

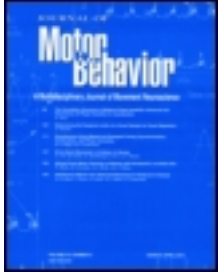
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### Verbal Implicit Sequence Learning in Persons Who Stutter and Persons With Parkinson's Disease

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## RESEARCH ARTICLE

# Verbal Implicit Sequence Learning in Persons Who Stutter and Persons With Parkinson's Disease

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**ABSTRACT.** The authors investigated the integrity of implicit learning systems in 14 persons with Parkinson's disease (PPD), 14 persons who stutter (PWS), and 14 control participants. In a 120-min session participants completed a verbal serial reaction time task, naming aloud 4 syllables in response to 4 visual stimuli. Unbeknownst to participants, the syllables formed a repeating 8-item sequence. PWS and PPD demonstrated slower reaction times for early but not late learning trials relative to controls reflecting delays but not deficiencies in general learning. PPD also demonstrated less accuracy in general learning relative to controls. All groups demonstrated similar limited explicit sequence knowledge. Both PWS and PPD demonstrated significantly less implicit sequence learning relative to controls, suggesting that stuttering may be associated with compromised functional integrity of the cortico-striato-thalamo-cortical loop.

**Keywords:** nonsense syllables, Parkinson's disease, serial reaction time, sequence learning, SRT, stuttering

**P**rocedural memory, or implicit memory, is relatively automatic, involves knowledge of cognitive or motor procedures (riding a bike), and develops over practice (Saint-Cyr, 2003). Implicit sequence learning is an example of procedural learning where participants learn to combine known movement components into a sequence but are unable to verbally describe the sequence (Nissen & Bullemer, 1987).

Implicit sequence learning is acknowledged as a relatively independent functional brain system associated with specific structures and connections (particularly the basal ganglia and cortico-striato-thalamo-cortical connections; Doyon & Benali, 2005). There exists a well-established protocol for examining implicit sequence learning using manual (Nissen & Bullemer, 1987), and verbal serial reaction time tasks (Smith & McDowall, 2004; Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998). An extensive body of research suggests implicit sequence learning deficits are associated with Parkinson's disease (Siegert, Taylor, Weatherall, & Abernethy, 2006).

In general, persons with Parkinson's disease (PPD) demonstrate impaired implicit learning but relatively good explicit (recall and recognition) learning skills. In contrast, patients with intact striatal systems (e.g., Alzheimer's disease) have relatively good implicit learning but poor explicit learning, due to damage in the hippocampal region (Saint-Cyr, Taylor, & Lang, 1988). These double-dissociation studies emphasize the importance of the striatal system, relative to the hippocampal system, for implicit learning-type tasks. It should be emphasized that both systems can be affected by pathology, and other areas of

the brain (e.g., the cerebellum) are also active in implicit learning (Sanes, Dimitrov, & Hallett, 1990).

Serial reaction time tasks have reliably found poor implicit sequence learning in patients with impaired striatal systems such as Huntington's disease (Saint-Cyr et al., 1988) and Parkinson's disease (Siegert et al., 2006) for both speech (Smith & McDowall, 2004; Westwater et al., 1998) and non-speech tasks (Siegert et al., 2006). This is unsurprising due to the striatal system deficits shared by these populations. Researchers have suggested implicit sequence learning impairments associated with Parkinson's disease are likely independent of dopaminergic medication (Feigin et al., 2003; Muslimovic, Post, Speelman, & Schmand, 2007).

Many researchers have proposed dysfunction within the cortico-striato-thalamo-cortical circuit as a possible etiological factor in stuttering. This hypothesis is based on comparisons of PPD and persons who stutter (PWS) in many areas including brain activity patterns during neuroimaging, sequencing performance, and speech symptoms (Smits-Bandstra & De Nil, 2007). PWS have demonstrated some evidence of *explicit* sequence learning deficits relative to fluent speakers for both finger-tapping sequences (Smits-Bandstra, De Nil, & Rochon, 2006; Smits-Bandstra, De Nil, & Saint-Cyr, 2006; Webster, 1986), and verbal sequences (Cooper & Allen, 1977; Ludlow, Siren, & Zikira, 1997; Smits-Bandstra & De Nil, 2009). However, the implicit sequence learning capabilities of PWS have not been investigated. If PWS and PPD demonstrate similar deficits on an implicit sequence-learning task known to involve the cortico-striato-thalamo-cortical loop, this would provide information regarding possible etiological factors of stuttering. Therefore, the primary objective of the present study was to compare implicit sequence learning of a nonsense syllable sequence in PWS, PPD, and control participants.

## Method

### Participants

Participant information is presented in Tables 1 and 2. Written informed consent was obtained and all participants were treated according to ethical treatment of human participant guidelines established by McGill University, the

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**TABLE 1. Participant Information and Screening Test Scores**

Group	Control	PWS	PPD
Sample size	14 (6♀)	14 (6♀)	14 (7♀)
Age ( <i>M, SD</i> )	65.5 (5.6)	65.1 (5.7)	64.5 (6.9)
Years from diagnosis	—	Childhood onset	8 (1–5 years), 6 (6–12 years)
Medication	None	None	Anti-Parkinson's
Handedness	14 R	14 R	13 R, 1 Ambidex.
Forward digit span	12.1 (2.3)	12.1 (1.9)	11.4 (2.1)
Backward digit span	8.9 (2.4)	8.5 (2.1)	8.1 (2.2)
SSI-IV (10–17 = very mild)	—	10.3 (7.2)	2.8 (2.7)
MMSE (out of 30)	—	—	29.6 (0.5)
BDI (normal = less than 6)	—	1.3 (1.8)	0.2 (0.6)

*Note.* Screening measures included the Edinburgh Handedness Inventory (Oldfield, 1971), the Verbal Digit Span Subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997), the Stuttering Severity Index 4 (SSI-IV; Riley, 2009), the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), and the Beck Depression Inventory (BDI; Beck, Epstein, Brown, & Steer, 1988). Diagnosis of idiopathic Parkinson's disease by a licensed neurologist was based on the presence of a rigidity-akinesia syndrome, and responsiveness to levodopa, without signs of pyramidal, cerebellar, or oculomotor deficits. All participants were screened for hearing, vision, medication use, neurological and motor control difficulties, and speech and language difficulties. Participants who received speech therapy within the previous six months were excluded. PWS = persons who stutter; PDD = persons with Parkinson's disease.

University of Toronto, and the Baycrest Centre in Toronto. A total of 14 control participants, 14 PWS, and 14 PPD self-selected to participate in the study by responding to support group web page advertisements as well as poster advertisements placed on campuses, in nursing homes, in outpatient centers and in hospitals of Quebec and Ontario. Neurologists and speech language pathologists at the Montreal Neurological Hospital and the Baycrest Centre in Toronto served as initial contacts to PPD who met eligibility requirements.

PWS were also identified using Dr. Gracco's database of stuttering subjects who participated in past studies and gave written informed consent to participate in other studies.

PPD were outpatients with idiopathic Parkinson's disease. Diagnosis by a licensed neurologist was based on the presence of a rigidity-akinesia syndrome responsive to levodopa, without signs of pyramidal, cerebellar, or oculomotor deficits. All PPD were tested during the ON-cycle of their medication within 60–90 min of their last dose.

**TABLE 2. Screening Information for Persons With Parkinson's Disease**

Subject	Dysarthria characteristics	Stage H&Y	Speech UPDRS	Anti-Parkinson's medication
1	–Loud, +Harsh	2	2	Levodopa, Carbidopa
2	+Tremor, + Harsh	1	0	Levodopa, Comtan
3	+Tremor, –Loud	1	1	Recrit, Sinemet, Comtan
4	–Loud, –Variation	1	0	Sinemet
5	–Loud, –Rate	3	2	Levodopa, Amantadine, Comtan
6	+Pitch, +Harsh	3	2	Not disclosed
7	+Rate, + Harsh	2.5	1	Sinemet, Mirapex
8	+Rate, + Harsh	1	0	Levodopa, Carbidopa, Amantadine, Sinemet, Comtan, Mirapex
9	+Harsh, –Precision	1	1	Levodopa, Carbidopa
10	+Rate, +Nasal	1	0	Levodopa, Carbidopa, Pmantadine, Parsitan
11	–Loud, +Rate	1	0	Levodopa, Carbidopa
12	–Rate, –Loud	1	0	Levocarb, Mirapex, Selegiline
13	+Rate, –Precision	3	2	Levodopa, Sinemet, Comtan
14	+Rate, –Loud	1	0	Levodopa, Sinemet, Requip

*Note.* Patient's medication is self-reported. Specific dosage information was not collected. Persons with Parkinson's disease were tested within 60–90 min of their last dose of medication. H&Y = Modified Hoehn & Yahr scale (Hoehn & Yahr, 1967), UPDRS = Unified Parkinson's Disease Rating Scale Section II (activities of daily living), subsection 5 (speech; Fahn, Elton, & Members of the UPDRS Development Committee, 1987).

Because dopaminergic treatment speeds up the execution of motor sequences (Benecke, Rothwell, Dick, Day, & Marsden, 1986), we specifically studied medicated patients to minimize bradykinesia at baseline.

All PWS and PPD were screened for depression. All PPD were screened for mental state. All participants were screened for forward and backward digit span, hearing, vision, medication use (other than PPD medication), neurological and motor control difficulties (other than PD), and speech and language difficulties (other than those associated with PD or stuttering). PWS and PPD who had received speech therapy within the last 6 months were excluded, as these treatments typically teach slowed rate of speech which may have interfered with the task.

### Procedures

All participants completed the screening tests, training trials and the experimental protocol in one 120-min session. There were 16 training trials in which no data were collected. Participants were instructed to say aloud one of four syllables when an X appeared over one of four horizontal lines on a computer screen. For example, participants said PA when an X appeared above the top left line on the screen, PE for top right, PI for bottom left, and PO for bottom right. In the first eight trials the correct syllable appeared below the X as a learning cue. The investigator provided accuracy feedback to the participant immediately after each trial by saying aloud whether the trial was correct or incorrect (e.g., “Good,” “Oops, that was a PA”).

Stimuli for the experiment were presented on a 15-inch laptop screen with a viewing distance of 18–20 inches. Unlike the training trials, in the experimental practice trials participants were only presented with an X, without any cues or syllables below. Each trial was followed by a jittered interstimulus interval of 3600–3900 ms. Catch trials, in which the alerting cue and tone were presented but no imperative cue appeared, were interspersed among trials. Jittered interstimulus intervals and catch trials were used to prevent anticipatory reaction times.

Participants were instructed to respond immediately upon seeing the stimulus (X) by saying aloud the correct corresponding syllable (PA). Stimuli were presented using the Presentation 0.8 (Neurobehavioral Systems, 2004) software program. Unknown to the participants, the stimulus locations appeared in a predictable sequence of eight locations or syllables (i.e., PO PI PO PE PI PA PE PA). Participants practiced each sequence nine times per block for a total of four blocks (288 trials). Trials in Block 5 were random, with the constraint that no syllable was repeated (e.g., PA PA). The order of the sequence and random trials is shown in Appendix A.

No feedback was provided during the experiment with the exception that, after every 16–24 trials, a reminder was presented on the computer monitor. Identical to the training trials, the reminder briefly showed the correct syllable under each X location. Error data for those participants who made

consistent and persistent errors and did not remediate after a reminder were excluded from the analyses (see Dependent Variables section). If the reminder was not attended to the investigator came into the session during a scheduled break and provided direct instruction (e.g., “If the X appears here you need to say PI”). No effort was made to differentiate reaction times that followed reminders or errors for the present analyses.

Participants completed the Day One explicit learning questionnaire after the experiment (see Appendix B). Similar to previous research (Eimer, Goschke, Schlaghecken, & Sturmer, 1996; Ghilardi et al., 2007; Russeler & Rosler, 2000), the questionnaire presented two-, three-, and four-syllable portions of the sequence so as not to underestimate explicit knowledge of parts of the sequence.

### Dependent Variables

The dependent variables, accuracy and reaction time, are well established in the neuroscientific literature as important indicators of skill learning. Inaccuracy was defined as incorrect syllable substitutions resulting from an incorrect vowel (e.g., PA for PE). PPD were in early stages of the disease with well-preserved speech skills (see Table 2). Dysarthria, voicing errors, or distorted articulation of the initial consonant did not noticeably affect single syllable productions for these patients. All productions were categorized as correct productions or incorrect substitutions.

An entire block was removed if there were three consecutive presentations or 4 out of 5 presentations when the same incorrect syllable (e.g., PI) was substituted in place of the correct syllable (e.g., PE), indicating the participant had forgotten the instructions during training. In these cases, participants typically made the same substitution consistently throughout the block.

Disfluencies were defined as silent blocks or any repeated, prolonged, or effortful sounds or syllables observed on-line, through videotape recordings, or through waveform acoustic analyses by Speech Analyzer 3.0.1 (SIL, 2007). Disfluencies were omitted from accuracy and reaction time analysis.

Inordinately long or short reaction times were categorized as outliers ( $\pm 2$  standard deviations from each group mean) and were removed from analysis. Minimum and maximum reaction times were set a priori at  $\pm 2$  standard deviations to eliminate reaction times shortened by anticipation or lengthened by inattention. One reason for the removal of these outliers was to control for akinesia or speech freezing in PPD.

Syllable reaction time was measured as the time (ms) from the onset of the stimulus presentation to the voice onset of the syllable. Participants' speech was recorded using a dual channel digital audio tape recorder (Tascam DA-01, Mississauga, Ontario, Canada) with 16-bit resolution and 48 kHz sampling rate. Reaction times were calculated off-line using the waveform acoustic analysis software program Speech Analyzer 3.0.1 (SIL, 2007).

## Questionnaires

Explicit questionnaire score was a dependent variable reflecting the extent to which sequencing performance could be accounted for by explicit rather than implicit knowledge. For the Day One questionnaire (see Appendix B), participants were awarded single points for portions of the sequence they correctly identified as occurring always or often. Additional single points were awarded for sequence violations correctly identified as occurring rarely or never.

## Data Analysis

Reaction times were a reflection of general (nonspecific) learning, meaning they included aspects of implicit sequence learning, general task adjustment, and stimulus-response learning (PA = lower left corner). General learning was inferred from a gradual reduction in reaction time over practice. Reaction time means from the first eight or nine<sup>1</sup> trials of Blocks 1–4 were compared to assess general learning.

It was decided a priori that means would be taken from the beginning of each practice block to observe the process of sequence learning, particularly as it progressed from early trials in Block 1. Experience with data collected in previous studies (Smits-Bandstra et al., 2006; Smits-Bandstra et al., 2009) indicated that averaging trials across entire blocks masked important early changes noted for these populations.

In order to separate general learning from implicit (sequence-specific) learning, two different analyses were conducted. In past experiments implicit learning was assessed by comparing reaction times of a practice block (sequence trials) to reaction times of a random block. Random trials were typically presented last in the experiment to control for practice effects. Shorter reaction times for the practice block relative to the random block, despite practice effects, was thought to reflect anticipation associated with implicit knowledge of the sequence. The mean reaction time of trials 2–9 (trial 1 was eliminated, see note 1 and Appendix A) of practice Block 4 and the first eight trials of random Block 5 were included in the analyses. This traditional analysis is referred to as Block 4 versus Block 5 contrasts in the Results section.

This traditional analysis is problematic, however, because many of the syllables in the random block happened to fall into pairs or triplets that conformed to the sequence. Recently, researchers proposed the use of probability as a more sensitive indicator of implicit learning of pair-wise and other higher-order associations within a sequence. Wilkinson and Jahanshahi (2007) compared reaction time for frequent (sequence) items to rare (sequence violation) items. They demonstrated that the reaction time of the second syllable in each sequence pair captured the anticipation associated with implicit learning effectively.

Probability-based analysis was conducted in the present study. Based on Wilkinson and Jahanshahi's (2007) probability-based analyses, random block (Block 5) trials

were divided into syllable pairs that conformed to the sequence (SEQ) or violated the sequence (RAN). The first eight RAN trials and the first eight SEQ trials of Block 5 were included in analyses (see Appendix A). This probability-based analysis is referred to as SEQ versus RAN contrasts in the Results section.

## Reliability

The kappa coefficient for agreement with an independent rater on the occurrence of disfluencies versus inaccuracies was 96.7%, and 99.9%, respectively, based on 10% of the sequences. An independent trained rater, blind to the conditions of the study, reanalyzed 10% of the participants' acoustic waveforms to determine reaction time. Occurrence agreement interrater reliability for cursor placement to determine reaction time within 10 ms was 98% ( $r = .99$ ,  $r^2 = .98$ ).

## Results

### Accuracy for General (Nonspecific) Learning

Control participants, PWS, and PPD had 7.9%, 7.4%, and 7.4% excluded trials (yawns, sneezes, equipment glitches), respectively. Despite investigators' efforts, one control participant dozed occasionally during the experiment (eyes closed and lack of response). These 70 (excluded) trials were not included in the previous sum. As this participant was one of the fastest controls, his remaining trials had minimal if any negative effect on the group score. Disfluencies were omitted from analysis. Control participants, PWS, and PPD had 70, 109, and 187 of trials excluded as disfluent, respectively.

Ten controls, 11 PWS, and 10 PPD had complete accuracy data sets for the Group (3)  $\times$  Block (4) analysis of variance (ANOVA). Analysis was completed using 47 blocks for controls, 46 blocks for PWS, and 52 blocks for PPD (see Dependent Variables section). A logarithmic transformation of the data was successful in equalizing the group variances for three of four Levene's tests. A significant block main effect was found indicating accuracy improved from Block 1 to Block 4,  $F(2, 28) = 16.8$ ,  $p < .00$ ,  $\eta^2 = .38$ . A significant group main effect was also found,  $F(1, 28) = 4.4$ ,  $p < .02$ ,  $\eta^2 = .24$ . A between-groups least significant difference (LSD) post hoc test revealed PPDs' accuracy rate of 95.2% ( $SD = 3.8$ ) across blocks was significantly lower than that of control participants, 97.0% ( $SD = 3.3$ ) and PWS, 97.8% ( $SD = 2.2$ ). No other significant effects were found.

### Accuracy for Implicit Sequence-Specific Learning (Block 4 vs. Block 5)

Thirteen controls, 12 PWS, and 12 PPD had complete data sets for the Group (3)  $\times$  Condition (2: Block 4 vs. Block 5) ANOVA. Analysis was completed using 26 blocks for controls, 22 blocks for PWS, and 26 blocks for PPD. A logarithmic transformation of the data was successful in equalizing the group variances for one of two Levene's tests.

A significant condition main effect was found indicating accuracy was greater for Block 4 relative to Block 5,  $F(1, 34) = 2734.2, p < .00, \eta^2 = .98$ . No other significant effects were found.

### Accuracy for Implicit Sequence-Specific Learning (SEQ vs. RAN, Block 5)

Thirteen controls, 11 PWS, and 14 PPD had complete data sets for the Group (3)  $\times$  Condition (2: RAN vs. SEQ) ANOVA. Analysis was completed using 26 blocks for controls, 22 blocks for PWS, and 28 blocks for PPD. A logarithmic transformation of the data was successful in equalizing the group variances for one of two Levene's tests. No significant differences were found.

### Reaction Time for General (Nonspecific) Learning

Reaction time means were obtained from 14 control participants, 14 PWS, and 14 PPD. After excluded trials, disfluencies, errors, and outliers were eliminated (see Dependent Variables section) analysis was completed using 425 trials for controls, 432 trials, for PWS and 435 trials for PPD.

Mauchly's test indicated a violation of the assumption of sphericity, therefore the Greenhouse-Geisser adjusted degrees of freedom were used for comparisons. A Group (3)  $\times$  Block (4) ANOVA revealed a significant Block main effect indicating reaction times improved from Block 1 to Block 4,  $F(1.9, 39) = 68.2, p = .00, \eta^2 = .64$  (see Figure 1). A significant Group  $\times$  Block interaction was also found,  $F(3.8, 39) = 3.8, p = .03, \eta^2 = .16$ . No other significant effects were found.

Three Group (2)  $\times$  Block (4) post hoc ANOVAs were used to contrast the reaction times of controls versus PPD, controls versus PWS, and PPD versus PWS over practice blocks. A significant group main effect was found for controls versus PPD,  $F(1.7, 26) = 33.8, p = .00, \eta^2 = .57$ . A significant group main effect was found for controls versus PWS,  $F(1.9, 26) = 38.2, p = .00, \eta^2 = .60$ . A significant group main effect was found for PWS versus PPD,  $F(2.0, 26) = 72.5, p = .00, \eta^2 = .74$ . Two significant group by block interactions were found. This result indicated that controls' reaction times improved more quickly after practice relative to both PPD,  $F(1.7, 26) = 4.8, p = .04, \eta^2 = .16$ ; PWS,  $F(1.9, 26) = 6.3, p = .02, \eta^2 = .20$ , respectively. No other significant effects were found.

### Reaction Time for Implicit Sequence-Specific Learning (Block 4 vs. Block 5)

Reaction time means were obtained from 14 control participants, 14 PWS, and 14 PPD. Excluded trials, disfluencies, errors, and outliers were eliminated (see Dependent Variables section). Analysis was completed using 216 trials for controls, 221 trials for PWS, and 215 trials for PPD. A Group (3)  $\times$  Condition (Block 4 vs. Block 5) ANOVA revealed a significant condition main effect,  $F(1, 39) = 8.2, p = .01,$

$\eta^2 = .17$ . Block 4 reaction times were faster than Block 5 reaction times. No other significant effects were found.

### Reaction Time for Implicit Sequence-Specific Learning (SEQ vs. RAN, Block 5)

Reaction time means were obtained from 14 control participants, 14 PWS, and 14 PPD. After excluded trials, disfluencies, errors and outliers were eliminated (see Dependent Variables section) analysis was completed using 218 trials for controls, 224 trials for PWS, and 216 trials for PPD. A log transformation successfully equalized the error variance between groups. A Group (3)  $\times$  Condition (SEQ vs. RAN) ANOVA revealed a significant condition main effect,  $F(1, 39) = 8.2, p = .01, \eta^2 = .17$ . SEQ reaction times were faster than RAN reaction times. A significant condition by group interaction was also found,  $F(2, 39) = 3.3, p = .05, \eta^2 = .15$  (see Figure 2).

Data transformations were not successful in equalizing error variances between groups or normalizing the distributions for post hoc comparisons therefore nonparametric tests were used. Three independent samples Mann-Whitney  $U$  tests compared the difference scores (SEQ reaction time subtracted from RAN reaction time) of controls versus PPD, controls versus PWS, and PPD versus PWS. Control participants had significantly larger difference scores (SEQ was faster than RAN) relative to both PWS ( $z = -2.6, p = .01$ ) and PPD ( $z = -2.0, p = .05$ ). Controls, PWS, and PPD had average ranks of 18.6, 10.4, and 11.4, respectively, demonstrating the size of these significant effects. The difference scores of PWS relative to PPD were not significantly different.

### Explicit Questionnaires

Control participants, PWS, and PPD scored 3.1 ( $SD = 2.1$ ), 3.4 ( $SD = 1.8$ ), and 3.2 ( $SD = 1.8$ ) of 10, respectively, on the Day One questionnaire. A one-way ANOVA revealed that participant groups' scores did not significantly differ, and all groups performed near chance levels.

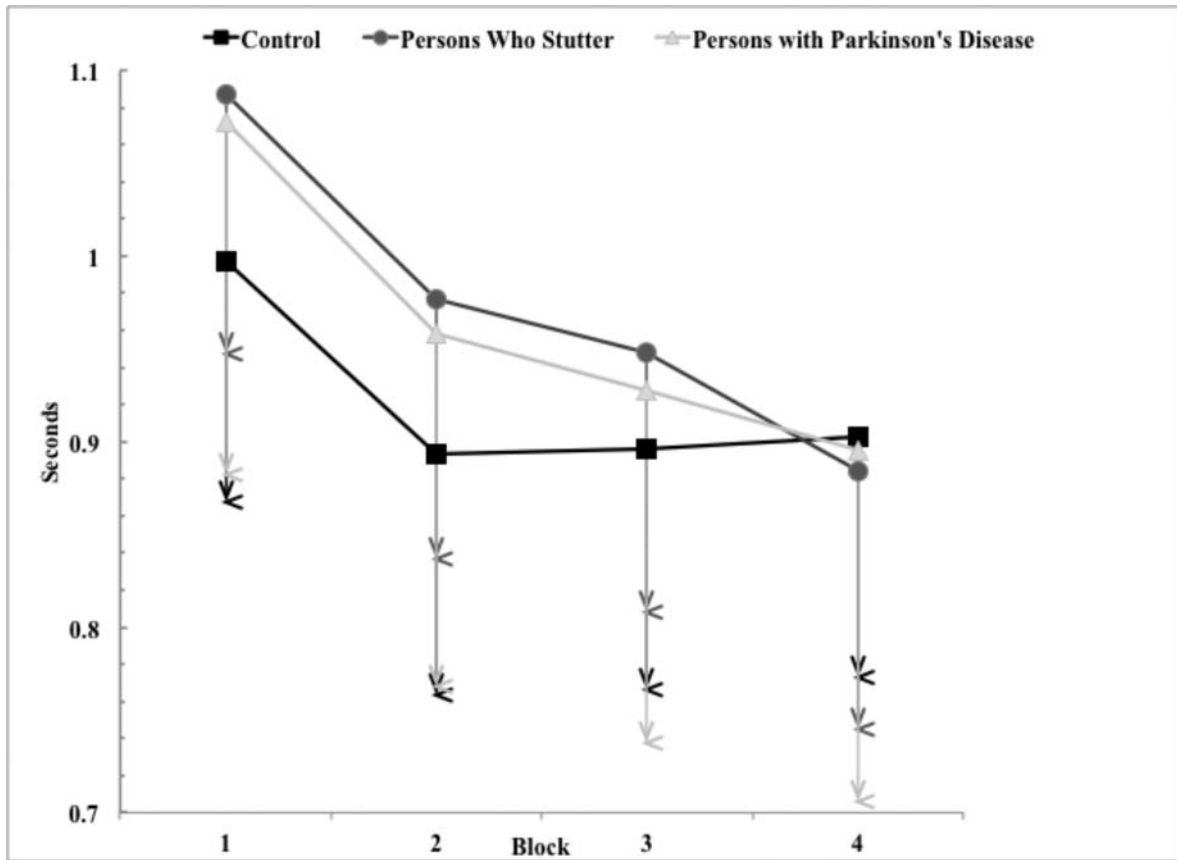
## Discussion

### Explicit Questionnaires

It has been shown that greater explicit knowledge is associated with better sequencing performance in healthy participants (Mayr, 1996), although not for PPD (Boyd & Winstein, 2006). No groups showed explicit knowledge, indicating better sequencing performance by any group was not likely due to a greater degree of explicit knowledge. The present study was limited in that there was no opportunity to observe changes in performance as explicit knowledge developed.

### Accuracy and Reaction Time for General (Nonspecific) Learning

All groups showed significant general learning, achieving a mean reaction time of approximately 900 ms by



**FIGURE 1.** Reaction time means in seconds for control participants, persons who stutter, and persons with Parkinson's disease for the initial eight trials of Blocks 1–4. The vertical lines at each point, capped with horizontal markers (<) are error bars. Error bars represent one standard deviation of intersubject variability unique to each group. Block 1 reaction time included trials 1–8; Blocks 2–4 reaction time included trials 2–9.<sup>1</sup>

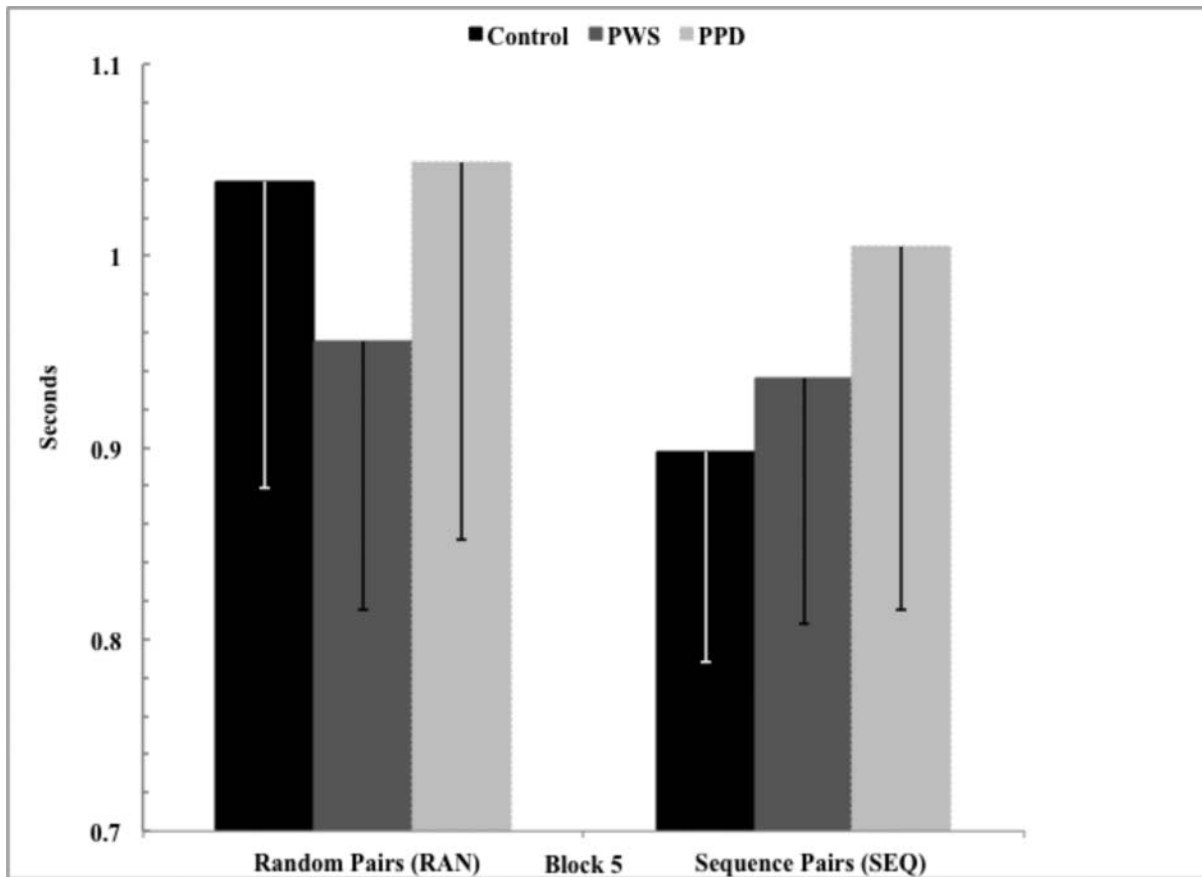
Block 4. This result suggested that PPD and PWS were not slower overall relative to controls. Our choice of early stage, medicated PPD appeared successful in minimizing akinesia/bradykinesia effects for motor execution of the sequence (Benecke et al., 1986).

In the present study PPD demonstrated significantly poorer accuracy in general learning over practice. These findings were in agreement with Wilkinson and Jahanshahi (2007) but in contrast with the findings of others. Smith and McDowall (2004) and Westwater et al. (1998) found slow reaction times rather than accuracy differences when comparing the general learning of PPD and controls.

One reason the present results concur with Wilkinson and Jahanshahi (2007) may be because participants in both studies were required first, to learn simple motor responses to a stimulus and second, to implicitly learn the sequence of responses. In the present experiment subjects learned to say an arbitrary symbol in response to a stimulus while in Wilkinson and Jahanshahi's study they were required to push a button. In Smith and McDowall's (2004) study and Westwater et al.'s

(1998) study, the stimulus-response task was already highly automated (e.g., Saying "one" upon seeing the number 1). It could be argued that the additional requirement of learning the stimulus-response pattern resulted in more difficulty and more likelihood of increased errors by PPD, as was found in the present study and in Wilkinson and Jahanshahi's study.

PPDs' and PWS' difficulties were limited to reaction time differences in early trials (Block 1 vs. Block 4; see Figure 1). This slow start has been noted for sequence learning (Smits-Bandstra & De Nil, 2009; Smits-Bandstra et al., 2006) and on previous reaction time studies (as reviewed by Smits-Bandstra, 2010) for PWS. PPDs' difficulty on early trials or acquisition of set has also been noted in previous studies (Saint-Cyr, 2003). During early trials participants use compiled sensory information to guide recognition and facilitation of appropriate preexisting learned movement patterns (synergies) while inhibiting irrelevant ones (Saint-Cyr, 2003). The critical role of the cortico-striato-thalamo-cortical circuit for this process is well established (Carbon & Eidelberg, 2006; Grafton, Hazeltine, & Ivry, 2002). Peigneux et al.



**FIGURE 2.** The reaction time means in seconds for Block 5 syllables in random pairs and Block 5 syllables in sequenced pairs are contrasted for control participants, persons who stutter, and persons with Parkinson's disease. The vertical lines within each column, capped with horizontal markers, are error bars. Error bars represent one standard deviation of intersubject variability unique to each group.

(2000) had 14 healthy patients complete a serial reaction time task while undergoing positron emission tomography scanning. They reported that the striatum was important for implicit automatization of serial information through prefrontal cortex-caudate nucleus networks. They further proposed that the striatum facilitated selection of the most appropriate responses within the context created by both the present and previous stimuli. In this way the striatum contributed to efficient quick response preparation for sequential tasks.

In light of Peigneux et al.'s (2000) research, PWS' and PPDs' shared difficulty in early stages of general learning on the serial reaction time task can be interpreted to suggest a potential functional impairment in cortex-caudate nucleus networks in both populations.

### Reaction Time for Implicit Sequence-Specific Learning

Block 4 reaction times were significantly faster than Block 5 reaction times. Similarly, SEQ reaction times were significantly faster than RAN reaction times. These results indi-

cated that our experimental manipulation was successful in eliciting implicit learning (Nissen & Bullemer, 1987). The probability-based comparisons (SEQ vs. RAN within Block 5) were more sensitive contrasts than the traditional comparison (Block 4 vs. Block 5) as indicated by significant group by condition interactions found solely in the former contrast.

PPD showed the expected pattern of slightly (but still significantly) slower reaction times on implicit (sequence-specific) learning tasks relative to controls found in previous studies (Smith & McDowall, 2004; Westwater et al., 1998). These smaller differences are in contrast to the large differences found for patients with cerebellar damage (Sanes et al., 1990).

The key interpretation of these results was that implicit sequence learning of PWS and PPD did not significantly differ; however, both groups demonstrated impaired implicit sequence learning relative to controls. These results can be interpreted to suggest a similar functional impairment evidenced by both PPD and PWS in translating the recognized implicit sequence associations into quicker motor responses.



In addition to their similarities, PWS and PPD significantly differed from each other in two ways in the present study. PWS had significantly better accuracy than PPD and PWS had significantly faster reaction times overall relative to PPD (averaged across blocks). Recent neuroimaging research presented in the Theoretical Implications section provides insight into whether differences between PWS and PPD may be due to structural deficits, functional deficits, or both.

### Theoretical Implications

Guenther and Perkell (2004) suggested that proficient sequence movements are typically performed in feed forward mode of motor control (i.e., automatized movements that are preplanned using an internal model). The feed forward mode is characteristic of a mature sensorimotor integration system and is proposed to be used when planned utterances are rapid and automatized (Max, Gracco, Guenther, Ghosh, & Wallace, 2003). A number of authors have hypothesized that both Parkinson's disease (Dominey et al., 1997; Fattapposta et al., 2002) and stuttering (Civier, Tasko, & Guenther, 2010; Max, 2004) are associated with an impaired feed forward mode and overreliance on the feedback mode of (speech) motor control. The critical role of the cortico-striato-thalamo-cortical loop in feed forward, automatized movements is well established in the literature (Graybiel, 1998).

As stated in the introduction, implicit sequence-learning tasks are known to involve the cortico-striato-thalamo-cortical loop (Carbon & Eidelberg, 2006; Grafton et al., 2002). Research has shown that Parkinson's disease and stuttering are associated with aberrances in structures within the cortico-striato-thalamo-cortical loop. Parkinson's disease is associated with structural differences (cell death of dopamine producing cells) in the substantia nigra of the midbrain while stuttering is associated with structural differences (white matter density/uniformity) underlying the left premotor and primary motor cortex (Sommer, Koch, Paulus, Weiller, & Buchel, 2002).

Multiple researchers have confirmed connectivity differences in PWS in the white matter underlying left premotor and primary motor cortices responsible for articulatory movements (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Sommer et al., 2002; Watkins, Smith, Davis, & Howell, 2008). In addition to these structural differences, Chang, Horwitz, Ostuni, Reynolds, and Lucknow (2011) and Lu et al. (2010) reported effective and functional connectivity differences in thalamo-cortical pathways between PWS and controls. These neuroimaging findings support Giraud et al.'s (2008) theoretical model in which white matter structural differences in stuttering result in negative functional consequences for the striatal system. We propose that similar deficits in general and implicit learning found for PWS and PPD in the present study may have reflected functional deficits in the cortico-striato-thalamo-cortical loop while differences found in overall speed and

accuracy may have been due to differences in *structural integrity*.

### Alternative Hypotheses

Smiley-Oyen, Lowry, and Kerr (2007) proposed that PPD may not take advantage of feed forward movement plans because of inherent movement variability. They proposed it was more advantageous for PPD to approach the movement sequence in a segmented fashion, anticipating only one or two targets in advance. There is evidence to suggest PWS and PPD share this problem of increased inherent movement variability. Results of many studies have confirmed this effect in the speech and nonspeech movements of PWS (Smith, Sadagopan, Walsh, & Weber-Fox, 2010; Smits-Bandstra, De Nil, & Rochon, 2006). It is possible to postulate that, for both of these populations, the stability of the system on any given day will determine how well learned sequences can be expressed as long sequences planned in advance of the movement. Motor learning and feed forward control may, in fact, be intact, but are only incompletely or sporadically expressed due to instability of the motor planning and execution systems. This tentative proposal requires further investigation.

Similarly, if attention and cognitive processing resources required for implicit sequence learning are diverted for speech motor execution, reduced implicit sequence learning results. Both PPD and PWS have demonstrated difficulties in the face of dual task demands (Smits-Bandstra & De Nil, 2007) indicating a need for further study of the effects of attention in this area.

### Clinical Implications

Several studies have been conducted to investigate the neural correlates of intensive training of the Lee Silverman Voice Treatment program for PPD (Fox, Ramig, Ciucci, Sapir, McFarland, & Farley, 2006; Narayana et al., 2010). These studies seem to suggest that while treatment is effective in changing behavior, the training required to institute such a change is intensive, supplemented by many types of feedback and frequent knowledge of results, and is not accompanied by the expected neural changes in the primary motor and sensory cortices (Karni et al., 1998). Instead, these studies report increased neural activity in areas associated with top-down (explicit) attention and monitoring, suggesting compensation and/or explicit strategy use rather than implicit learning per se (Fox et al., 2006; Narayana et al., 2010). This emphasis on monitoring may have evolved as a response to difficulties patients have transitioning to implicit learning as well as retaining proficiency for new speech patterns. Results of the present study suggest that further research is necessary to establish the optimal remediation approach (explicit vs. implicit focus) for patients for whom implicit learning is suspect.

## Conclusion

The purpose of this study was to compare the functional integrity of procedural learning and implicit memory systems in PPD, PWS, and control participants. The key finding of the present study was that implicit sequence learning of PWS and PPD did not significantly differ; however, both groups demonstrated impaired implicit sequence learning relative to controls. Both groups also demonstrated reaction time delays but not deficiencies in general learning relative to controls. In addition to these similarities, two significant differences were found between PWS and PPD. PPD demonstrated less accuracy and slower overall reaction times (averaged across practice) relative to both controls and PWS. Based on reviewed neuroimaging studies we proposed that similar deficits in general and implicit learning found for PWS and PPD in the present study may have reflected functional deficits in the cortico-striato-thalamo-cortical loop while differences found in overall speed and accuracy may have been due to differences in structural integrity.

The findings of the present study are sufficiently promising to embolden further research investigating implicit learning and retention in populations with motor speech disorders. As a next step, it will be necessary to investigate how the manipulation of variables such as explicit instruction, practice, and feedback will influence learning and retention in disordered populations. Future researchers must also have greater generalizability to functional speech tasks and speech treatment techniques than the present study.

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## NOTE

1. The mean reaction time of trials 1–8 was taken from Block 1. This mean was a baseline of participants' reaction time as general and sequence specific learning began. The mean reaction time of trials 2–9 was taken from Blocks 2–4. It was assumed that by Block 2 some sequence learning had occurred and participants would be able to anticipate to some degree the next syllable based on implicit knowledge of the sequence. Based on this assumption, the first trials of Blocks 2–4 were eliminated because they occurred after a break between blocks. There was no syllable immediately prior to the initial trial of the block to facilitate anticipation; therefore, reaction time for the initial trial would not reflect any sequence learning that had occurred. Similar to Block 1, the mean reaction time of trials 1–8 was taken from Block 5 (random block). Block 5 trials were random and did not reflect sequence learning, so the lack of a syllable prior to the initial trial was not important.

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**APPENDIX A. Experimental Session**

Block 1 = Total 72 trials

<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA*</i>
<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA - Break</i>
9	10	11	12	13	14	15	16
<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>
17	18	19	20	21	22	23	24
<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI - Break</i>
25	26	27	28	29	30	31	32
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>
33	34	35	36	37	38	39	40
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>
41	42	43	44	45	46	47	48
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI - Break</i>
49	50	51	52	53	54	55	56
<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>
57	58	59	60	61	62	63	64
<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>
65	66	67	68	69	70	71	72

Block 2 = Total 72 trials

<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>
<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
<i>PO*</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA - Break</i>
9	10	11	12	13	14	15	16
<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>
17	18	19	20	21	22	23	24
<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI - Break</i>
25	26	27	28	29	30	31	32
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>
33	34	35	36	37	38	39	40
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>
41	42	43	44	45	46	47	48
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI - Break</i>
49	50	51	52	53	54	55	56
<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>
57	58	59	60	61	62	63	64
<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>
65	66	67	68	69	70	71	72

Block 3 = Total 72 trials

<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>
<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
<i>PO*</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA - Break</i>
9	10	11	12	13	14	15	16
<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>
17	18	19	20	21	22	23	24
<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI - Break</i>
25	26	27	28	29	30	31	32
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>
33	34	35	36	37	38	39	40
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>
41	42	43	44	45	46	47	48
<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI - Break</i>
49	50	51	52	53	54	55	56
<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>
57	58	59	60	61	62	63	64
<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>	<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>
65	66	67	68	69	70	71	72

Block 4 = Total 72 trials

<i>PO</i>	<i>PI</i>	<i>PO</i>	<i>PE</i>	<i>PI</i>	<i>PA</i>	<i>PE</i>	<i>PA</i>
<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>

*(Continued on next page)*

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**APPENDIX A. (Continued)**

<b>PO*</b>	<b>PI</b>	<b>PO</b>	<b>PE</b>	<b>PI</b>	<b>PA</b>	<b>PE</b>	<b>PA - Break</b>
9	10	11	12	13	14	15	16
PO	PE	PI	PA	PE	PA	PO	PI
17	18	19	20	21	22	23	24
PO	PE	PI	PA	PE	PA	PO	PI - Break
25	26	27	28	29	30	31	32
PA	PE	PA	PO	PI	PO	PE	PI
33	34	35	36	37	38	39	40
PA	PE	PA	PO	PI	PO	PE	PI
41	42	43	44	45	46	47	48
PA	PE	PA	PO	PI	PO	PE	PI - Break
49	50	51	52	53	54	55	56
PI	PA	PE	PA	PO	PI	PO	PE
57	58	59	60	61	62	63	64
PI	PA	PE	PA	PO	PI	PO	PE
65	66	67	68	69	70	71	72

Pseudorandom Block (Block 5) = Total 72 trials

<b>PI**</b>	<b>PE</b>	<b>PI</b>	<b>PA</b>	<b>PI</b>	<b>PO</b>	<b>PI</b>	<b>PE*</b>
RAN 1	RAN 2	SEQ 1	SEQ 2	RAN 3	SEQ 3	SEQ 4	RAN 4
PI	PO	PE	PA	PO	PI	PA	PE - Break
SEQ 5	SEQ 6	SEQ 7	SEQ 8	SEQ 9	SEQ 10	SEQ 11	SEQ 12
PI	PA	PO	PI	PE	PI	PE	PI
RAN 5	SEQ 13	SEQ 14	SEQ 15	RAN 6	SEQ 16	RAN 7	SEQ 17
PO	PE	PI	PO	PE	PI	PA	PE - Break
SEQ 18	SEQ 19	SEQ 20	SEQ 21	SEQ 22	SEQ 23	SEQ 24	SEQ 25
PI	PO	PE	PA	PO	PE	PO	PE
RAN 8	SEQ 26	SEQ 27	SEQ 28	SEQ 29	SEQ 30	RAN 9	SEQ 31
PA	PI	PE	PA	PE	PO	PA	PO
SEQ 32	RAN 10	RAN 11	SEQ 33	SEQ 34	RAN 12	RAN 13	SEQ 35
PA	PI	PO	PA	PO	PA	PO	PE - Break
RAN 14	RAN 15	SEQ 36	RAN 16	SEQ 37	RAN 17	SEQ 38	SEQ 39
PI	PE	PI	PA	PI	PO	PI	PE
RAN 18	RAN 19	SEQ 40	SEQ 41	RAN 20	SEQ 42	SEQ 43	RAN 21
PO	PE	PI	PA	PE	PA	PO	PI
RAN 22	SEQ 44	SEQ 45	SEQ 46	SEQ 47	SEQ 48	SEQ 49	SEQ 50

*Note.* \*Statistical analysis included means of **BOLDED** trials of each block (see data analysis section for more detail).

PI\*\*—Random trials (indicated as RAN) were syllables that violated the sequence order.

For the implicit sequence specific learning comparison (Block 4 vs. Block 5), the mean of trials two through nine was taken from Block 4 and the mean of trials one through eight was taken from Block 5.

For the implicit sequence specific learning comparison (SEQ vs. RAN, Block 5), the mean of the first RAN syllables was compared to the mean of the first eight SEQ syllables.

**APPENDIX B. Day One Questionnaire**

1) Did you notice anything about the syllables? YES NO. If yes, what did you notice?

2) Circle the number that fits best with what you remember about the syllables.

	The syllables always appeared in this order 1	The syllables often appeared in this order 2	The syllables sometimes appeared in this order 3	The syllables rarely appeared in this order 4	The syllables never appeared in this order 5
1) PO PI	1	2	3	4	5
2) PE PA	1	2	3	4	5
3) PI PA	1	2	3	4	5
4) PE PO PE	1	2	3	4	5
5) PA PO PE	1	2	3	4	5
6) PI PA PE	1	2	3	4	5
7) PE PO PA	1	2	3	4	5
8) PE PA PO PE	1	2	3	4	5
9) PA PO PI PA	1	2	3	4	5
10) PI PO PE PI	1	2	3	4	5