use of structurally similar sequences S1 and S2 to assess sequence learning has become the gold standard in the general SRTT literature when working with deterministic sequences. The standard has not yet been adopted in the schizophrenia literature. Until investigators consider the expression of sequence knowledge and begin to use more rigorous methods to assess sequence learning, it will be difficult to determine (1) whether sequence learning is impaired in patients; (2) whether medications impair sequence learning; and (3) what types of sequential information patients have difficulty learning, if any. This review has offered suggestions for future research that, hopefully, will be useful in beginning to answer these three questions.

References


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