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Interleaved Training and Cerebellar Transcranial Direct Current Stimulation Can Enhance Fine Motor Transfer Learning

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Interleaved Training and Cerebellar Transcranial Direct Current Stimulation Can Enhance Fine Motor Transfer Learning

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Psychology

by

Renee Evelyn Shimizu

2016

ABSTRACT OF THE DISSERTATION

Interleaved Training and Cerebellar Transcranial Direct Current Stimulation Can Enhance Fine Motor Transfer Learning

by

Renee Evelyn Shimizu
Doctor of Philosophy in Psychology
University of California, Los Angeles, 2016
Professor Barbara Knowlton, Chair

A crucial goal of many real-world sequence learning tasks is the transfer of knowledge to novel sequences. The current work utilized the serial reaction time task, in which participants press keys in response to visual cues that appear in sequence. The first study examined the ability to transfer to new sequences after practicing sequences in a repetitive order compared to a non-repeating interleaved order. Interleaved practice resulted in better performance on repetitive or interleaved novel sequences than repetitive practice. Interleaved training may reduce interference from sequence-specific knowledge when the learner is faced with new variations of a task. In the 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 blood oxygen level dependent (BOLD) activity during practice, indicating that greater engagement of the cerebellum during training resulted in better subsequent transfer performance. The cerebellum is thought to contribute to error-based learning through the instantiation of internal models (Wolpert, Miall, & Kawato, 1998). When novel variations of a task are encountered, it is hypothesized that relevant features from other previously-formed internal models are selected and form the basis for performance on the novel task (Imamizu, Higuchi, Toda, & Kawato, 2007). Those learners in which internal models are more readily formed may be better at later tests of transfer. Based on these results, the cerebellum was targeted with transcranial direct current stimulation (tDCS) during training in order to enhance transfer learning. Results indicate that anodal tDCS can lead to better transfer to novel sequences, but this change was apparent only after a delay. On the other hand, cathodal tDCS had a detrimental online effect on learning. These results are consistent with the theory that the cerebellum plays a large role particularly in the early learning stage of fine motor skills. Overall, this work demonstrates that easily implementable and relatively inexpensive manipulations can improve transfer learning of motor sequences.

The dissertation of Renee Evelyn Shimizu is approved.

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2016

Dedicated to Stephen Godina

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This dissertation is the basis of two manuscripts that are currently in preparation or under review, and I would like to thank my co-authors for their contributions.

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CHAPTER 1. General Introduction

Learning to effectively perform sequences of movements underlies many skills that are performed throughout the life span, such as typing, playing a musical instrument, or tying shoelaces. A common paradigm to examine sequence learning is the serial reaction time (SRT) task, which was first developed by Nissen and Bullemer (1987) to examine the role of attention in learning. In a typical version of the SRT task, participants practice a repeating sequence using the fingers of one or both hands. A visual stimulus, such as an asterisk, appears in one of four locations as a cue for the participant to push a corresponding button as quickly and as accurately as possible. Participants demonstrate a decrease in response time (RT) as training progresses, which reflects learning of the sequence as well as non-specific improvement on the SRT task. In a transfer phase, the participant is switched from the repeating sequence to stimuli that are randomly ordered with at least the one constraint that no element may consecutively repeat. Comparing the last sequence block to the random block usually reveals a sharp increase in RT at the presentation of the random block. This pattern is indicative of sequence-specific knowledge since participants are impaired once the sequential structure has changed. Experimenters may administer tests of explicit knowledge in order to determine states of awareness during learning.

Shea and Morgan (1979) demonstrated that a distinction between learning and performance can be observed when interleaved training is compared to repetitive training in the motor skill learning domain. Participants practiced three sequential arm movements either in a blocked, repetitive order (e.g., A-A-A-B-B-B-C-C-C, if each letter represents a different task) or a non-repeating intermixed order (e.g., A-C-B-C-B-A-B-C-A). Those participants who trained in a repetitive fashion showed a greater increase 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 arm 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). Thus learning can be improved by introducing a greater amount of interference (caused by the interleaved schedule of tasks), although training is more difficult.

Two hypotheses have been put forth to explain the benefits of interleaved practice. The first, referred to as the elaboration-distinctiveness 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). During interleaved practice, poorer performance results from the need to keep action plans separated, whereas in repetitive practice, it may only be necessary to keep them unambiguous at the beginning of a new task block. As a result, more elaborate representations of the tasks are developed through interleaved training which in turn leads to improved performance on tests of learning. Furthermore, these differences in processing between interleaved and repetitive practice should lead to distinct types of memory traces (Shea & Zimny, 1983). 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; 1985). This sustained need for forgetting and reconstruction of the different action plans during practice results in poorer performance during practice, but more efficient retrieval of those action plans during tests of learning. Repetitive practice performance does not suffer as much because the need to retrieve a pattern would only be necessary in the first trial of a task block, and it could remain in working memory for the remainder of the task block.

Research shows that greater demands are placed on attention when greater levels of CI are present. Li and Wright (2000) conducted a study in which the primary task consisted of three 4-item sequences. Each sequence had different timing requirements for each key press, and thus each sequence was a pattern of different timing goals. Participants practiced these sequences in either a repetitive or interleaved fashion. The secondary task was a probe choice reaction time (CRT) task in which participants had to press one of two keys in response to a high tone, and the other key in response to a low tone as quickly as possible. Participants in the single task condition practiced only the sequences, whereas others in the dual task condition practiced both sequences and the CRT. The researchers examined the pre-response interval, during which it was hypothesized that processes related to reconstruction of action plans take place, and the inter-trial interval, when the intra-task processing suggested by the elaboration account may take place. Thus the CRT could take place in either of these intervals, with the purpose of interfering with either pre-response or inter-trial processes. Under dual-task conditions, there were increases in response time for the CRT during both pre-response intervals and inter-trial intervals. This finding suggests that interleaved practice does require greater attentional resources during motor planning than repetitive practice, which both the elaboration and the forgetting-reconstruction accounts propose.

Klapp (1995; 1996) suggested that motor programming consists of two independent processes called the INT and SEQ processes. The INT process organizes the internal features of a motor chunk. The complexity (e.g., the duration of the chunk or the number of elements in the chunk) of the response determines the length of the INT process. The SEQ process sequences motor chunks into the correct order for output. The length of the SEQ process depends on the number of elements in the sequence. An assumption is that the INT process can be prepared in advance, whereas the SEQ process cannot until just before the response is made. In one study (Immink & Wright, 2001), participants were asked to practice short- and long-duration individual responses, which should affect INT processing times differently. The length of the sequences was also varied, since a single-chunk sequence should lead to shorter SEQ times in comparison to multi-chunk sequences. Relatively shorter amounts of interleaved practice led to reduced INT times during a retention test, indicating that those who underwent interleaved practice were more efficient in selecting and retrieving motor chunks (Immink & Wright, 2001). The SEQ times were not significantly different between practice groups. However, a second study demonstrated that with longer practice times, interleaved practice could also reduce the time of the SEQ process (Wright, Black, Immink, Bruekner, & Magnusson, 2004). Moreover, they found that both repetitive and interleaved practice groups appeared to get faster by reducing the number of chunks during practice, but after a delay only the interleaved group continued to prepare responses based the reduced motor chunks. The repetitive practice group returned to preparing responses based on more motor chunks, suggesting that the memory traces that are maintained are different as a result of practice schedule. Thus it appears that both elaborative processing and retrieval practice could explain the benefits of interleaved practice on retention in certain circumstances.

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.

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. Training on different key press sequences would examine fine motor skill, which is crucial for many daily life activities, and would examine the effects on learning of distinct sequences, which has the potential for high levels of interference at test. Furthermore, some studies (e.g., Meira & Tani, 2001; Russell & Newell, 2007) indicate that for certain tasks, there is a lack of significant differences at transfer between practice groups, suggesting that the benefits of interleaved training might be somewhat task- or condition-specific. Therefore it is important to understand transfer and how its enhancement can be facilitated.

CHAPTER 2. Interleaved Practice Benefits Transfer Learning

2.1. Introduction

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. As mentioned previously, Shea and Morgan (1979) first demonstrated the CI effect in the motor learning domain, showing that interleaved training is more beneficial for learning than repetitive training despite poorer training performance. This phenomenon 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 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 (Morris, Bransford, & Franks, 1977). Therefore, those who practice in an interleaved fashion should be 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 (Magill & Hall, 1990; Brady, 2004) 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.

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. However, transfer learning was not evaluated in this study.

While the evidence for the benefit of interleaved practice on long-term retention is robust, the evidence for a benefit for transfer is mixed (e.g., Meira & Tani, 2001). Transfer has been studied less frequently than retention, and 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.

2.2. Method

(a) 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. Using a modified questionnaire based on the Edinburgh Handedness Inventory (Oldfield, 1971), it was determined that 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.

(b) 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 $N = 14$).

(c) 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.

(d) 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 training session. Sequences presented for the training session were consecutive runs (e.g., 1-2-3-4-3-2-1-2).

Once the instructions and the brief training 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 2.1 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.

2.3. 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 2.2.

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 2. 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. 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.

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.

2.4. Discussion

This behavioral experiment 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 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 novel sequences was impeded.

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. Thus, interleaved practice is at least as beneficial or better than repetitive practice. This pattern is not congruent 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 subsequent interleaved and repetitive transfer.

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 should result in higher interference during transfer. A neuroimaging study 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 (Lin, Knowlton, Chiang, Iacoboni, Udompholkul, & Wu, 2011). 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. It is possible that interleaved practice exerts its effects on retention and transfer in distinct ways.

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 the next experiment, 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.

2.5. Figures

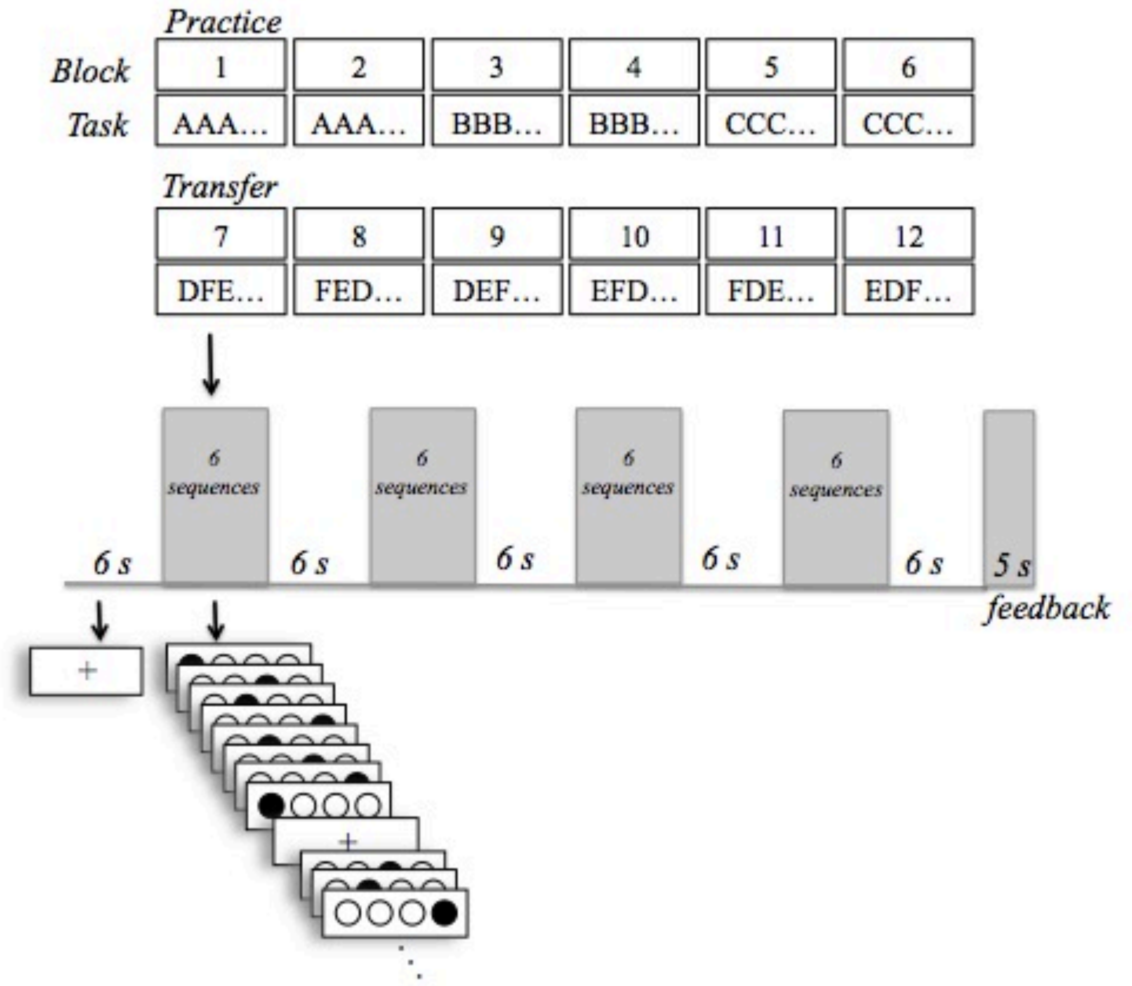

Figure 2.1. An example of a repetitive practice – interleaved transfer (RI) procedure. Participants first practiced three sequences in a repetitive or interleaved order (blocks 1-6), and then three novel sequences in a repetitive or interleaved order (blocks 7-12). Each letter A-F represents a different 8-element sequence.

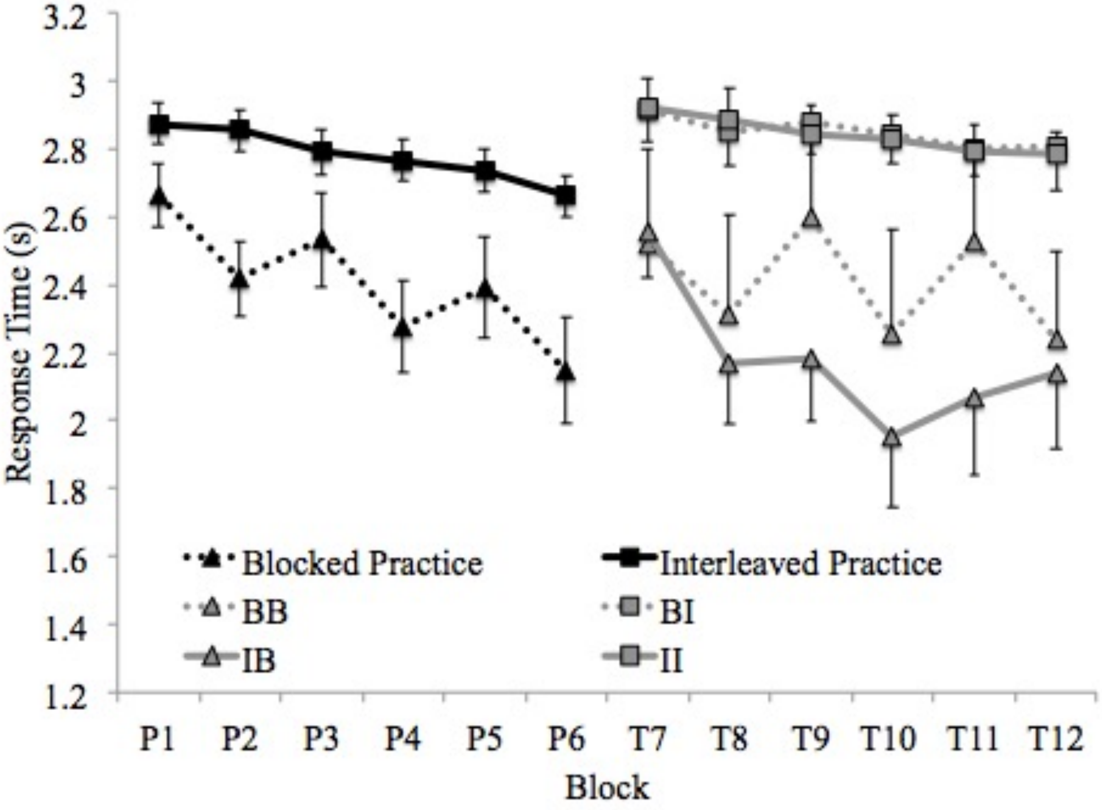

Figure 2.2. Median RT for each practice block (P1-P6) and each transfer block (T7-T12) for repetitive and interleaved training groups and practice-transfer conditions.

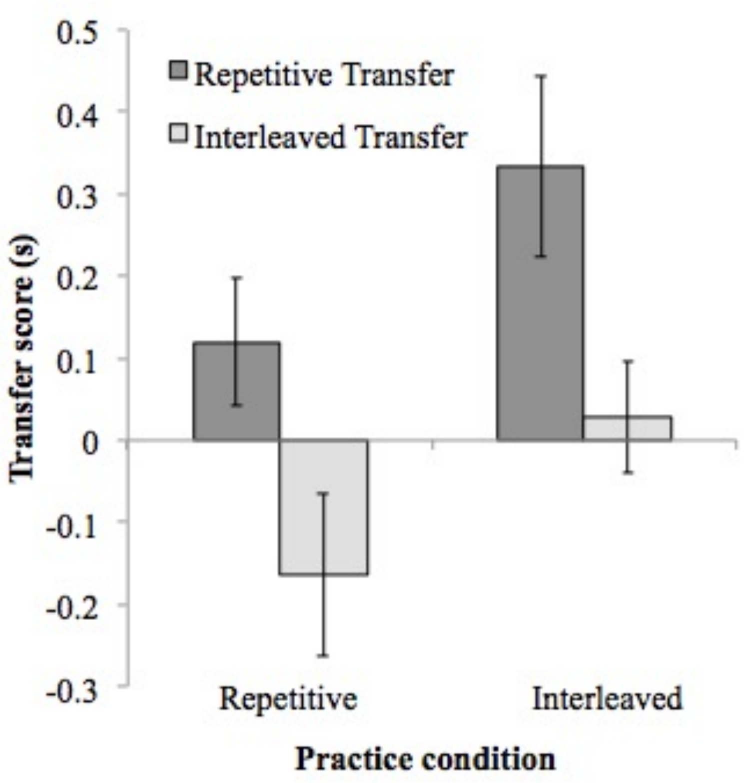

Figure 2.3. Interleaved practice resulted in better transfer to novel sequences than repetitive practice. Transfer scores were calculated using adjusted median RTs.

CHAPTER 3. The Neural Bases of Interleaved Sequence Learning and Transfer

3.1. Introduction

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. These studies typically give participants one repeating sequence, but a few have studied the interleaved training of sequences. In a between-subjects design, Cross, Schmitt, and Grafton (2007) specifically examined the pre-movement period during interleaved practice and blocked practice, and found greater activation in the dorsal and ventral premotor areas, the supplementary motor area (SMA), parietal regions, and prefrontal regions in comparison to those who went through blocked practice. They also found that those who underwent interleaved practice had longer pre-movement periods than those who practiced in a blocked fashion. This might suggest greater retrieval effort during interleaved practice. However, as Wymbs and Grafton (2009) point out, participants were allowed to take as much time as they wanted to prepare, so it is unclear whether the greater activation during interleaved practice is a result of the practice schedule or a more general effect of sequence preparation.

Using a within-subjects design, Wymbs and Grafton (2009) asked participants to practice different sequences in a blocked or interleaved schedule inside the scanner. For half of the sequences, a GO signal cued participants to execute the sequence. For the other half of the sequences, a NO-GO cue indicated that particiapnts should refrain from responding. Finally, participants received a blocked and interleaved test of all sequences during the final functional scanning runs. Dorsal and ventral premotor, SMA, pre-SMA, parietal, and cerebellar regions showed greater activity later in interleaved practice preparatory times, suggesting that the retention benefits of interleaved training results from increased recruitment of these areas believed to support sequence learning (Nakamura, Sakai, & Hikosaka, 1998; Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Nachev, Kennard, & Husain, 2008). During preparation trials of repetitive practice, areas typically associated with the default mode network (the medial prefrontal cortex and the posterior cingulate; Greicius, Supekar, Menon, & Dougherty, 2009) showed greater activity than during interleaved preparation trials. This pattern suggests that as repetitive practice continues, individuals are less engaged in preparation of the task before execution, thus leading to poorer efficiency of retrieval later.

Lin and colleagues (2011) also examined the neural correlates of superior learning due to interleaved practice using functional magnetic resonance imaging (fMRI) and paired-pulse transcranial magnetic stimulation. 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. Like the results of Cross et al. (2007) and Wymbs and Grafton (2009), 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.

Inspection of the interleaved practice-interleaved transfer (II) group in the previous behavioral study 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. Transfer performance would likely suffer from retrieving the exact memory traces that support the practiced sequences due to interference. It would instead be the most beneficial to determine which features or characteristics are common to the practiced and novel sequences, and then retrieve and apply those when creating new memory traces to support the novel sequences. Those individuals who showed the most positive transfer may be better at extracting these features during training and selecting them during transfer.

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 the prior experiment described in Chapter 2 so that a substantial number of participants would show positive transfer. Here, we investigate the neural basis of sequence learning that can support subsequent transfer to new sequences.

3.2. Method

(a) Participants

Twenty-two young adults with right-hand dominance and normal or corrected-to-normal vision recruited in the study ($M_{\text{age}} = 22.59$ years, $SD_{\text{age}} = 4.72$ years, 15 women). None of the participants had any contraindications to MRI, nor any significant medical, neurological, or psychiatric history or current diagnosis. Handedness was determined using a modified questionnaire based on the Edinburgh Handedness Inventory (Oldfield, 1971). 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_{\text{age}} = 22.80$ years, $SD_{\text{age}} = 4.91$ years, 13 women).

(b) Behavioral task

All participants received interleaved practice and interleaved transfer schedules. The practice phase format was identical to that described in Chapter 2, 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 also the same as described in Chapter 2, except that due to the nature of the blocked 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. Figure 3.1 illustrates the experimental design.

(c) 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.

(d) Procedure

Each participant read instructions and completed a short training session on a laptop computer before entering the scanner. Both the accuracy and speed of responses were emphasized in the instructions as described for Study 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) and SUIT normalization yield mutually unbiased results (Diedrichsen et al., 2009).

3.3. 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 3.2 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 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 et al., 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; Penhune & Steele, 2012). 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). Tables 3.1 and 3.2 presents a list of regions of activation during SRT task performance and Figure 3.3 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 3.3 presents a complete list of these regions of activation that were correlated with transfer scores during the practice and transfer phases. Figure 3.4 shows these clusters overlaid onto cortex and cerebellum templates (Van Essen, 2005; Van Essen, 2002) and Figure 3.5 depicts the correlations between cerebellar BOLD signal and individual transfer scores.

3.4. Discussion

In this experiment, we found that cerebellar BOLD activity during practice and transfer was positively correlated with transfer ability. 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 the learner was 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, Ibañez, Honda, Sadato, Raman, & Hallett, 1998; Krams, Rushworth, Deiber, Frackowiak, & Passingham, 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).

Activations of the cerebellar vermis may be related 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).

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.

In their investigation of the benefit of interleaved practice on retention of practiced sequences, Lin and colleagues (2011) found that there was greater BOLD signal in sensorimotor and prefrontal areas during interleaved practice, but these regions showed decreased activation during retention as compared to after repetitive practice. Both of these effects were related to better retention of sequences that had been interleaved during practice. They also found increased excitability of M1 just prior to retention testing after interleaved practice. Together, along with reduced RT during retention, these results support the idea that the need to inhibit previous action plans and repeated retrieval of different memory traces results in an enhanced ability to retrieve memories during retention. However, there were two major differences between Lin et al.'s study and the present study. First, their study assessed retention of the same sequences that had been practiced rather than transfer to new sequences. Second, they imposed a delay between practice and test whereas testing immediately followed practice in the current study. Thus increased efficacy of retrieval reflected by reduced BOLD signal in their study could be due to the opportunity for consolidation of practiced sequences. 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).

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 the memory traces supporting sequence learning 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.

3.5. Figures and Tables

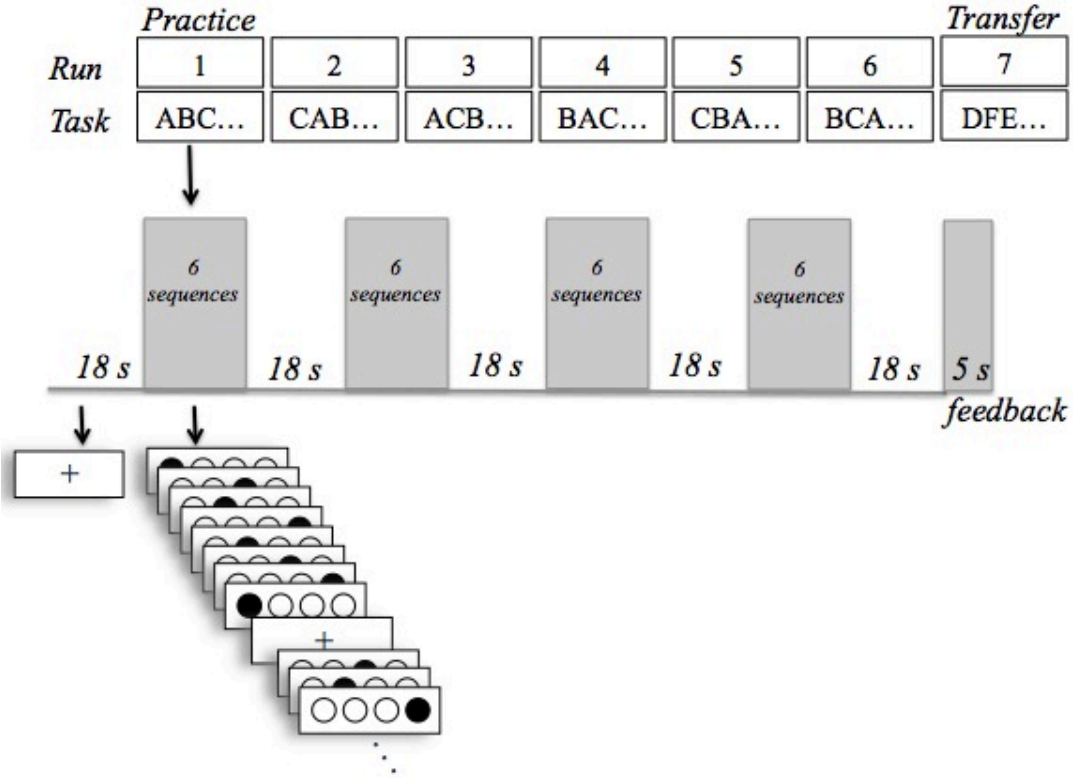

Figure 3.1. Inside the scanner, participants first practiced three sequences in an interleaved order (runs 1-6), and then received three novel sequences in an interleaved order (run 7). Each letter A-F represents a different 8-element sequence.

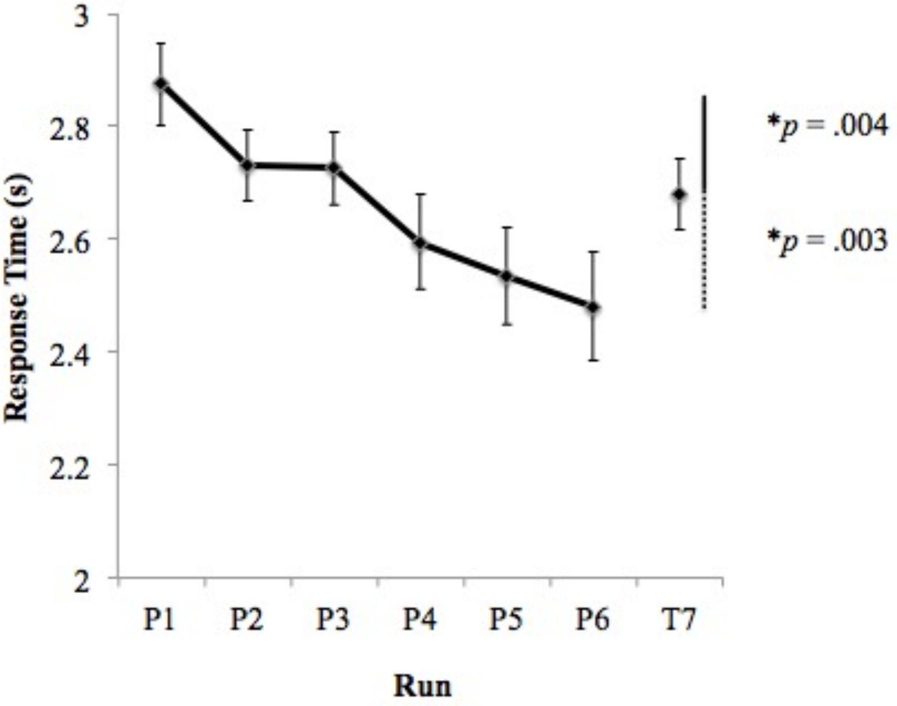

Figure 3.2. The pattern of average median RTs during the six practice runs (P1-P6) and the transfer run (T7). Participants demonstrated significant transfer, as calculated by the difference between P1 and T7 (solid line), and significant sequence-specific learning as calculated by the difference between T7 and P6 (dashed line).

			MNI coordinates			
Regions	Left Max *z*	Right Max *z*	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 3.1. 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.

Regions	Left Max *z*	Right Max *z*	MNI coordinates			Cluster size
			x	y	z	
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 3.2. 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.

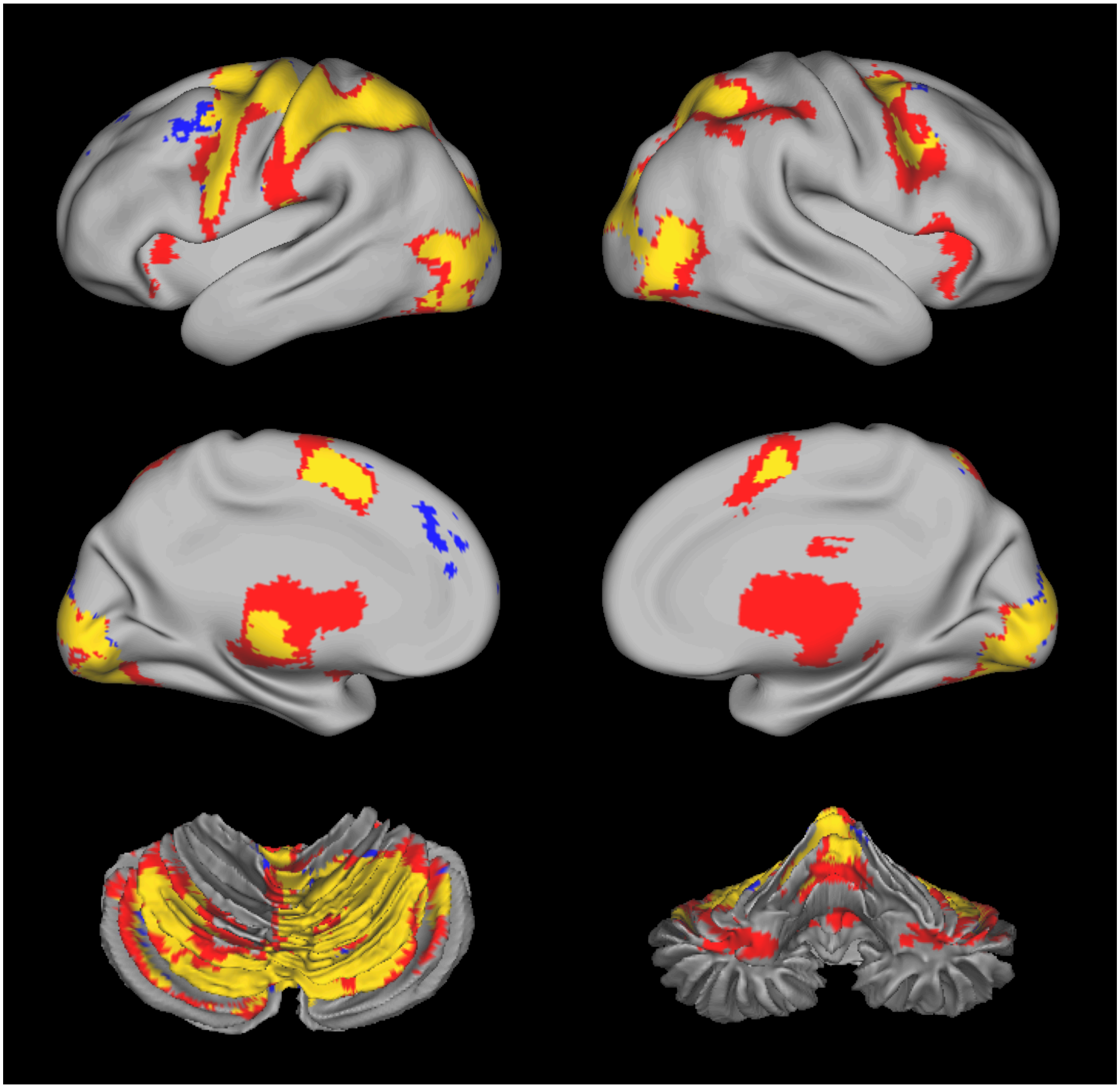

Figure 3.3. Areas that are significantly activated during performance of the SRT task during practice and transfer. A dorsal and anterior view of the cerebellum are presented in the final row. Activation during practice is shown in red and activation during transfer is shown in blue; yellow indicates 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 3.3. 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.

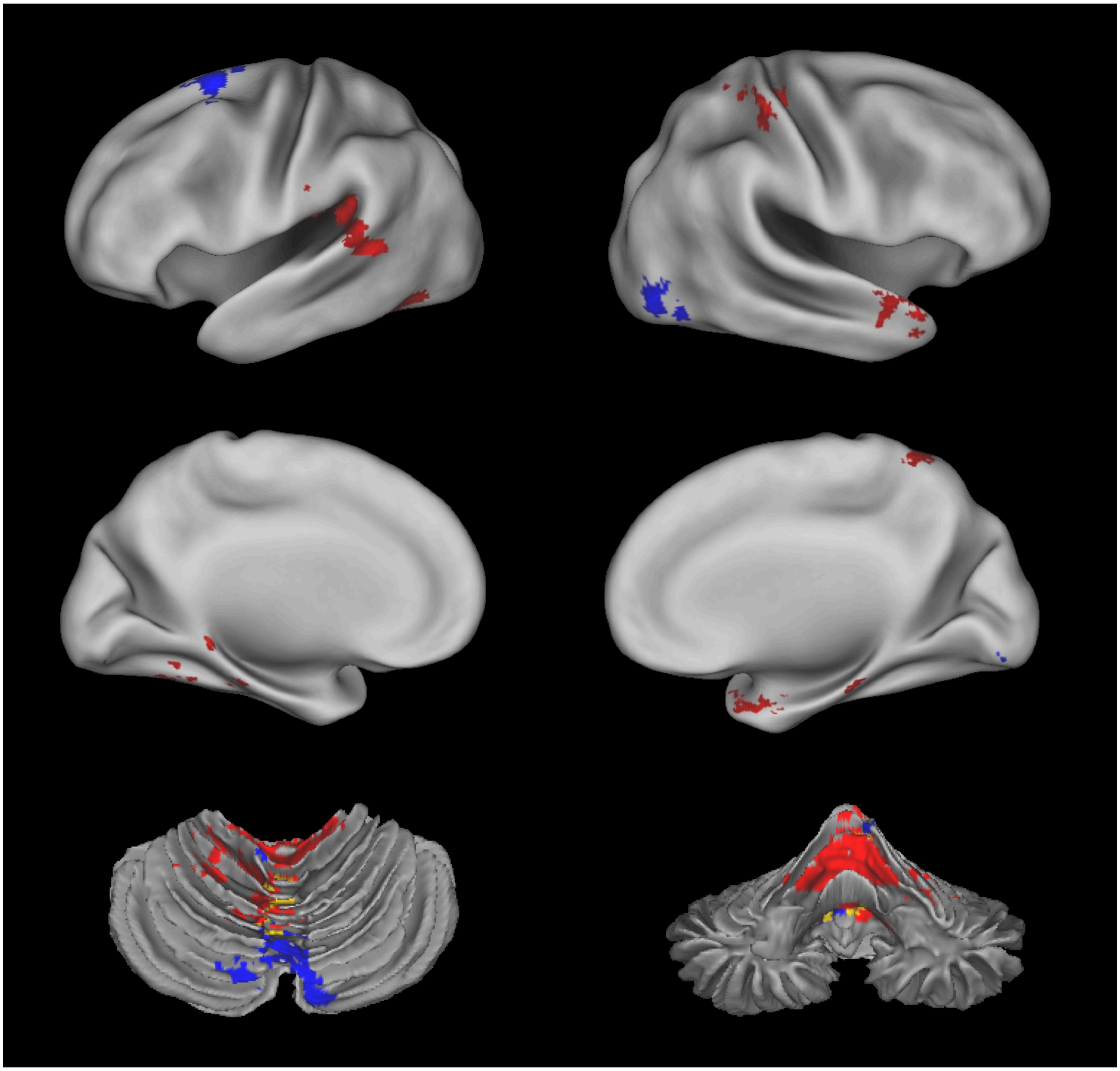

Figure 3.4. The clusters indicate areas in which increased activation during practice and transfer was correlated with higher transfer scores. A dorsal and anterior view of the cerebellum are shown in the last row. Activations during practice are shown in red and activations during transfer are shown in blue; yellow indicates overlap.

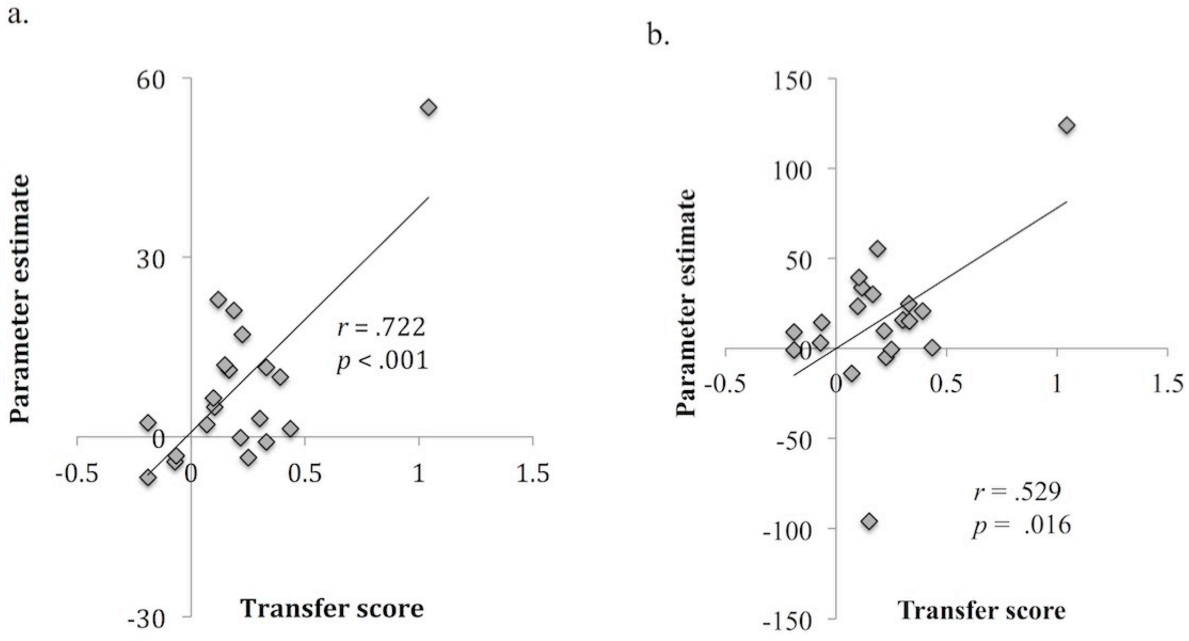

Figure 3.5. Correlations between parameter estimates from the practice phase and individual transfer scores (a), and correlations between parameter estimates from the transfer phase and individual transfer scores (b).

CHAPTER 4. Cerebellar Transcranial Direct Current Stimulation Enhances Transfer Learning

4.1. Introduction

Our previous research has examined the ability to transfer the knowledge gained from training to novel instances of the task. Chapters 2 and 3 indicated that interleaved practice of similar yet distinct tasks is more beneficial for both repetitive and interleaved transfer in comparison to repetitive practice, and also that cerebellar activity during practice predicted subsequent transfer. This work suggested that those who benefit the most from interleaved practice at transfer are those who more readily form internal models during practice and can better apply generalized knowledge to aid performance during transfer. Based on these results, another way that transfer learning could be enhanced is through the application of non-invasive brain stimulation to the cerebellum during interleaved training.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that has been demonstrated to induce changes in cortical excitability. It has been shown that anodal stimulation increases excitability by inducing membrane depolarization, whereas cathodal stimulation decreases excitability through hyperpolarization (Purpura & McMurtry, 1965). The effects of tDCS in humans also appear due to changes in membrane polarization. In humans, anodal stimulation to M1 did not result in increased excitability after administration of the sodium channel blocker carbamazepine or the calcium channel blocker flunarizine, but inhibition of M1 due to cathodal stimulation still occurred (Nitsche et al., 2003). Furthermore, administration of the NMDA receptor antagonist dextromethorphane prevented aftereffects induced by anodal or cathodal stimulation. These results suggest that tDCS-induced aftereffects may be caused by prolonged membrane polarization changes that then result in changes in intracellular calcium ion levels.

Given that the cerebellum is a superficial structure, and appears to be involved in many motor and cognitive tasks (Stoodley, Valera, & Schmahmann, 2011; Stoodley, 2012), it is a promising target for tDCS in facilitating learning. Using a cerebellum-cheek electrode montage, Galea and colleagues (2009) demonstrated that cathodal stimulation at an intensity of 2.0 mA for 25 minutes resulted in diminished cerebellar excitability with its aftereffect lasting for about 30 minutes. Stimulation at 1.0 mA for the same amount of time did not result in an aftereffect. In a separate experiment, they provided evidence that anodal stimulation for 25 minutes at 2.0 mA resulted in the facilitation of cerebellar excitability. In another study using a cerebellum-right shoulder electrode montage (Ferrucci et al., 2008), no changes in visual evoked potentials before and after cerebellar tDCS were observed, indicating that the occipital cortex is not being significantly influenced by stimulation directed to the cerebellum. Modeling the electric field and current density of cerebellar tDCS suggests that current density spread is minimal to the occipital lobe as well as other brainstem structures (Parazzini et al., 2014). Moreover, when the modeled electrodes' positions were changed by 1 cm, the change in the spread and intensity of the current density field was minimal, suggesting that it is cerebellar anatomy that has a larger influence in determining the spread of direct current, at least for relatively large electrodes. Therefore, the effects of cerebellar tDCS are presumed to be specific to the cerebellum, without great risk to autonomic function (see also Parazzini et al., 2013a; 2013b). Another modeling study found that relatively high electric field values were achieved in comparison to other common montages targeting cortical structures (Rampersad et al., 2014). Thus, the cerebellum may be a particularly effective target for enhancing motor learning.

A recent study (Ferrucci et al., 2013) examined the effects of cerebellar anodal and sham stimulation on motor sequence learning. As a pre-test measure, participants were given a repeating sequence to practice and then a retention test. They then received 20 minutes of anodal or sham stimulation, and then performed the same task as before as a post-test 35 minutes after the end of stimulation. Total learning during the course of practice and retention of the practiced sequence were examined. After sham stimulation, participants did not show significant learning over practice or sequence-specific learning. In contrast, participants demonstrated greater total learning and sequence-specific knowledge during practice after anodal tDCS, suggesting that the cerebellar stimulation enhanced subsequent acquisition of the same task. This study is in agreement with other work (e.g., Pascual-Leone et al. 1993; Jenkins et al., 1994; Grafton, Hazeltine, & Ivry, 1995; Toni et al. 1998) that suggests that the model of performance acquired by the cerebellum can support retention as well as transfer.

Since anodal and cathodal stimulation do appear to have differential effects on cerebellar excitability levels (Galea et al., 2009), it suggests that at least for some tasks, the effects on learning might be polarity dependent. Therefore, it is worthwhile to include a cathodal stimulation condition when investigating a sensorimotor task. Based on our neuroimaging study in which cerebellar activity during practice was positively correlated with transfer scores, this study will utilize the cerebellum as the stimulation site. If the cerebellum is building internal models during acquisition that later aid in transfer during the development of new ones, we anticipate that anodal tDCS will enhance fine motor sequence learning, whereas cathodal tDCS will have an inhibitory effect.

4.2. Study 1

In this study, we administered cerebellar tDCS during interleaved practice of three motor sequences. Immediately after practice and concurrent stimulation were finished, participants were given three novel sequences in an interleaved order during the same visit.

4.2.1. Method

(a) Participants

Eighty young adults with a mean age of 21.19 years (SD_{age} = 4.54 years; 44 women, 35 men, 1 declined to state; 71 right-handed, seven left-handed, two ambidextrous) were recruited and underwent an informed consent process as approved by the Institutional Review Board at UCLA. Inclusion requirements were that participants were between the ages of 18 and 35 years, had normal or corrected-to-normal vision, and were able to make quick movements with fingers, hands, or arms. Exclusion criteria were a current medical, neurological, or psychiatric diagnosis; chronic medication (excluding contraceptive pills) that could affect sensory processing, movement, or cognition; or metals located in the head. Participants rated handedness on a modified questionnaire based on the Edinburgh Handedness Inventory (Oldfield, 1971). Participants who did not perform the task with 90% accuracy or greater during practice, or 75% accuracy or greater during transfer were excluded from the analysis. Fourteen participants were excluded due to low accuracy during the task, and one participant was excluded due to technical difficulties with the stimulation device. This yielded a final count of 65 participants (M_{age} = 21.12 years, SD_{age} = 3.91 years; 33 women, 31 men, 1 not stated; 58 right-handed, five left-handed, and two ambidextrous). Participants were compensated with course credit or with cash at a rate of $15/hour.

(b) Behavioral task and procedure

The format of the task was the same as detailed previously in Chapter 2, except that all participants received interleaved practice and transfer. In one visit, participants practiced three sequences in an interleaved order and then received three novel sequences in an interleaved order. RT and accuracy were recorded.

(c) tDCS procedure

tDCS was delivered by a 9V battery-driven ActivaDose Iontophoresis Delivery Unit produced by ActivaTek, Inc. Two carbon electrodes were inserted into 5 x 7 cm^2 sponges soaked in saline solution and held in place on the scalp with plastic and rubber straps. The active electrode was centered 2 cm below the inion in order to target the cerebellum (Ferrucci et al., 2008; 2013). The reference electrode was placed on the cheek ipsilateral to the dominant hand in order to keep the path of current flow similar relative to the hand being used. In both real and sham stimulation conditions, stimulation was automatically ramped up from 0 mA to 2.0 mA over 20 seconds and the behavioral task began once stimulation reached 2.0 mA. In real stimulation conditions, 2.0 mA current was delivered for 20 minutes and then automatically ramped down to 0 mA. In sham stimulation conditions, 2.0 mA current was delivered for only 30 seconds and then switched to 0.1 mA for the remainder of the 20 minutes. Each participant experienced only one tDCS condition (anode, cathode, or sham stimulation). Stimulation was only applied during the practice session of the behavioral task. At the end of the practice session and the concurrent tDCS, the stimulation device was turned off but the electrodes remained in place while the participants completed the transfer session. The researcher remained in the testing room with the participant during the entire experiment to monitor stimulation. Figure 4.1 illustrates the experimental design.

4.2.2. Results

For each participant, the median RT of each block to complete each sequence during practice and transfer was calculated. Then, the mean of the median RTs to complete each sequence for each block during the practice and the transfer sessions were normalized to the first practice block's average median RT so that any initial differences in RT between stimulation groups were controlled for. Next, three different types of learning scores were calculated using the normalized RTs. First, two total learning scores, one for the practice session and one for the transfer session, were calculated by subtracting the normalized RT of the last block from the first block in each session. The total learning scores include sequence-specific and non-specific task learning. Sequence-specific learning was defined as the difference between the normalized RTs of the first transfer block and the final practice block. Finally, transfer learning was defined as the difference between the normalized RTs of the first practice block and the first transfer block. Figure 4.2 shows the normalized RTs for each stimulation group throughout the practice and transfer sessions.

The normalized RTs from practice and transfer sessions were analyzed with MANOVAs, with tDCS condition as a between-subjects factor and practice block as a within-subjects factor. A significant interaction between tDCS condition and practice block was found, $F(10, 116) = 2.34$, $p = .015$. Post-hoc univariate ANOVAs and t-tests were then conducted to look for significant differences in RT among the tDCS groups at each practice block. A significant main effect of tDCS condition was found for the fourth practice block, $F(2, 62) = 3.67$, $p = .031$. This was because the cathodal group was significantly slower than the sham group at this point, $t(40) = 2.35$, $p = .024$, and significantly slower than the anodal group as well, $t(42) = 2.37$, $p = .023$. However, the anodal group was not significantly different from the sham group, $t(42) = .071$, $p = .944$. No other significant differences between RTs among tDCS conditions during practice were found, all p's > .05. This pattern of results indicates that the cathodal group slowed during practice in comparison to the first practice block, but this effect was eliminated later in practice. No interaction was found between tDCS condition and transfer block, *F*(10, 116) = 0.401, *p* = .944. Furthermore, no main effect of tDCS condition was found during the practice or transfer sessions.

Further examination of each tDCS group individually revealed that only the anodal group showed learning during the practice session, as indicated by a significant difference between the first and final practice block, *t*(22) = 3.00, *p* = .007. It was also the only group to show significant sequence-specific learning, as indicated by a significant difference between the final practice block and the first transfer block, *t*(22) = -2.78, *p* = .033. No significant transfer was found, *t*(22) = 0.649, *p* = .523. The sham and cathodal groups did not demonstrate significant learning over practice, sequence-specific learning, nor transfer learning, all *p*'s > .05.

4.3. Study 2

Participants in the first tDCS study performed practice and transfer sequences in one visit. Although the majority of participants were able to perform with high accuracy in both sessions, participants from all tDCS conditions (sham and real) often commented on being tired or bored. It is possible that mental fatigue overcame any effects of stimulation, so for the following study, we added a period of 24 hours in between practice and transfer. We also asked participants to rate their level of attention and level of mental fatigue before and after tDCS using visual analog scales to ensure no differences occurred between sham and real stimulation groups. Because we were primarily interested in improving learning with stimulation, and an inhibitory effect of cathodal stimulation was found in the first study, only sham and anodal tDCS were given to participants for the second study.

4.3.1. Method

(a) Participants

A total of 38 participants with a mean age of 20.55 years (SD_{age} = 2.07 years; 18 women;

35 right-handed) were recruited from the undergraduate student population at UCLA. The same inclusion and exclusion criteria were applied as in the first study, and all participants underwent an informed consent process as approved by the Institutional Review Board at UCLA. Two participants were excluded due to low accuracy during practice, one participant was excluded due to incomplete data, and one participant felt dizzy during the initial ramp-up of stimulation and the study was stopped. Thus our final sample consisted of 34 participants (M_{age} = 20.06 years, SD_{age} = 1.67 years, 16 women, 29 right-handed), with 20 participants in the anodal stimulation group and 14 participants in the sham group.

(b) Behavioral task and tDCS procedure

The behavioral task was the same as described previously for Study 1 of this chapter with some exceptions. First, the experiment took place over two visits. Once the practice session was finished, participants were asked to return 24 hours later to complete the experiment. The next day during the transfer session, participants performed the three novel sequences. On visual analog scales (VASs) consisting of 100 mm horizontal lines, participants were asked to draw one vertical line on each to indicate levels of mental fatigue and attention. The number of mm out of 100 mm indicated by the participants' vertical line was recorded. Participants were asked to complete the two VASs three times: once during the first visit before practice and concurrent tDCS, again during the first visit immediately after practice and tDCS, and finally during the second visit before performing novel sequences.

4.3.2. Results

Figure 4.3 shows the normalized RTs throughout the practice and transfer sessions for the anodal and sham groups. Total learning, transfer learning, and sequence-specific learning were evaluated as described for the first study. MANOVAs did not reveal a significant interaction between tDCS condition and practice block nor a significant interaction between tDCS condition and transfer block, both *p*'s > .05, meaning that both groups were similar in their rates of learning during practice and during transfer. Neither tDCS group showed significant total learning during practice or transfer, both *p*'s > .05. We next examined transfer learning by comparing the RTs of the first practice and first transfer blocks for each of the stimulation groups. As shown in Figure 4.4, both the sham and anodal groups showed significant positive transfer, *t*(13) = 3.49, *p* = .004, and *t*(19) = 5.95, *p* < .001, respectively. Furthermore, there was a significant difference between transfer performance of the sham versus anodal groups, *t*(32) = 2.45, *p* = .020. Finally, no significant differences were found between stimulation groups for sequence-specific learning, *p* > .05. Both the sham and anodal groups showed a lack of sequence-specific learning (i.e., significant negative difference scores), *t*(13) = 2.17, *p* = .049, and *t*(19) = 3.58, *p* = .002, respectively.

The ratings of mental fatigue and attention levels were analyzed next. There was a main effect of the time of the VAS for mental fatigue, *F*(2, 31) = 5.19, *p* = .011, meaning that participants in both the sham and anodal groups gave ratings of higher mental fatigue immediately after practice compared to immediately before transfer, *p* = 008. There was also a marginally significant main effect of test time for attention, *F*(2, 31) = 2.93, *p* = .068, such that the participants rated themselves as significantly more attentive before transfer in comparison to before practice, *p* = .024. However, there were no main effects of tDCS on ratings of mental fatigue and attention, and no interactions with tDCS and VAS rating time for mental fatigue and attention, all *p*'s > .05.

4.4. General discussion

In the experiments reported here, tDCS applied to cerebellum was shown to affect performance and learning of motor sequences. In Study 1, the finding that cathodal stimulation impaired performance of the sequences during practice is a novel finding concerning tDCS and sequence learning. Furthermore, although there was no interaction between tDCS condition and block, the anodal group was the only group to show significant learning over practice, as indicated by the difference in RTs between the first and final practice blocks. Because subjects were required to practice three interleaved sequences, learning was relatively difficult in this task. The anodal group was also the only group that showed significant sequence-specific learning, as shown by the difference between the final practice block and the first transfer block of novel sequences. These results are consistent with the enhanced learning that Ferrucci et al. (2013) observed after anodal tDCS was applied after the baseline SRT task.

The online effect of cathodal stimulation does not appear to be inhibitory for the entire length of practice, as the initial increase in practice RTs was eliminated during the final two practice blocks. It is possible that homeostatic plasticity mechanisms are responsible for this change in that the neurons may engage in compensatory regulation of their excitability. One study examining anodal stimulation of 1.0 mA delivered to the primary motor cortex (M1) in various schedules found evidence of homeostatic plasticity (Monte-Silva et al., 2013). Some participants were given only one 13-minute session of anodal tDCS, whereas some were given two 13-minute sessions without a break in between (i.e., a 26-minute continuous session). M1 excitability was increased by about 20% after the single session of 13-minute tDCS compared to an initial baseline measurement, which was the expected excitatory effect of anodal tDCS. In contrast, M1 excitability was reduced by about 20% compared after 26 minutes of continuous stimulation. Thus there appears to be a reversal in the expected effect of tDCS between 13 and 26 minutes. In the current experiment, stimulation only lasted for 20 minutes, and the fourth practice block (where the slowest average RT occurs) took place between approximately the 10th and 14th minute of stimulation. The decrease in RTs in the fifth and sixth practice blocks is consistent with a reversal in the direction of excitability change between 13 and 26 minutes. Monte-Silva et al.'s experiment also differs since excitability changes were assessed after stimulation (in addition to site of stimulation) whereas we are inferring excitability changes through performance change during stimulation. But perhaps similarly in our experiment, homeostatic plasticity mechanisms could have been engaged after a certain amount of time to counteract the excitability shift due to cathodal stimulation. Synaptic scaling, a type of homeostatic plasticity, can be caused by prolonged changes in neuronal excitation and serves to reduce or increase the strength of all synapses accordingly (Turrigiano, 2012). This could possibly explain why some learning, as shown by increasingly faster RTs, becomes apparent at the end of practice. In the same vein, another study (Fricke, Seeber, Thirugnanasambandam, Paulus, Nitsche, and Rothwell, 2011) found that when a five-minute session of cathodal tDCS was given alone to M1, the expected inhibitory effect on motor-evoked potentials was found. If it was followed with five minutes of cathodal tDCS three minutes later, it facilitated motor-evoked potentials starting five minutes after the end of stimulation and lasting up to 30 minutes later, in comparison to a continuous 10-minute session of cathodal stimulation. This suggests a time course of about 13 to 18 minutes for homeostatic effects to be observed.

Another recent study examined the effects of cerebellar tDCS on a sequential pinch task (Cantarero et al., 2015). Over three consecutive days, anodal, cathodal, or sham tDCS was given during practice of the task. Task difficulty was individually adjusted to prolong learning. Anodal stimulation to the cerebellum was found to improve acquisition starting on the first day, mainly by reducing error rates. Our finding of an online effect of stimulation is consistent with theirs.

However, it is unclear why we observed an effect of cathodal stimulation whereas they observed an online effect of anodal stimulation. These results together might suggest that cathodal stimulation does not lead to the exact behavioral inverse of anodal tDCS (Cantarero et al., 2015), and might depend on characteristics of the task.

It has been found that interleaved practice benefits retention and transfer for a variety of motor skills in comparison to repetitive practice (Magill & Hall, 1990; Brady, 2004). In Study 2, it appears that anodal tDCS to the cerebellum was able to increase the benefit of interleaved training on transfer performance. Although both the sham and anodal tDCS groups appeared to benefit from a 24-hour period of consolidation as demonstrated by significant positive transfer, the anodal tDCS group demonstrated greater transfer than the sham group. This difference does not appear to be due to effects of tDCS on levels of attention or mental fatigue. This result is similar to other research indicating that the effects of tDCS are better observed at a delay (Ferrucci et al., 2008; 2013; Peters, Thompson, Merabet, Wu, & Shams, 2013). It suggests that tDCS may serve to improve consolidation, which in turn would better support transfer performance than the more labile memory traces that were likely present in Study 1 due to a lack of a prolonged consolidation period. It is possible that the aftereffect of cerebellar tDCS, which can last up to 30 minutes after stimulation is over (Galea et al., 2009), could be directly enhancing consolidation processes. However, although the cerebellum may be involved in the consolidation of adaptation skills (Shadmehr & Holcomb, 1997, Debas et al., 2010), consolidation of motor sequence tasks seem to be more dependent on the striatum (Debas et al., 2014) and/or M1 (Steele & Penhune, 2010) while the cerebellum may be more crucial for early learning (Bernard & Seidler, 2013). Alternatively, anodal tDCS could be improving the instantiation of generalized internal models during acquisition by increasing the prediction error sensitivity of Purkinje cells (Galea et al., 2009). It has been hypothesized that interleaved learning allows for more opportunities to compare and contrast different tasks, leading to better encoding of abstract features that would be useful to retrieve during transfer (Shea & Morgan, 1979; Shea & Zimny, 1983). Both sham and anodal groups practiced sequences in an interleaved fashion, but perhaps anodal stimulation led to improved detection and encoding of general rules and features that were relevant to the practiced and novel sequences in the task. Consolidation also took place for both stimulation groups, but consolidation of a more developed internal model would better support transfer performance.

tDCS is non-invasive, portable, and a relatively inexpensive means to manipulate neural activity. It is easy to use and thus it is feasible to use in real world settings. We have demonstrated that anodal tDCS delivered to the cerebellum can be used to enhance learning of fine motor sequences that supports generalization.

4.5. Figures

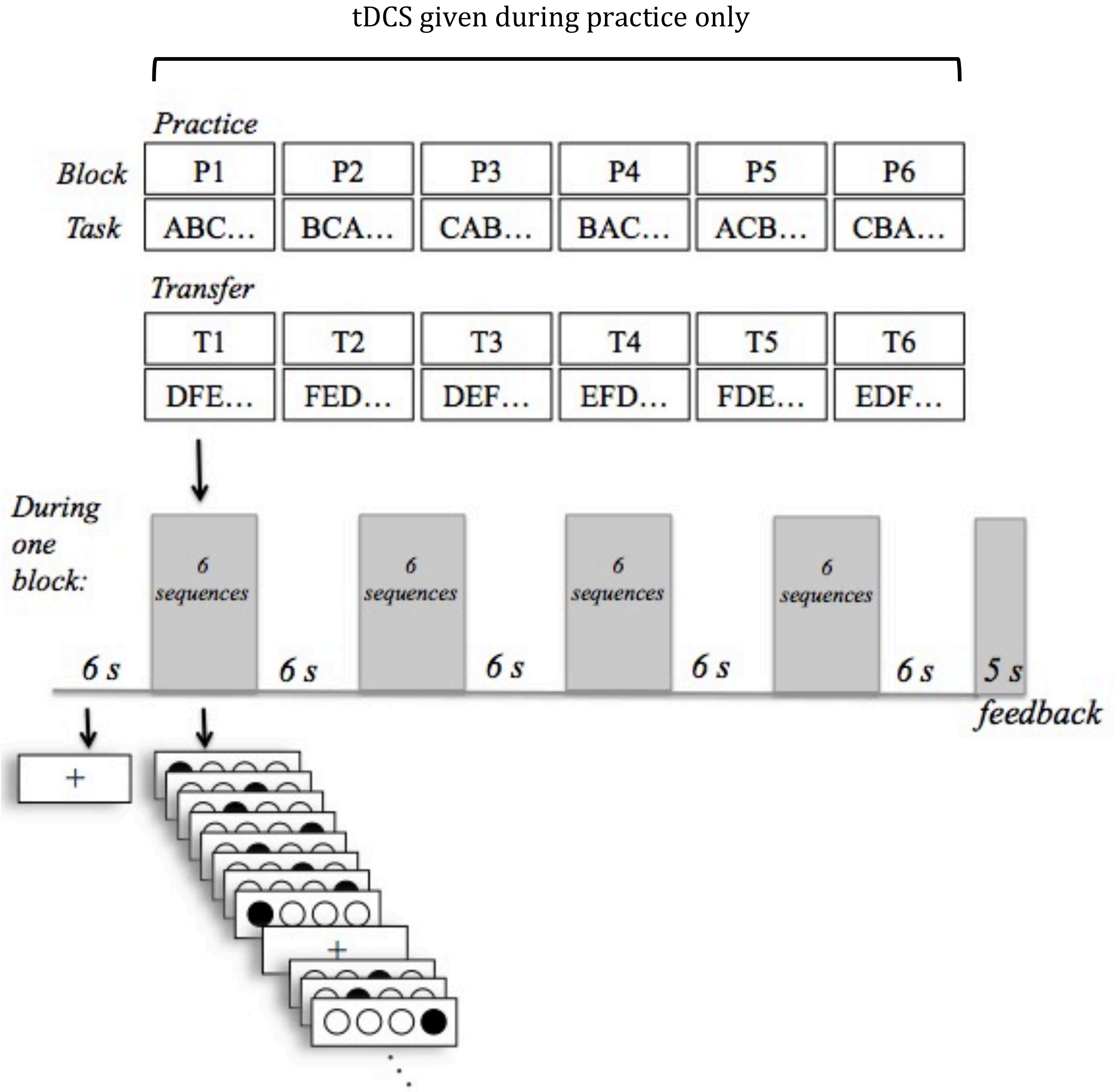

Figure 4.1. Participants practiced three sequences in an interleaved order (blocks P1-P6), and then received three novel sequences in an interleaved order (blocks T1-T6). Transcranial direct current stimulation (tDCS) was delivered to the cerebellum for the duration of the practice session. In Study 1, transfer occurred immediately after practice and concurrent stimulation. In Study 2, transfer occurred after a 24 hour delay. Each letter A-F represents a different 8-element sequence.

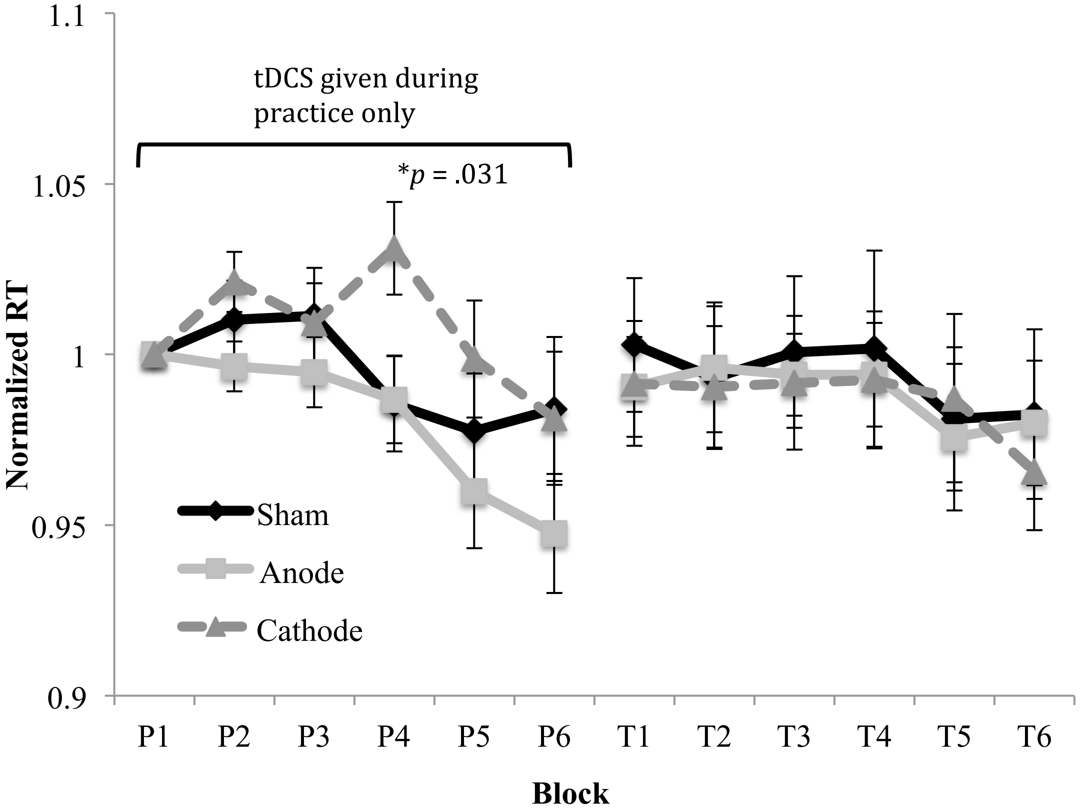

Figure 4.2. Study 1: RTs normalized to the first practice block RT (P1) to control for any pre-existing differences in performance. The practice session consists of P1 through P6, where the number indicates the block. The transfer session consists of T1 through T6.

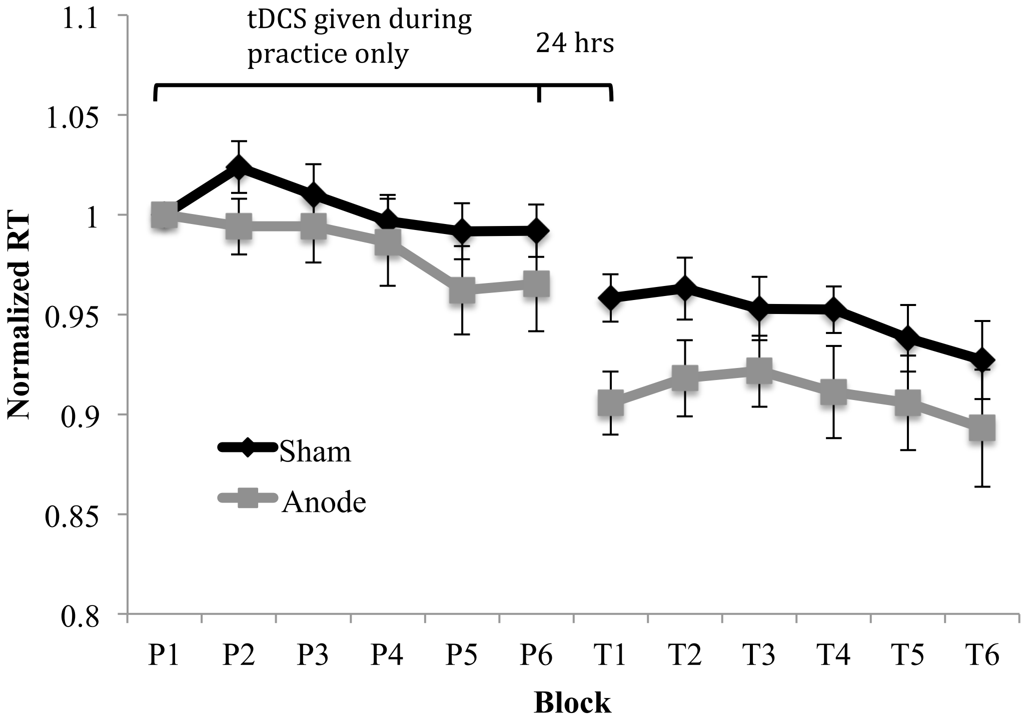

Figure 4.3. Study 2: RTs normalized to the first practice block RT (P1) to control for any pre-existing differences in performance. The practice session consists of P1 through P6, where the number indicates the block. The transfer session consists of T1 through T6.

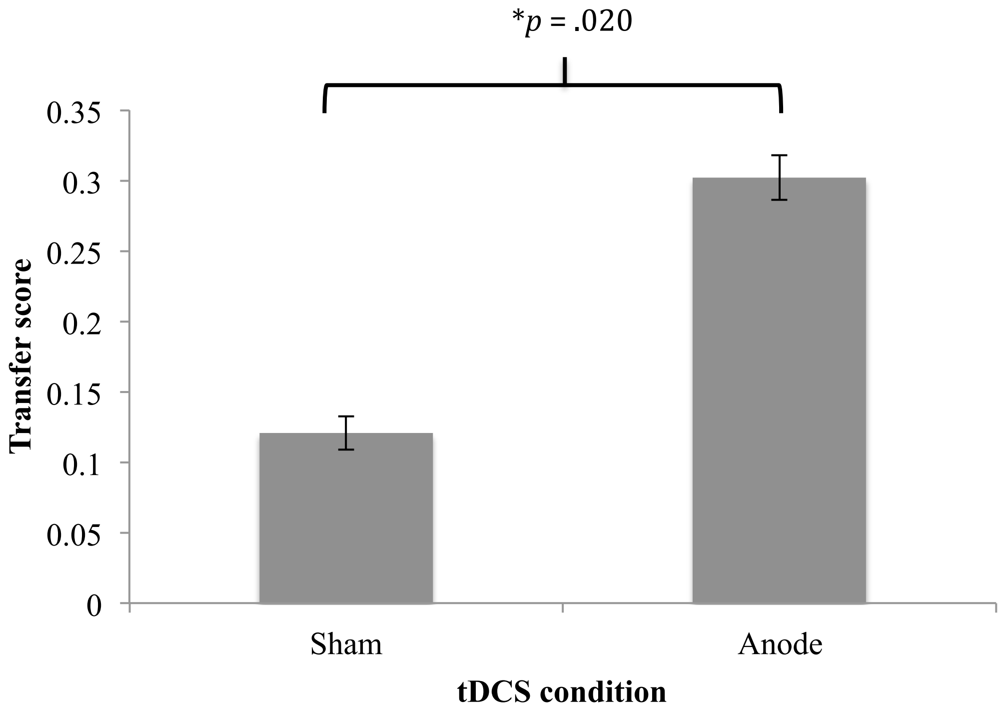

Figure 4.4. In Study 2, there was a significant difference between transfer scores of the sham and anodal tDCS groups, such that the anodal tDCS group showed greater positive transfer than the sham group.

CHAPTER 5. Conclusion

In general, we were interested in the ability to generalize or transfer to novel sequences of movements, and specifically, ways that we could enhance transfer learning. In the first behavioral study, we were able to apply a relatively simple manipulation of interleaving the practiced sequences to promote transfer performance. The benefit of interleaved training was apparent for both repetitive and interleaved novel sequences, which suggests that higher levels of CI can ultimately reduce the amount of interference from sequence-specific knowledge. This benefit could be a result of more opportunities to compare and contrast the different sequences during training, which would allow the learner to detect and eventually apply the more abstract features of the sequences during transfer. This finding served as the motivation for the second neuroimaging study in which we examined correlations between BOLD activity and transfer performance. In particular, cerebellar activity during practice was associated with better subsequent transfer performance, suggesting that those who are better at forming internal models may acquire abstract features to select and retrieve when forming new internal models corresponding to novel sequences. Thus the cerebellum appeared to be a favorable target for tDCS in trying to enhance transfer learning, with those results still pending. We observed a polarity-specific effect of tDCS during practice, since we found an inhibitory effect on learning rate of cathodal but not anodal or sham stimulation. Furthermore, the second tDCS experiment reveals a trend towards an offline effect of anodal stimulation on transfer learning.

Future directions could resolve some of the limitations in these studies. Our initial behavioral study may not have been optimized to examine differences in the rate of transfer learning. Longer encoding sessions could lead to larger, detectable differences in the rate of learning for novel sequences. More training would likely lead to overall greater levels of interference from sequence-specific knowledge for both practice groups, but the memory traces formed through interleaved practice that are perhaps fundamentally distinct from those formed through repetitive practice might provide a more stable foundation that supports faster learning during transfer to novel sequences. Using an adaptation task, Seidler and Noll (2008) have found that the rate of positive transfer to a novel visuomotor mapping was associated with lower activation in brain regions that are generally recruited earlier in adaptation, and greater activation in other areas typically recruited later in the process. They interpreted these findings to mean that successful transfer relies at least in part on the previously formed memories, which allows the learner to proceed more quickly through the early stage of adaptation when faced with a novel visuomotor mapping. It is possible that more interleaved practice on the first three sequences would allow their more abstract features to become more stable or salient in comparison to blocked practice, and thus would lead changes in the rate of learning novel sequences.

For the neuroimaging study, our interest was in examining individual neural differences that could underlie the benefits of interleaved learning; however, a repetitive practice control condition would be informative in determining what underlies the benefit of interleaved compared to repetitive training. Currently, our data only indicate that differential engagement of the cerebellum predicts subsequent transfer performance. As mentioned previously, Kantak et al. (2010) found that the dorsolateral prefrontal cortex and M1 were differentially engaged depending on the practice structure. Similarly, we might find that the cerebellum is overall more engaged during interleaved learning compared to repetitive practice. If that were the case, tDCS could be applied during both repetitive and interleaved practice. Perhaps a larger effect on learning might be seen for repetitive practice since there is more room for improvement.

An issue that limits comparison between our tDCS study to other studies is that the electrode montage used here is slightly different than that of other studies that attempted to specifically target the right cerebellar hemisphere whereas we targeted the midline with slightly larger electrodes. This change was motivated by our neuroimaging results showing more medial BOLD activity was correlated with transfer scores. Some use a cerebellum-right shoulder montage (Ferrucci et al., 2013) whereas others used a cerebellum-right cheek montage (e.g., Galea et al., 2009; 2011; Cantarero et al., 2015). Although the modeling study by Parazzini and colleagues (2014) suggests that small changes in the position of 7 x 8 cm^2 electrodes do not have a significant effect on the electric field density of the cerebellum, smaller electrodes with dimensions like 5 x 5 cm^2 and their relative positions might have a discernable change in effect when compared to our montage using 5 x 7 cm^2 electrodes. Models of electric field density and current path would be informative; in particular, those based on anisotropic head models since current tends to flow along fiber paths in white matter (Rampersad et al., 2014).

We have also observed individual differences in the benefits of interleaved practice, so it would be interesting to determine if there are factors that contribute to greater responsiveness to tDCS when individuals engage in interleaved training of fine motor skills. For example, the catechol-O-methyltransferase (COMT) enzyme is responsible for degrading dopamine, especially in the prefrontal cortex. A polymorphism in the COMT gene that arises due to an amino acid exchange from valine (Val) to methionine (Met) can affect enzyme activity; thus, those with Met-Met homozygosity tend to have greater amounts of available dopamine in the prefrontal cortex compared to Val carriers. It appears that those with the Met-Met carriers were more responsive to tDCS, whereas Val carriers were not (Plewnia, Zwissler, Längst, Maurer, Giel, & Krüger, 2013). The authors mention that if the genetic differences had been ignored, they would not have detected a significant effect of stimulation. Identifying those individual differences that contribute to responsiveness of tDCS would aid in developing effective clinical applications of tDCS.

Together, our results indicate that interleaved practice or tDCS could potentially be applied to enhance transfer in situations such as occupational rehabilitation, where certain fine motor tasks might be practiced during sessions with a therapist but must be also carried out effectively at home. Brady (2004) found a smaller effect size when interleaving was applied to tasks outside of a lab setting, which might suggest that interleaving is more useful particularly for less complex tasks with fewer motor demands. These types of task might occur earlier in rehabilitation sessions. More recent work has examined the benefits of the distribution of practice in non-motor learning domains, such as mathematics (e.g., Rohrer, Dedrick, & Burgess, 2014). tDCS is portable, with minimal equipment requirements, and it relatively easy to teach others how to use it safely. These changes could facilitate transfer learning through enhancement of cerebellar functioning.

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