Cerebellar Activation during Motor Sequence Learning is Associated with Subsequent Transfer to New Sequences

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Abstract

Effective learning results not only in improved performance on a practiced task, but also in the ability to transfer the acquired knowledge to novel, similar tasks. Using a modified serial reaction time task, we examined the ability to transfer to novel sequences after practicing sequences in a repetitive order versus a non-repeating interleaved order. Interleaved practice resulted in better performance on new sequences than repetitive practice. In a second study, participants practiced interleaved sequences in a functional magnetic resonance imaging (fMRI) scanner and received a transfer test of novel sequences. Transfer ability was positively correlated with cerebellar BOLD activity during practice, indicating that greater cerebellar engagement during training resulted in better subsequent transfer performance. Interleaved practice may thus result in a more generalized representation that is robust to interference, and the degree of activation in the cerebellum may be a reflection of the instantiation and engagement of internal models.

Keywords: sequence learning, transfer, contextual interference, cerebellum

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Learning to effectively perform sequences of movements underlies many skills, such as typing or playing a musical instrument. Studies examining sequence learning in the laboratory have shown that learning depends on the cerebellum, motor cortical regions, and the striatum (e.g., Doyon et al., 1997; Seidler et al., 2005; Toni, Krams, Turner, & Passingham, 1998). These systems may act in concert yet each makes somewhat different contributions to learning and performance. Here, we investigate the neural basis of sequence learning that can support subsequent transfer to new sequences. While practice of a sequence of movements results in improved performance of that sequence, it may also result in improved performance on novel sequences. For example, practicing a musical piece on the piano is likely to benefit playing new pieces as well. When such positive transfer occurs, it suggests that a memory representation of the skill has been created that is more general than a representation that could only support the practiced sequence. However, learning could also be highly specific to the practice conditions and result in negative transfer (Obayashi, 2004), with performance of new sequences impaired due to interference. The degree of positive or negative transfer of motor sequence learning may be due to the conditions of practice and individual differences, which could result in more general or sequence-specific neural representations. Positive transfer to novel tasks or contexts is a crucial goal in many training situations as one often cannot train on every possible task variation or in every possible context.

One possible means of creating more generalizable representations of skills is training in the form of a non-repeating, interleaved order of tasks as opposed to repetitive practice. The first demonstration of this benefit in the motor learning domain is attributed to Shea and Morgan

(1979), who showed that those who practiced sequences of arm movements in an interleaved order performed worse during acquisition of the task in comparison to those who practiced in a repetitive order. However, performance on delayed retention and transfer tests consisting of novel sequences was superior for those who had undergone interleaved training compared to repetitive training. This phenomenon is known as the contextual interference (CI) effect and has been subsequently demonstrated in a number of motor tasks (Magill & Hall, 1990; Brady, 2004).

Increasing contextual interference to enhance later retention and transfer may be counterintuitive to many learners, as they may interpret enhanced performance as a sign of enhanced learning (Simon & Bjork, 2001). The idea of transfer-appropriate processing (Morris, Bransford, & Franks, 1977) suggests that the true extent of learning during practice can be best evaluated when the processing requirements of the test match those of the practice condition. Therefore, those who practice in an interleaved fashion are best suited for performing interleaved tasks at a later test, whereas those who practice in a blocked fashion should perform best on blocked tasks. The study by Shea and Morgan (1979) and many others that have followed (see Magill & Hall, 1990, for a review) indicate that transfer-appropriate processing may not apply to all training situations, as interleaved practice was demonstrated to be beneficial for both blocked and interleaved motor task performance.

Two hypotheses have been put forward to explain the benefits of interleaved practice. The first, referred to as the elaboration account, proposes that the intermixed practice order provides the learner with many opportunities to compare and contrast the tasks (Shea & Morgan, 1979; Shea & Zimny, 1983). As a result, more elaborate representations of the tasks are developed which in turn leads to improved performance on tests of learning. This suggests that the action programs or plans are present in working memory at the same time during interleaved training, which therefore allows the learner to compare and contrast them. Furthermore, it implies that fundamentally different types of memory traces are created through interleaved versus repetitive practice. The second view, called the forgetting-reconstruction account, suggests that the non-repetitive nature of interleaved practice causes the learner to inhibit or drop the prior action plan from working memory in order to plan for the execution of the upcoming task (Lee & Magill, 1983; Lee & Magill, 1985). This sustained need for reconstruction of the different action plans during practice results in more efficient retrieval of those action plans during tests of learning. This account differs from the elaboration account in that it is assumed that an action plan must be discarded from working memory so that another one that is relevant to the current task can take its place. Both accounts therefore agree that greater use of working memory takes place during interleaved practice, but they differ in the proposed manipulations of action plans within working memory that would lead to improved learning (Lee & Simon

Recently, the benefit of CI was demonstrated on subsequent retention of learned motor sequences of key presses (Lin, Wu, Udompholkul, & Knowlton, 2010). During acquisition, participants were faster after interleaved practice compared to after repetitive practice, but at a delayed retention test, participants were faster if they had received interleaved practice compared to repetitive practice. This study indicated that introducing CI in the form of interleaved practice benefited participants' sequence-specific learning. That is, although performance during interleaved practice was relatively poor in comparison to repetitive practice, tests revealed that interleaved practice resulted in superior long term learning of the practiced sequences. Using functional magnetic resonance imaging (fMRI) and paired-pulse transcranial magnetic stimulation, Lin and colleagues (2011) also examined the neural correlates of superior learning due to interleaved practice. Consistent with the CI effect, participants were slower during interleaved practice compared to repetitive practice, but were faster at a delayed retention test. Further, greater fronto-parietal blood oxygen level dependent (BOLD) signal and greater excitability of the primary motor cortex (M1) were found during interleaved compared to repetitive practice. However, during retention after interleaved practice, BOLD activity in these areas was reduced whereas fronto-parietal activity was increased during retention after repetitive practice. M1 excitability during retention following interleaved practice was still greater than after repetitive practice. Greater frontal BOLD activity during practice and the within-session increase in M1 excitability during interleaved practice was associated with better retention test performance. This pattern supports the idea that interleaved practice requires forgetting and reconstruction of memory traces which results in poorer performance during training, but results in more efficient memory retrieval during a retention test.

While the evidence for the benefit of interleaved practice on long-term retention is robust, the evidence for a benefit for transfer is more mixed (e.g., Meira & Tani, 2001; Russell & Newell, 2007). While some studies, including Shea and Morgan (1979), have examined transfer to variations of a task in skills such as playing badminton (Goode & Magill, 1986; Wrisberg & Liu, 1991), baseball (Hall, Domingues, & Cavazos, 1994), and volleyball (French, Rink, & Werner, 1990; Bortoli, Robazza, Durigon, & Carra, 1992), most of these experiments have studied gross motor skills with variations in parameters of the same movement rather than different sequences of fine motor behavior. Furthermore, many of the studies that have been published have been underpowered (Brady, 2004). Another factor may be that interleaved practice only benefits some components of motor skill learning; interleaved practice would be beneficial only to the extent to which transfer depends on these components (Seidler & Noll, 2008). The goal of our first experiment is to determine whether interleaved practice of sequences enhances transfer to novel fine motor sequences. While learning motor sequences is a crucial type of skill learning and is relevant to many daily life activities, effective transfer requires the subject to overcome interference among sequences, and thus it is an important case. Our second experiment aims to determine the neural correlates of individual transfer ability of motor sequence learning using fMRI.

Experiment 1

Method

Participants. A total of 64 young adults with normal or corrected-to-normal vision and no medical, psychiatric, or neurological diagnoses were recruited from the undergraduate student population at the University of California, Los Angeles (UCLA; M_{age} = 20.14 years, SD_{age} = 2.29 years, 48 women). All participants underwent informed consent as approved by the Institutional Review Board of UCLA. Sixty of the participants were right-handed. Seven participants were excluded for low accuracy either below 90% during the practice phase or below 75% during the transfer phase. Another participant was excluded because of missing data due to a technical error. When left-handed participants were excluded, the results maintained a similar significant pattern, and therefore left-handed participants were included in the analysis of this study as long as the accuracy criteria were reached. These exclusions yielded a final sample of 56 young adults (M_{age} = 20.21 years, SD_{age} = 2.39 years, 48 women, 52 right-handed). Course credit was given in return for participation in the study.

Design. This study used a two-way between-subjects design. The first independent variable was the Practice Schedule and consisted of two levels: repetitive and interleaved schedules of sequence performance. The second independent variable was the Transfer Schedule and also consisted of two levels: repetitive and interleaved schedules of sequence performance.

Participants were randomly assigned to one of four possible combinations of Practice Schedule and Transfer Schedule: repetitive practice-repetitive transfer (RR; final *N* = 11), repetitive practice-interleaved transfer (RI; final *N* = 16), interleaved practice-repetitive transfer (IR; final *N* = 14), or interleaved practice-interleaved transfer (II; final *N* = 14).

Materials. Stimulus presentation and data collection were performed on a 2.6 GHz Macintosh computer using MATLAB (The MathWorks, Inc., Release 2012a) with the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007). Four white circles outlined in black were presented on a white background. A target circle was filled with the color black as a cue for the participant to respond by pressing the spatially corresponding key. The other three circles remained white while the target circle was filled. The participant had 800 ms to respond by pressing a key. An error was recorded if the key press was incorrect or if no key was pressed within the 800 ms response interval. Once a response was made, the target circle turned white for the remainder of the 800 ms. At the end of the response interval, the next target circle turned black. For each sequence, each of the four possible stimulus cues appeared twice for a total of eight elements. Once all eight elements of a sequence were presented, a fixation cross lasting 600 ms appeared before the onset of the next sequence. Between every six sequences, a fixation cross lasting 6 s appeared, and turned red for the final 2 s to alert participants of upcoming sequences.

Two sets of three 8-item sequences each were devised so that for each participant, one set could be experienced during the practice phase and the other set during the transfer phase. Sequences could not contain trills (e.g., 1-2-1-2), consecutive runs (e.g., 1-2-3-4), or immediate repetitions (e.g., 2-2). Each element appeared twice within each sequence. The practice phase was divided into six blocks of 24 sequences each; thus, each of the three sequences was presented 48 times for a total of 144 sequence presentations in each phase. At the end of each block, feedback appeared on the screen for 5 s that showed the average key press RT in ms and the percentage of correct key presses for that block were given. If the percentage correct was equal to or greater than 90%, a message appeared indicating that performance was satisfactory. However, if the percentage correct was below 90%, a message appeared encouraging the participant to aim for greater accuracy in the following blocks. The format of the transfer phase was the same as the practice phase except that three novel sequences from the opposite sequence set were presented.

Depending on the condition, sequences in the practice and transfer phases could be performed in a repetitive or an interleaved order. If the three sequences appeared in a repetitive order, the order of the sequences was randomly determined, and every two consecutive blocks within a phase consisted of the same sequence. If the three sequences appeared in an interleaved order, the order of the sequences within every group of six sequences that occurred between the 6000 ms fixation crosses was determined pseudorandomly with the constraints that a sequence could not repeat and that each sequence must appear twice.

Key press RT was measured as the time between cue onset to key press. The eight key press RTs for each sequence were summed to obtain the total sequence RT to be used in data analysis. The number of errors in each block was also recorded.

Procedure. Participants were randomly assigned to one of four practice-transfer schedule combinations (i.e., RR, RI, IR, or II) and the assignment of the sequence sets to practice and transfer phases were counterbalanced. At the beginning of the experiment, they were seated in front of the computer at a comfortable distance of their choosing in a private testing room and were instructed to place the four fingers of the dominant hand on the four consecutive keys *C, V,* *B,* and *N* of a keyboard (for a right-handed person, the index finger would be on *C*, whereas for a left-handed person, the index finger would be on *N*). On the screen, instructions told the participants to respond as quickly as possible but also to aim for an accuracy rate of 90% or better. They were informed that they would receive intermittent feedback, and should use it to improve performance. Participants were not aware of practice or transfer schedules they were to receive, nor that novel sequences (the transfer phase) would be presented later. After the instructions were read, the participant went through a short practice session. Sequences presented for the practice session were consecutive runs (e.g., 1-2-3-4-3-2-1-2).

Once the instructions and the practice session were complete and participants confirmed that they understood the task, participants began the actual experiment. Each participant underwent either repetitive or interleaved practice and then either repetitive or interleaved transfer. Figure 1 illustrates the experimental procedure.

For each participant, the median RT of each block during practice and transfer phase as well as three different learning scores were calculated. The first was a total learning score, which consisted of the difference in RT between the first practice block and the last practice block, such that a positive number indicated that learning had occurred over practice. The second score was a sequence-specific learning score, which was calculated by subtracting the last practice block median RT from the first transfer block median RT. A positive score indicated the presence of sequence-specific learning. Finally, we calculated a transfer learning score by subtracting the first transfer block median RT from the first practice block median RT. Comparing initial performance of the three practice sequences (before any experience with the task has occurred) to initial performance of novel sequences after practice indicates the extent of any benefit or disadvantage of prior experience with the task when generalizing to novel task variations. A positive score therefore indicated positive transfer, whereas a negative score indicated negative transfer. To obtain a more equivalent comparison between repetitive and interleaved blocks, the median RT for the first repetitive block was calculated by taking the first eight sequence RTs for each of the three sequences in either the practice or the transfer phase. Thus the median RT of both interleaved and repetitive blocks would reflect RT values for the eight initial presentations of each distinct sequence (as opposed to the repetitive median RTs for the first block being calculated from a block in which only one sequence was presented). Likewise, the last eight RTs for each of the three sequences were combined and the median RT for the final block was calculated from those values. Once these adjusted repetitive median RT values were calculated, the three learning scores were then obtained using these adjusted values.

Results

We first conducted a two-way ANOVA with Practice Schedule as the between-subjects independent variable, practice block as the within-subjects independent variable, and median RT to complete each sequence each block as the dependent variable. Because the assumption of sphericity was violated, Greenhouse-Geisser corrected values are reported. There was a significant interaction between Practice Schedule and block, $F(3.34, 180.15) = 3.83$, $p = .008$. A main effect of block was also found, $F(3.34, 180.152) = 15.70$, $p < .001$. These effects indicate that the interleaved practice group was slower than the repetitive practice group and also learned at a slower rate, consistent with previous reports of the CI effect where participants perform better during repetitive acquisition compared to interleaved acquisition. The patterns of RT for all conditions are shown in Figure 2.

To examine the effects of Practice and Transfer Schedules on total learning, sequence-specific learning, and transfer scores, two-way between-subject ANOVAs were conducted. Both repetitive and interleaved practice groups showed learning over time in acquisition when comparing the first practice block RT to the last practice block RT, $t(26) = 6.88$, $p < .001$, and $t(28) = 6.02$, $p < .001$, respectively. There was a main effect of Practice Schedule on total learning score, $F(1, 52) = 13.20$, $p = .001$, such that those who underwent repetitive practice had higher total learning scores than those who performed interleaved practice, again consistent with the CI effect.

Those that received interleaved practice showed transfer learning, $t(27) = 2.85$, $p = .008$, whereas those who received repetitive practice did not, $t(26) = -0.762$, $p = .453$. As shown in Figure 3, there was a main effect of Practice Schedule on transfer score, such that those who had practiced in an interleaved condition performed better overall in comparison to the repetitive condition when presented with repetitive or interleaved novel sequences, $F(1, 52) = 5.73$, $p = .020$. There was also a main effect of Transfer Schedule, indicating that participants were generally faster when faced with repetitive versus interleaved novel sequences, $F(1, 52) = 12.08$, $p = .001$. Six transfer blocks were given to determine whether better transfer manifests as an improved rate of acquiring the novel sequences. We tested this by running a Practice Schedule (2) x Transfer Schedule (2) x Transfer block (6) ANOVA but the interaction failed to reach significance, $F(3.84, 199.644) = 1.62$, $p = .172$ (Greenhouse-Geisser corrected values reported). Thus, the data do not clearly support a faster learning rate for new sequences after interleaved practice, but rather that performance of these new sequences is better overall. Perhaps a design with longer training on new sequences could potentially reveal an effect on learning rate.

When examining sequence-specific learning scores, the repetitive practice group showed significant learning, $t(26) = -6.60$, $p < .001$, whereas the interleaved group did not, $t(28) = -.464$, $p = .646$. Further, there was a main effect of Practice Schedule, $F(1, 52) = 29.64$, $p < .001$, such that those in the repetitive condition had better sequence-specific learning than those in the interleaved condition. A main effect of Transfer Schedule was found, $F(1, 52) = 16.94$, $p < .001$, meaning that participants who received repetitive novel sequences had lower sequence-specific learning scores compared to those who received interleaved novel sequences. No interaction between Practice Schedule and Transfer Schedule was found, $F(1, 52) = 0.020$, $p = .888$.

Inspection of the II group revealed that the average median RT in the first transfer block was not significantly different from the average median RT in the first practice block, $t(13) = 0.435$, $p = .671$. Thus, interleaved practice appears to have resulted in decreased interference with novel sequences. Further examination of the spread of the data points of the II group showed that five participants demonstrated negative transfer, and nine participants showed positive transfer. Because of this pattern of data, we were motivated to examine individual brain activity differences corresponding to individual differences in transfer performance in interleaved practice, and how they predict subsequent transfer performance.

Discussion

Experiment 1 demonstrated that interleaved practice of motor sequences reduces negative transfer when new sequences are performed, compared to the repetitive practice condition. Interleaved practice may have led to a more generalized memory representation of the skill that was less susceptible to interference. Learning in the repetitive condition was more specific to the practiced sequences, and thus learning different sequences was impeded.

Although the group receiving interleaved practice overall showed evidence of positive transfer to new sequences, some participants who received interleaved practice and transfer showed negative transfer. Thus, participants varied in the degree to which interleaved practice led to a generalizable representation of the skill. In Experiment 2 we took advantage of this variability by relating it to neural activation during interleaved practice using fMRI. In this way we were able to identify brain regions associated with the formation of a generalized skill representation that can support transfer.

Experiment 2

In this experiment, participants practiced three sequences in an fMRI scanner and transfer was measured by their performance on three new sequences. Sequences were designed for practice in the same interleaved manner as in Experiment 1 so that a substantial number of participants would show positive transfer.

Method

Participants. Twenty-two young adults with right-hand dominance and normal or corrected-to-normal vision recruited in the study (M_{age} = 22.59 years, SD_{age} = 4.72 years, 15 women). None of the participants had any contraindications to MRI, nor any significant medical, neurological, or psychiatric history or current diagnosis. All participants underwent informed consent as approved by the Institutional Review Board at UCLA, and were compensated for their time with a cash payment of $25 per hour. One participant was excluded because of technical problems and another was excluded for incomplete data, yielding a sample of 20 participants (M_{age} = 22.80 years, SD_{age} = 4.91 years, 13 women).

Behavioral task. All participants received interleaved practice and interleaved transfer schedules. The practice phase format was identical to that in Experiment 1, but for the transfer phase only one block was given. Participants received eight presentations each of three novel sequences in an interleaved order, for a total of 24 presentations during transfer.

Stimulus presentation and data collection were the same as in Experiment 1, except that due to the nature of the repetitive design for image acquisition, 18-s rest blocks occurred between every group of six sequences instead of 6 s rest periods. The fixation cross remained black through the entire rest block and turned red for the last two seconds. Participants placed the four fingers of the right hand on four response keys on a magnet-compatible button box and stimuli were viewed using magnet-compatible goggles.

Functional magnetic resonance imaging. Images were acquired using a Siemens (Erlangen, Germany) Trio MAGNETOM 3T scanner while the participant performed the SRT task. Six functional runs corresponded to the six practice blocks, and one functional run corresponded to the one transfer block, for a total of seven functional runs. Each functional run lasted for 4 min and 22 s, and consisted of 131 T2*-weighted echoplanar images (TR = 2000 ms, TE = 30 ms, flip angle = 90°), each with 34 transverse slices 4 mm thick with a 1 mm gap in between, and a 64 x 64 matrix yielding an in-plane resolution of 3 mm x 3 mm. Magnetization was allowed to approach equilibrium before beginning each task run. A T1-weighted MPRAGE structural volume (TR = 1900 ms, TE = 2.26 ms, flip angle = 8°) with 176 sagittal slices, each 1 mm thick with a 0.5 mm gap and 1.33 mm x 1.33 mm in-plane resolution. A T2-weighted matched-bandwidth scan with the same slice prescription as the functional volumes was also acquired (TR = 5000 ms, TE = 34 ms, flip angle = 90°) with 34 transverse slices covering the whole brain, each 4 mm thick with a 1 mm gap, a 128 x 128 matrix and an in-plane resolution of 1.5 mm x 1.5 mm.

Procedure. Each participant read instructions and completed a short practice session on a laptop computer before entering the scanner. Both the accuracy and speed of responses were emphasized in the instructions as in Experiment 1.

The practice phase lasted for six functional runs (corresponding to each of the six practice blocks) in the scanner. In the seventh and final run, participants received a set of novel sequences in an interleaved order. The assignment of the two sequence sets to the practice and transfer phases was counterbalanced across all participants.

Images were processed using FSL version 5.01 (Smith et al., 2004). Functional images were realigned to the middle volume in each functional run to correct for head movements by applying a rigid body transformation (6 degrees of freedom) (Jenkinson, Bannister, Brady, & Smith, 2002). No participants exhibited greater than 2 mm in relative translational movement. Slice acquisition timing differences were corrected and the data were smoothed using a 5-mm FWHM Gaussian kernel and temporally filtered with a high-pass filter with a cut off of 100 s. EPI images were registered to the matched-bandwidth high-resolution image, then to the structural MPRAGE image, and finally into standard Montreal Neurological Institute (MNI) space (MNI152, T1 2 mm) using linear registration with FMRIB's Linear Image Registration Tool (FLIRT).

FSL's FEAT package was used to analyze the imaging data by fitting a general linear model to the time series for each voxel. The task was modeled using a boxcar function that was convolved with a double-gamma hemodynamic response function. The fixation period between task blocks constituted an implicit baseline. For each run, an additional parametric regressor with the mean of the median RTs for each task block was added to the model to ensure that any differences in BOLD signal were independent of changes in RTs. Temporal derivatives were also included as regressors of no interest.

For the practice phase, the six runs for each participant were combined at the next level and treated as a fixed effect. For both the practice and transfer phases, a group-level analysis was performed across all runs for all participants using the FMRIB Local Analysis of Mixed Effects (FLAME) module (Beckmann, Jenkinson, & Smith, 2003). Any outliers were detected and deweighted in the multisubjects statistics using mixture modeling to minimize impact of outliers on computing correlations (Woolrich, 2008). Transfer scores, which were determined by subtracting the transfer median RT from the first practice block median RT, were added as an explanatory variable so that correlations between transfer scores and BOLD signal could be examined with whole brain analyses.

Clusters were determined by a cluster-forming threshold of $z > 2.3$ and a corrected extent threshold of $p < .05$, familywise error-corrected using the Theory of Gaussian Random Fields (Poline, Worsley, Evans, & Friston, 1997). Thresholded *z*-statistic images were mapped onto the standard MNI brain. The probabilistic atlas for Spatially Unbiased Infratentorial and Cerebellar Template (SUIT; Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009; Diedrichsen et al., 2011) space was used to identify activations of cerebellar nuclei, and the cerebellar atlas for MNI space after normalization with FLIRT was used to localize all other cerebellar activations. Although our images are in MNI space, affine alignment (FLIRT) was used so that our data could be considered to be unbiased relative to the SUIT atlas template (Diedrichsen et al., 2009).

Results

Participants demonstrated learning during the training phase, as indicated by a significant decrease in RT when comparing the median RT of the first practice block to the median RT of the final training block, $t(19) = 4.838$, $p < .001$. Furthermore, sequence-specific learning was defined as the difference between the median RTs of the transfer block and the last practice block, whereas transfer was determined by the difference between the transfer block and the first training block. Participants demonstrated significant sequence-specific knowledge of the three practiced sequences $t(19) = 3.405$, $p = .003$. Most importantly, participants on average demonstrated significant positive transfer, $t(19) = 3.283$, $p = .004$. Figure 4 presents the average pattern of RT for all participants. There was no correlation between sequence-specific learning and transfer learning ($r = -.045$, $p = .852$) across subjects, suggesting that specific and generalized learning are independent processes.

We next identified areas that were significantly activated by performing the SRT task. During the practice and transfer phases, we observed activations in areas typically associated with SRT task performance. Cortical regions included the sensorimotor cortex, the supplementary motor area (SMA), pre-SMA, and the dorsal premotor area (PMd). These areas have been associated with movement preparation and execution in interleaved motor sequence learning (Cross, Schmidt, & Grafton, 2007; Lin et al., 2011). Significant activity was also detected in the right superior parietal lobule, which may be associated with movement preparation during performance of interleaved sequences (Cross et al., 2007; Lin et al., 2011). Bilateral activity in the lateral occipital cortices was also present, possibly related to frontoparietal activation due to changes in spatial orienting of attention during a motor task (Praamstra, Boutsen, & Humphreys, 2005). Subcortical areas included the thalamus, the caudate, and the putamen. It has been suggested that the thalamus supports both implicit and explicit learning in the SRT task (Rauch et al., 1998; Willingham, Salidis, & Gabrieli, 2002). The striatum is important for learning stimulus-response associations and chunking movements (Poldrack et al., 2005). Finally, activation of the cerebellum was observed. The cerebellum is involved in the formation of internal models predicting sensory consequences, which contributes to motor control (Wolpert, Miall, & Kawato, 1998). Table 1 and Table 2 present lists of regions of activation during SRT task performance during practice and transfer, respectively, and Figure 5 shows these clusters overlaid onto cortex and cerebellum templates using Caret (www.nitrc.org/projects/caret/; Van Essen, 2005; Van Essen, 2002).

Whole brain correlational analyses were conducted separately for practice and transfer phases to determine whether changes in BOLD signal intensities were correlated with sequence-specific learning scores and transfer scores. No correlations emerged between BOLD activity and sequence-specific learning scores. However, greater BOLD activity during the practice phase in the anterior lobe of the cerebellum (lobules I-IV), left supramarginal gyrus, right post-central gyrus, and the left temporal pole correlated positively with better transfer ability to novel sequences. Additionally, participants who demonstrated better transfer ability showed greater BOLD activity during the transfer phase in vermal VI of the cerebellum, the left PMd, and the right lateral occipital cortex. No negative correlations between BOLD activity and transfer ability were found. Table 3 presents a complete list of these regions of activation that were correlated with transfer scores during the practice and transfer phases. Figure 6 shows these clusters overlaid onto cortex and cerebellum templates (Van Essen, 2005; Van Essen, 2002) and Figure 7 depicts the correlations between cerebellar BOLD signal and individual transfer scores.

General Discussion

In Experiment 1, introducing contextual interference during practice was shown to benefit subsequent transfer to novel sequences. Consistent with the CI effect in motor learning, participants who underwent interleaved practice were significantly slower and also learned at a slower rate than those who received repetitive practice. However, transfer was significantly better for participants in the interleaved practice group. Importantly, even when tested with new sequences under repetitive conditions, the group that had received interleaved practice showed better transfer than participants that had received repetitive practice. This pattern is not consistent with the concept of transfer-appropriate processing (Morris, Bransford, & Franks, 1977), which would predict that the level of successful transfer is determined by the matching of test conditions to encoding conditions. In other words, we did not find evidence that the benefits of interleaved practice only manifest for subsequent interleaved transfer; rather, interleaved practice is beneficial for interleaved and repetitive transfer.

In Experiment 2, we found that cerebellar BOLD activity during practice and transfer was positively correlated with transfer ability. In particular, activations of the cerebellar vermis during practice and transfer that were correlated with transfer scores may be related to learning. Increases in vermal activity have been associated with performance of a novel sequence in comparison to a previously learned sequence (Jenkins, Brooks, Nixon, Frackowiak, & Passinham, 1994) or an overlearned sequence (Jueptner et al., 1997; Jueptner & Weiller, 1998), suggesting that it is not simply involved in movement execution. Another study has shown that vermal activity during a new language learning task was correlated with subsequent improvement in performance (Lesage, Nailer, & Miall, 2015), perhaps reflecting the vermis's role in working memory (Desmond & Fiez, 1998). Resting-state fMRI analyses indicate that vermis VI and vermis Crus II, regions of activation in our study that correlated with transfer scores, are functionally connected to more cognitive areas such as the dorsolateral prefrontal cortex and the anterior cingulate (Bernard et al., 2012). Rauch et al. (1995) found that increased cerebellar vermis activity was associated with explicit learning of the SRT task, which they suggested was a reflection of the use of conscious strategies during learning. Although we did not inform the participants beforehand that they would be learning different sequences, at the ed of the study most participants reported being aware that sequences were present. The vermis has also been linked to anticipatory eye movements. Simó, Krisky, and Sweeney (2005) utilized a predictive saccade task in which participants had to visually track a target that appeared in different positions in a predictable order. Once participants learned the sequence, saccades became anticipatory instead of visually-driven, and these were associated with greater activity in the vermis. Eye movements in the SRT task are presumably similar in nature as the sequence becomes learned, and vermal activations could reflect the learning of sequential eye movements. However, we did not track eye movements and it is possible that participants eventually relied on covert instead of overt shifts of attention to each upcoming cue. A study of patients with cerebellar lesions suggests that damage to vermal lobules VI and VIII are important for orienting of covert attention (Baier et al., 2010). Another study showed that patients with abnormal cerebellums who had smaller vermal lobules VI and VII had the largest deficits in covert orienting of attention (Townsend et al., 1999).

During the practice phase, there was greater BOLD activity in a large cluster that had multiple peaks, suggesting the multiple regions of the cerebellum contributed to learning that supported transfer. Activation related to subsequent transfer was observed bilaterally in the anterior lobe of the cerebellum, a region that has been associated with sensorimotor processing (Stoodley, 2012). The cerebellum may predict specific sensory consequences of movements through internal forward models (Wolpert, Miall, & Kawato, 1998) and detect changes in sensorimotor patterns (Tesche & Karhu, 2000). Any error signal due to discrepancies between predicted and actual sensory consequences acts to refine the internal model so that future predictions are more accurate. Studies on tool use suggest that distinct internal models are formed for similar tools (Imamizu, Higuchi, Toda, & Kawato, 2007). In this study, the experimenters hypothesized that when faced with a novel yet similar tool, relevant internal models that had been previously formed are combined by prefrontal and parietal areas. In a similar manner, a distinct internal model may be formed for each sequence learned during practice, and later utilized to support transfer to novel sequences. Interleaved practice may require more effort from cortical regions in deciding which model to select and in switching between internal models, which may better highlight the similarities and differences among the learned sequences. At the transfer test, this information would be useful in the selection and blending of relevant internal models. Thus, the cerebellar activation cluster during practice in our experiment may be indicative of the formation and modification of distinct internal models that correspond to each of the three sequences. Because more intense cerebellar BOLD activity was associated with better transfer scores, the degree of activation may be a reflection of the level of sensitivity of predictive error detection. Higher predictive error sensitivity would result in more elaborate internal models that could be retrieved and applied later when performing novel sequences.

Parietal activations that correlate with transfer performance were present during practice, which have been hypothesized to be involved in selecting and switching internal models (Imamizu et al., 2007). Furthermore, the left supramarginal gyrus was also activated during practice and showed a positive correlation with transfer scores. It has been hypothesized that this area is involved with motor attention (Rushworth, Krams, & Passingham, 2001), as left parietal lesions result in impairments in redirecting motor attention to a different movement (Rushworth et al., 1997) and other studies have revealed left inferior parietal activations during movement preparation (Deiber et al., 1998; Krams et al., 1998). Improved control of motor attention to different finger movements would be a non-specific aspect of the task that would aid in subsequent transfer. Activation in the right superior parietal lobule (SPL) could indicate improved shifting of spatial attention (Vandenberghe, Gitelman, Parrish, & Mesulam, 2001) and tactile discrimination (Stoeckel et al., 2004). Both could contribute to distinguishing between elements of the sequences, and anterior SPL activity in particular might reflect increased encoding of tactile information due to key press feedback and its connection to the visual stimuli-motor response chains. Greater recruitment of the right postcentral gyrus was also related to superior transfer ability, supporting the possibility that increased processing of tactile information supports increased distinction among the sequential elements. More incorporation of tactile information may serve to enhance the error-based formation of cerebellar internal models.

During the transfer phase, increased cerebellar activation in Crus I and II was associated with better transfer ability. These regions are connected to the prefrontal cortex (Kelly & Strick, 2003) and their activity can be evoked by the application of first- and second-order rules (Balsters et al., 2013). In addition to generalizable aspects such as S-R associations and kinematics, the nature of the sequences used in this experiment was such that higher order rules could be learned and applied. One example of such a rule is that in each 8-element sequence, each element could only appear twice. Another is that sequences could not consecutively repeat. These rules could be used in a process of elimination to help determine the upcoming element or response. Furthermore, part of the cerebellar cluster extended into left lobule V and bilaterally into lobule VI and Crus I, areas around the posterior-superior fissure where internal models are thought to be stored (Imamizu et al., 2000; Seidler & Noll, 2008). Thus, increased cerebellar activation during the transfer phase of the task may reflect enhanced retrieval and blending of relevant features of previously formed internal models, or the retrieval of more developed internal models. Because successful transfer likely relies on common features shared among all sequences, only generalizable information gained during practice must be retrieved to yield successful subsequent transfer learning (Obayashi, 2004; Seidler, 2010).

Additional clusters of BOLD activity that were positively correlated with transfer learning were seen in the left PMd and extending into pre-SMA. The PMd plays a role in the selection of appropriate responses based on visual cues (Mushiake et al., 1991) and may be important in online error corrections of movements (Lee & van Donkelaar, 2006), both of which could aid in an unanticipated experience with novel sequences. The PMd was also hypothesized to receive output from cerebellar internal models (Tamada, Miyauchi, Imamizu, Yoshioka, & Kawato, 1999; Imamizu et al., 2007). The pre-SMA is involved in cognitive control, crucial in feedforward error processing (Isoda & Hikosaka, 2007; Chen, Scangos, & Stuphorn, 2010; Siedler, Kwak, Fling, & Bernard, 2013) and has been shown to be active in response inhibition (Chao, Luo, Chang, & Li, 2009; Duann, Ide, Luo, & Li, 2009; Obeso, Robles, Marrón, & Redolar-Ripoll, 2013). The cerebellar cluster extends into the dentate nucleus, the ventral part of which is considered to be a non-motor region and sends projections to the pre-SMA (Akkal, Dum, & Strick, 2007). Thus the pre-SMA may receive information from the encoded internal models that serve as a basis for improved motor and cognitive control during the performance of novel sequences.

Our data do not speak directly to whether the elaboration view or the forgetting-reconstruction view account for the improved transfer performance we observed after interleaved practice. However, the elaboration account of the CI effect (Shea & Morgan, 1979; Shea & Zimny, 1983), which states that the learner benefits from the extra opportunities for comparison and contrast during interleaved practice, seems to be the most logical when discussing transfer. The deeper processing that occurs during interleaved training would aid participants in determining the features that the sequences have in common, which would be the most useful to retrieve when transferring to novel sequences. It would result in interference if the memory traces that support the specific practiced sequences were retrieved. The forgetting-reconstruction account suggests that interleaved practice requires many instances of retrieving memory traces that support the trained sequences (Lee & Magill, 1983; 1985). This extra retrieval practice should result in better performance of the practiced sequences (i.e., sequence-specific learning), but therefore could also result in higher interference during transfer. The neuroimaging study by Lin et al. (2011) examining sequence-specific learning after interleaved practice found greater activation in frontal and parietal areas during interleaved practice in comparison to blocked practice, but reduced activation in those areas during retention testing after interleaved practice. This pattern of results is consistent with a need to reconstruct action plans during interleaved practice, but constant reconstruction ultimately leads to enhanced retrieval at testing. In the present study, we did not find that interleaved practice led to reduced activation during performance of novel sequences. In fact, participants showing the greatest level of activation in cerebellum and other motor learning structures during performance of the novel sequences showed better transfer. It may be that interleaving leads to enhanced retrieval practice as well as the development of a more generalized neural representation of the skill. Greater retrieval practice may result in better retention of the practiced skill after interleaving (Lee & Magill, 1983), whereas a more elaborate and abstract memory trace results in superior transfer to related skills (Shea & Zimny, 1983). It is possible that interleaved practice exerts its effects on retention and transfer in distinct ways.

Finally, previous work has demonstrated that the engagement of different brain regions depends on practice structure (Kantak, Sullivan, Fisher, Knowlton, & Winstein, 2010). Skill practice that was high in contextual interference resulted in a memory trace that could be disrupted by repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex. In contrast, memory for the skill after practice in a low contextual interference condition was insensitive to rTMS delivered to the dorsolateral prefrontal cortex but could be disrupted by rTMS to M1. Similarly, in the present study, the cerebellum may be differentially engaged depending on the practice schedule. Interleaved practice of motor sequences may have resulted in greater plasticity of cerebellar circuitry than repetitive practice, thus allowing the formation of a more generalizable representation of the practiced skill.

In summary, the constant comparing and contrasting of the different motor sequences in our two experiments may have resulted in more distinctive memory representations that were more resistant to interference (Shea & Morgan, 1979; Shea & Zimny, 1983). As a result of this elaborative processing, the non-specific features and rules that were shared among the sequences could be determined and encoded as parts of a generalized memory trace that could be retrieved to aid performance of novel sequences. Therefore, it appears that transfer is improved because of the opportunity for deeper processing of task features that eventually allows one to determine the common aspects among them. This deeper processing appears to be related to enhanced engagement of the cerebellum during practice, which is associated with better subsequent transfer.

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Figure 1. An example of a repetitive practice – interleaved transfer (RI) procedure. In Experiment 1, participants first practiced three sequences in a repetitive or interleaved order (blocks 1-6), and then three novel sequences in a repetitive or interleaved order (blocks 7-12). In Experiment 2, participants did not experience blocks 8-12 and the rest periods in each block were extended to 18 s.

Figure 2. Median RT for each practice block (P1-P6) and each transfer block (T7-T12) for repetitive and interleaved training groups and practice-transfer conditions.

Figure 3. Interleaved practice resulted in better transfer to novel sequences than repetitive practice. Transfer scores were calculated using adjusted median RTs.

Figure 4. The pattern of average median RTs during the six practice runs (P1-P6) and the transfer run (T7). Participants demonstrated significant transfer, as calculated by the difference between P1 and T7 (solid line), and significant sequence-specific learning as calculated by the difference between T7 and P6 (dashed line).

Regions	Left Max *z*	Right Max *z*	MNI coordinates x	y	z	Cluster size
Lateral occipital cortex	**6.52**	5.82	-18	-62	58	45,220
Cerebellum, lobule VI	6.3	5.33				
Vermis VI		5.24				
Lobule V		5.58				
Crus I	4.49	5.54				
Lobules I-IV	3.97	5.29				
Dentate nucleus	4.54	3.65				
Vermis Crus II		4.39				
Lobule VIIIa		4.26				
Interposed nucleus		3.9				
Lobule X	3.83					
Lobule IX		3.12				
Superior parietal lobule	6.25	5.30				
Thalamus	6.16	4.83				
Pre-supplementary motor area	5.99	4.92				
Precentral gyrus	5.80	4.96				
Postcentral gyrus	5.76	4.07				
Fusiform gyrus	5.67	5.42				
Putamen	5.64	5.21				
Brain stem	5.51					
Occipital pole	5.4	4.53				
Lingual gyrus	5.26	5.29				
Insular cortex	3.27	5.21				
Intracalcarine cortex		5.19				
Supplementary motor area	5.17					
Dorsal premotor area	3.27	5.11				
Central opercular cortex	4.98					
Paracingulate cortex		4.79				
Superior frontal gyrus	4.78					
Globus pallidus	4.61					
Caudate		4.31				
Supramarginal gyrus		3.73				
Planum polare	3.58					
Angular gyrus		3.37				
Inferior frontal gyrus, pars triangularis		3.18				
Hippocampus	3.12					
Frontal opercular cortex		3.11				
Frontal orbital cortex	2.96	2.48				

Table 1. MNI coordinates of the cluster activation during SRT task performance in the practice phase. Regions in bold and MNI coordinates indicate the locations of peak voxel activation. Additional regions listed for the cluster are local maxima, with the maximum *z*-statistic listed for each side when applicable. Cluster size refers to the number of voxels in each cluster.

			MNI coordinates			
Regions	**Left Max *z***	**Right Max *z***	**x**	**y**	**z**	**Cluster size**
Cerebellum, lobule VI	3.8	**5.92**	24	-72	-20	13,011
Lobule V		5.05				
Vermis VI		4.88				
Dentate nucleus	2.82	3.76				
Crus II	3.56	3.65				
Crus I	3.55	4.19				
Lobules I-IV	3.44	3.52				
Vermis Crus II	3.42					
Vermis VIIIa	3.38					
Lingual gyrus		5.61				
Intracalcarine cortex		5.55				
Occipital pole	5.49	4.92				
Fusiform	5.04	4.8				
Lateral occipital cortex	4.27	4.45				
Brain stem	4.18					
Precentral gyrus	**6.6**		-38	-10	-64	9749
Postcentral gyrus	5.9					
Lateral occipital cortex	5.09					
Pre-supplementary motor area	4.92					
Dorsal premotor area	4.52					
Superior parietal lobule	4.38					
Paracingulate gyrus	3.85					
Inferior frontal gyrus, pars opercularis	3.68					
Frontal pole	3.35					
Central opercular cortex	3.11					
Thalamus	**4.42**		-10	-18	6	1246
Putamen	4.17					
Globus pallidus	2.79					
Precentral gyrus		**4.68**	28	-4	48	1089
Dorsal premotor area	2.73	3.04				

Table 2. MNI coordinates of cluster activations during SRT task performance in the transfer phase. Regions in bold and MNI coordinates indicate the locations of peak voxel activation. Additional regions listed for each cluster are local maxima, with the maximum *z*-statistic listed for each side when applicable. Cluster size refers to the number of voxels in each cluster.

Figure 5. Areas that are significantly activated during performance of the SRT task during practice and transfer. A dorsal and anterior view of the cerebellum are presented in the final row. Activation during practice is shown in red and activation during transfer is shown in blue; yellow indicates overlap.

Task phase	Regions	Left Max *z*	Right Max *z*	MNI coordinates x	y	z	Cluster size
Practice	**Cerebellum, lobules I-IV**	4.25	**4.48**	8	-42	-20	2849
	Lobule VI	4.44					
	Lobule V	3.56					
	Dentate nucleus	3.46	2.91				
	Lobule IX	3.27	3.21				
	Vermis VIIIa	3.09					
	Fusiform gyrus	3.99					
	Brain stem	3.61					
	Inferior temporal gyrus	3.53					
	Parahippocampal gyrus	3.53	3.42				
	Supramarginal gyrus	**4.26**		-52	-42	10	863
	Superior temporal gyrus	3.25					
	Postcentral gyrus		**4.27**	44	-26	56	662
	Superior parietal lobule		3.91				
	Precuneous		3.46				
	Temporal pole		**3.91**	34	12	-30	528
	Parahippocampal gyrus		3.71				
	Planum polare		3.35				
	Insular cortex		2.95				
Transfer	**Cerebellum, vermis VI**		**3.81**	-2	-74	-16	992
	Vermis VIIIa		3.6				
	Crus II		3.54				
	Crus I	3.53					
	Lobules I-IV	3.11					
	Lobule IX		3.08				
	Lobule V	3.07					
	Vermis IX		2.96				
	Dorsal premtor area	**3.67**		-18	4	60	566
	Lateral occipital cortex		**4.42**	50	-80	4	484

Table 3. MNI coordinates of cluster activations correlated with transfer scores. Regions in bold and MNI coordinates indicate the locations of peak voxel activation. Additional regions listed for each cluster are local maxima, with the maximum *z*-statistic listed for each side when applicable. Cluster size refers to the number of voxels in each cluster.

Figure 6. The clusters indicate areas in which increased activation during practice and transfer was correlated with higher transfer scores. A dorsal and anterior view of the cerebellum are shown in the last row. Activations during practice are shown in red and activations during transfer are shown in blue; yellow indicates overlap.

Figure 7. Correlations between BOLD signal change (%) during the practice phase and individual transfer scores (a), and correlations between BOLD signal change (%) from the transfer phase and individual transfer scores (b). Parameter estimates were taken from the entire cerebellar cluster during practice and during transfer, respectively.