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Neural evidence of a role for spatial response selection in the learning of spatial sequences

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ABSTRACT

Despite over 20 years of behavioral research, considerable disagreement remains regarding the locus of the cognitive mechanisms (e.g., stimulus encoding, response selection or response production) responsible for the acquisition and expression of learned sequences. Functional neuroimaging may prove invaluable for resolving this controversy. The cortical mechanisms underlying spatial response selection (i.e., right dorsal prefrontal, dorsal premotor and superior parietal cortices) are well known. These regions as well as supplementary motor area, striatum and the hippocampus have also been implicated in sequence learning. This neural overlap lends support for the hypothesis that spatial response selection is involved in learning spatial sequences; however, these experimental factors have not been investigated in the same experiment so the extent of neural overlap is debatable. The present study investigates the role of spatial response selection in sequence learning during the performance of the serial reaction time task. We orthogonally manipulated spatial sequence learning and spatial response-selection difficulty to precisely identify the neural overlap of these cognitive systems. Results demonstrate near complete overlap in regions affected by the spatial response selection and spatial sequence learning manipulations. Only right dorsal prefrontal cortex was selectively influenced by the response selection difficulty manipulation. These findings emphasize the importance of spatial response selection for successful spatial sequence learning.

1. Introduction

Most human goal-directed behavior must be learned. Whether driving a car, baking a cake or programming our DVR we rely on procedural knowledge, or "how-to" knowledge, every day. Many tasks require that we learn the appropriate mapping between environmental stimuli and behavioral responses (stimulus–response, S–R, association learning). Frequently these tasks require the completion of a sequence of behaviors. We learn some of these behaviors explicitly, but others are learned without our awareness. This *implicit* sequence learning and S–R association learning have typically been studied separately — even though both types of procedural learning are involved in many of the tasks we perform every day. The neuroimaging research of these separate literatures demonstrate considerable overlap in the brain regions (viz., dorsal premotor, dPMC; superior parietal, SPC; and dorsal prefrontal, dPFC) mediating spatial response selection (i.e.,

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the cognitive process that activates the appropriate response to a given environmental stimulus) and spatial sequence learning (Bischoff-Grethe et al., 2004; Dassonville et al., 2001; Grafton et al., 1995, 2001; Iacoboni et al., 1996; Jiang and Kanwisher, 2003; Merriam et al., 2001; Schendan et al., 2003; Schumacher and D'Esposito, 2002; Schumacher et al., 2003, 2005, 2007; van der Graaf et al., 2006). This extensive neural overlap as well as some behavioral research (discussed below) emphasizing the importance of response selection in sequence learning (Deroost and Soetens, 2006; Hazeltine, 2002; Schumacher and Schwarb, 2008; Willingham et al., 1989) suggests that these two seemingly separate areas of study may rely on the same underlying neurocognitive mechanisms. Yet, other research implicates other processing stages (e.g., stimulus encoding or response production) as the locus of the sequence learning effect (e.g., Bischoff-Grethe et al., 2004; Clegg, 2005; Cohen et al., 1990; Grafton et al., 2001; Howard et al., 1992; Mayr, 1996; Willingham, 1999; Willingham et al., 2000). The current research addresses this controversy directly by manipulating sequence learning and response selection difficulty in the same functional magnetic resonance imaging (fMRI) experiment.

For over two decades, spatial sequence learning has been studied using the serial reaction time (SRT) task (e.g., Nissen and Bullemer, 1987). Though it is not normally conceptualized as such, the SRT task is similar to the perceptual-motor tasks typically used to study response selection (e.g., Duncan, 1977; Fitts and Seeger, 1953). In the typical SRT task, participants make manual responses to the location of visual stimuli presented on a computer screen (usually 3–6 possible target locations). Unknown to the participants, the stimulus presentation follows an ordered sequence (typically 6–12 positions in length). Reaction times (RTs) are typically faster for sequenced than unsequenced blocks of trials, indicating that participants benefit from knowledge of the sequence during task performance.

There is considerable disagreement concerning the cognitive processes important for learning a spatial sequence in the SRT task. Several researches suggest that learning is mainly perceptual (e.g., Clegg, 2005; Cohen et al., 1990; Grafton et al., 2001; Howard et al., 1992; Mayr, 1996). According to this hypothesis, sequence learning is based on stimulus–stimulus associations: participants learn the specific sequence of stimuli. Other researchers propose that spatial sequence learning is not purely perceptual; rather it relies on response production (e.g., Bischoff-Grethe et al., 2004; Willingham, 1999; Willingham et al., 2000). This hypothesis states that during SRT task performance, participants learn the specific sequence of the responses made throughout the experiment. Finally other researchers propose that sequence learning has both perceptual and motor components. This hypothesis emphasizes the importance of learning the S–R rules for a task; thus implicating response selection (e.g., Deroost and Soetens, 2006; Hazeltine, 2002; Schumacher and Schwarb, 2008; Schwarb, 2008; Willingham et al., 1989) suggesting that participants learn the ordered sequence of S–R rules required to perform the task.

As previously noted, response selection is often conceptualized as the cognitive process that chooses representations for appropriate motor responses to particular stimuli, given one's current task goals (Duncan, 1977; Kornblum et al., 1990; Meyer and Kieras, 1997). The possible responses available for selection are defined by some set of previously learned S–R associations. Willingham et al. (1989) were the first to identify the importance of response selection for SRT task performance. They showed that when participants had to respond to stimuli that occurred in a sequence, sequences in ancillary experimental factors (e.g., the location of stimuli when participants responded to the color) did not affect performance. Furthermore, participants did not benefit from prior exposure to the location sequence (during an experimental phase when they responded to stimulus color) in a subsequent phase of the experiment when they began responding to stimulus location. Willingham et al. concluded that sequence learning involved learning associations between particular S–R pairs. Thus, when participants were asked to make a response to a different feature of the stimulus, the previously learned S–R rules were no longer relevant and could not aid task performance.

Data from our laboratory support this conclusion (Schwarb, 2008). We modified a procedure used by Willingham (1999) and trained participants in the SRT task using an incompatible S–R mapping (like the one shown in Fig. 1). After participants had learned the sequence (training phase), participants were divided into three different testing phase groups. One group used the incompatible S–R mapping throughout the duration of the experiment; a second group switched to a compatible mapping (Fig. 1) during the testing phase though the sequence of stimuli remained constant between phases; and the third group also switched to a compatible mapping at test, but the sequence of response locations remained constant between phases. Unlike Willingham, only the first group (i.e., the group in which the S–R mapping did not change) showed a benefit of sequence learning during the testing phase.[1] This suggests that response selection is important for successful sequence learning because only when the S–R rules were maintained did sequence knowledge transfer from the training to the testing phases.

The continuing controversy in the literature regarding the locus of the sequence learning effect (e.g., stimulus encoding, response selection, response production) suggests that a resolution may require more than behavioral dependent measures. Existing neuroimaging evidence indirectly links spatial response selection and spatial sequence learning through areas of common activity in studies focusing separately on each process. The current study investigates this issue directly by manipulating both processes within the same procedure.

Right dPFC, bilateral dPMC and bilateral SPC are consistently shown to mediate spatial response selection (Dassonville et al., 2001; Iacoboni et al., 1996; Jiang and Kanwisher,

[1] Further research is needed to identify why we failed to replicate Willingham (1999). One possible reason may be that we used a more difficult S–R mapping than was used in the original experiment. This may have forced our participants to rely more on the S–R rules and response selection than did the participants in Willingham's study (for more details see Schwarb, 2008).

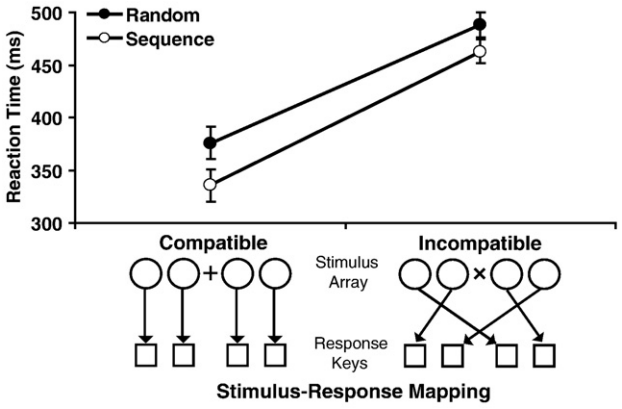

Fig. 1 – Mean reaction times and standard errors for each of the experimental conditions. Also shown are the compatible and incompatible stimulus–response mappings used. Bimanual responses were made with the middle and index fingers of each hand. Left middle and index fingers were placed on the left two buttons and right middle and index fingers were placed on the right two buttons.

2003; Merriam et al., 2001; Schumacher and D'Esposito, 2002; Schumacher et al., 2003, 2005, 2007). This fronto-parietal network is consistently active across many conditions, for example, when the task has been well practiced (Schumacher et al., 2005), during preparation before stimulus onset (Schumacher et al., 2007), and when the stimuli are held in working memory (Rowe et al., 2000). Furthermore, dPMC and SPC, as well as bilateral dPFC have also been implicated in spatial sequence learning studies using the SRT task (Bischoff-Grethe et al., 2004; Grafton et al., 1995, 2002; Olson et al., 2006; Rauch et al., 1997b; van der Graaf et al., 2006). Regional activation for sequence learning does not, however, correspond exactly to the characteristic pattern of response selection. Activation in additional regions is frequently reported in the sequence learning literature. These brain regions include supplementary motor area (SMA), (e.g., Bischoff-Grethe et al., 2004; Grafton et al., 1995, 2002; Hazeltine et al., 1997; Olson et al., 2006); striatum, (e.g., Destrebecqz et al., 2005; Grafton et al., 1995, 2002; Peigneux et al., 2000; Rauch et al., 1995; Schendan et al., 2003); and hippocampus (e.g., Fortin et al., 2002; Grafton et al., 1995; Schendan et al., 2003).

Common regions of activation reported in the sequence learning and response selection literatures suggest a relationship between these two cognitive processes; however, this crude comparison of neural activation is not conclusive. Differences in imaging procedures and analysis techniques do not allow for a direct comparison of precise neural regions of activation. In a given region, sites of peak activation as well as activation cluster sizes can vary dramatically between studies; thus two studies reporting the same active region could, in fact, refer to very different areas of cortex. Therefore, a more direct evaluation of the apparent neural overlap between spatial sequence learning and spatial response selection is necessary.

Our current experiment was designed to systematically investigate the overlap between the neurocognitive processes mediating spatial response selection and spatial sequence learning. To do this, we measured brain activation with fMRI while orthogonally manipulating spatial sequence structure (sequenced and random blocks) and spatial S–R compatibility (compatible and incompatible S–R mappings; see Fig. 1) in both practiced and unpracticed participants. Stimulus–response compatibility is a paradigmatic manipulation affecting response-selection difficulty (Kornblum et al., 1990; McCann and Johnston, 1992; Sanders, 1980; Schumacher et al., 1999; Sternberg, 1969). Specifically, we investigated the effects of the S–R compatibility and sequence structure manipulations in the brain regions previously implicated in studies of spatial response selection and spatial sequence learning (viz., right dPFC, dPMC, SMA, SPC, striatum and hippocampus). The sites of peak activation and extent of these regions are shown in Fig. 2 and Table 1. With this design, we can directly and precisely identify the neural overlap in spatial response selection and spatial sequence learning. These data may then inform cognitive theories of the processes underlying spatial sequence learning.

Consistent with the behavioral findings discussed above (Deroost and Soetens, 2006; Hazeltine, 2002; Schumacher and Schwarb, 2008; Schwarb, 2008; Willingham et al., 1989) and the apparent overlap in mediating brain regions, we hypothesized that spatial sequence structure and S–R compatibility would influence common mental processes. Appealing to additive factors logic (Sternberg, 1969, 2001) we expected that these factors would have interacting effects on mean RT, which would indicate that they affect at least one common stage (e.g., response selection). We also predicted that both factors would affect brain activity in regions previously implicated in response selection and sequence learning. However, because the relationship between stage processing and neural activity is not well understood, specific interacting patterns of factors on brain activity were not predicted (c.f., Sternberg, 2001).

2. Results

Two participants were removed from the data set because their learning scores were more than three standard deviations below the mean in the compatible condition (random blocks were 156 ms and 208 ms faster than sequenced blocks) indicating that these participants acquired no knowledge of the sequence over the course of the experiment.

Brain activity for the two Groups (practiced and unpracticed) did not interact with Sequence Structure (sequenced and random; $p>0.15$ in all cases) or S–R compatibility (compatible and incompatible mappings; $p>0.08$ in all cases) in any of the tested regions-of-interest (ROIs). Therefore, data from the two groups were combined and analyzed together to increase statistical power.

2.1. *Behavioral results*

2.1.1. *Reaction times*

Mean RTs were analyzed using a two-way ANOVA with within-subjects variables for S–R compatibility and Sequence

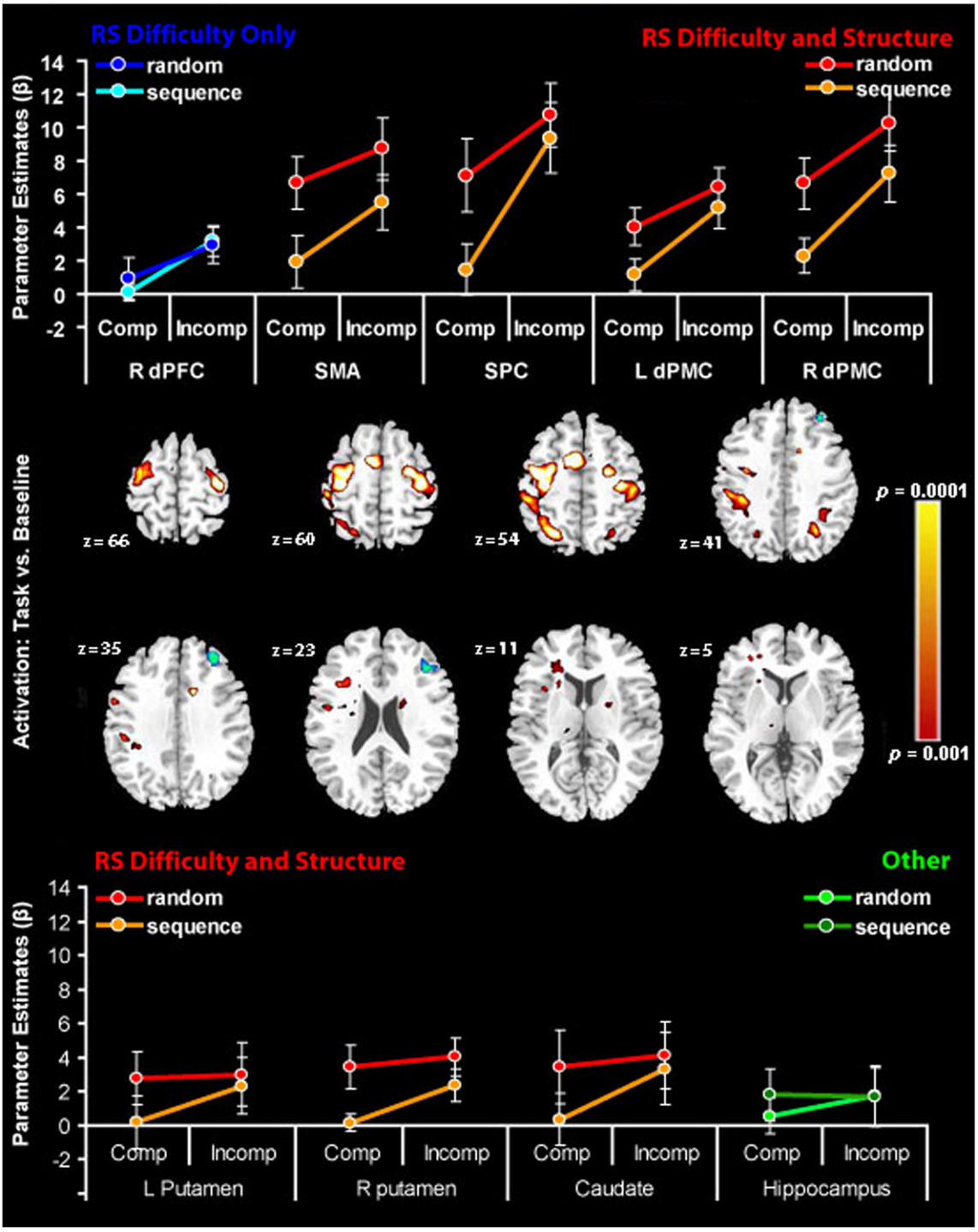

Fig. 2 – Axial brain slices show extent of activity for cortical regions from Table 1. Voxels with task-related activity (Task Conditions vs. Baseline) greater than $p<0.001$ (uncorrected) contiguous to peak activity are shown (warm colors). The right dorsal prefrontal region-of-interest defined in Schumacher et al., (2003) is also shown (cool colors). Line graphs plot mean activity and standard errors relative to baseline for each task (Incomp = incompatible; Comp = compatible).

Structure (Fig. 1). This analysis revealed a significant main effect of both S–R compatibility, $F(1, 21)=215.89$, $p<0.001$, and Sequence Structure, $F(1, 21)=43.46$, $p<0.001$. The S–R compatibility by Sequence Structure interaction did not reach statistical significance, $F(1, 21)=2.47$, $p=0.13$.

2.1.2. *Error rates*

Mean error rates were 3.4%, 4.5%, 9.7% and 8.8% for the compatible-sequenced, compatible-random, incompatible-sequenced and incompatible-random conditions, respectively. An arcsine transformation was performed on the

Table 1 – Coordinates for peak task-related activation, voxel and cluster size for each region-of-interest

Region		x	y	z	Cluster size	t-value
dPFC	R	36	39	31	215	
dPMC	R	27	−8	60	225	5.05
	L	−25	−5	55	327	4.47
SMA		−4	2	55	431	5.01
SPC	R	26	−62	52	89	4.02
	L	−24	−62	52	421	4.55
Caudate	R	20	2	22	23	3.88
	L	−20	7	19	3	3.28
Putamen	R	24	2	11	14	3.50
	L	−22	13	11	3	3.29

error rates of each participant to stabilize the variance (Kleinbaum et al., 1998). The data were then analyzed using a two-way ANOVA with within-subjects variables for S–R compatibility and Sequence Structure. The main effects of both S–R compatibility, $F(1, 21)=38.97$, $p<0.001$, and Sequence Structure, $F(1, 21)=5.60$, $p<0.05$, were significant. Thus, participants were more accurate on sequenced blocks compared to random blocks and compatible blocks compared to incompatible blocks. The interaction was not significant, $F(1, 21)=0.22$, $p=0.64$.

2.1.3. *Explicit knowledge*

Mean recognition scores were 52.1% and 54.9% for the compatible-sequenced and incompatible-sequenced explicit knowledge questionnaires respectively (50% was chance performance). *T*-tests were performed on these data and revealed that scores for the compatible-sequenced explicit knowledge questionnaires did not differ significantly from chance, $t(21)=0.67$, $p=0.51$. Scores on the incompatible-sequenced explicit knowledge questionnaire approached significance, $t(21)=2.02$, $p=0.06$. These results suggest that participants had at least partial explicit knowledge of the sequence when using the incompatible mapping. Further analysis revealed that this difference was driven by the scores from the practiced group's explicit knowledge questionnaires. Separate analyses of the incompatible-sequenced data were conducted for each group. The practiced group's scores were significantly different from chance, $t(11)=2.74$, $p<0.05$, however, the unpracticed group's scores were not, $t(9)=0.07$, $p=0.95$. This is perhaps unsurprising considering that the practiced group had twice as much exposure to the sequence. What is interesting, however, is that Group did not interact with either S–R compatibility or Sequence Structure in any of the ROIs investigated; thus it seems that despite different levels of explicit knowledge between the two Groups, this qualitative difference in learning did not effect brain activation in the brain ROIs.

2.2. *Imaging results*

For each participant and ROI, mean activation (β-value) relative to the baseline was extracted for each of the task conditions: compatible-random, compatible-sequenced, incompatible-random and incompatible-sequenced. This resulted in four β-values for each participant for each ROI. Separate two-way ANOVAs with within-subjects variables for S–R compatibility and Sequence Structure were performed for each ROI. If bilateral activation was evident, a three-way Hemisphere (right and left) by S–R compatibility by Sequence Structure ANOVA was also conducted. Activation maps and associated activation parameter estimates (β-values) for each ROI are shown in Fig. 2.

2.2.1. *Regions mediating both response selection and sequence learning*

2.2.1.1. Dorsal premotor cortex (Left: x=−25, y=−5, z=55; Right: x=27, y=−8, z=60). Bilateral dPMC activity was evident and a Hemisphere by S–R compatibility by Sequence Structure ANOVA revealed a significant main effect of Hemisphere, $F(1, 21)=12.50$, $p<0.01$, as well as significant Hemisphere by S–R compatibility, $F(1, 21)=4.53$, $p<0.05$, and Hemisphere by Sequence Structure, $F(1, 21)=4.52$, $p<0.05$, interactions; therefore the data from the left and right hemispheres were analyzed separately. The three-way interaction, $F(1, 21)=0.07$, $p=0.79$, was not significant. For the left dPMC, there was a significant main effect of S–R compatibility, $F(1, 21)=16.87$, $p<0.001$. The main effect of Sequence Structure, $F(1, 21)=4.14$, $p=0.06$, approached significance and the interaction, $F(1, 21)=0.99$, $p=0.33$, was not significant. For the right dPMC, the activation pattern was similar with a significant main effect of both S–R compatibility, $F(1, 21)=15.79$, $p<0.001$, and Structure, $F(1, 21)=6.06$, $p<0.05$. The interaction, $F(1, 21)=0.36$, $p=0.56$, was again not significant.

2.2.1.2. Superior parietal cortex (Left: x=−24, y=−62, z=52; Right: x=26, y=−62, z=52). Bilateral activity was evident in the SPC and there were no significant main or interacting effects of Hemisphere ($p>0.10$ in all cases) so data were combined across the hemispheres. The two-way ANOVA revealed a significant main effect of both S–R compatibility, $F(1, 21)=26.51$, $p<0.001$, and Sequence Structure, $F(1, 21)=4.48$, $p<0.05$. The S–R compatibility by Sequence Structure interaction, $F(1, 21)=2.44$, $p=0.13$, was not significant.

2.2.1.3. Supplementary motor area (x=−4, y=2, z=55). There was only one medial ROI for SMA, so Hemisphere was not included in the ANOVA. There was a significant main effect of S–R compatibility, $F(1, 21)=6.33$, $p<0.05$, and Sequence Structure, $F(1, 21)=6.69$, $p<0.05$. The S–R compatibility by Sequence Structure interaction was not significant, $F(1, 21)=0.38$, $p=0.54$.

To investigate possible practice-related changes in SMA activity across the experiment (discussed below), we analyzed the data from the unpracticed group with an ANOVA including Block (1–12) as a factor (i.e., mean activation, β-values , relative to baseline was extracted for each participant in the previously defined SMA ROI for both conditions, S–R compatibility and Sequence Structure). This analysis revealed significant main effects of Block, $F(11, 88)=2.65$, $p<0.01$, and Sequence Structure, $F(1, 8)=5.41$, $p<0.05$. As shown in Fig. 3, activity decreased across blocks and activity was greater in random than sequenced blocks. There was also a significant S–R Compatibility by Block interaction, $F(11, 88)=2.51$, $p<0.01$, with incompatible trials

demonstrating a greater decrease in activity across blocks compared to compatible trials. None of the other main or interacting effects were significant ($p>0.09$ in all cases).

2.2.1.4. Putamen (Left: x=−22, y=13, z=11; Right: x=24, y=2, z=11). Bilateral activity was evident in the putamen and there was a significant Hemisphere by Sequence Structure interaction, $F(1, 21)=4.55$, $p<0.05$, no other main or interacting effects of Hemisphere ($p>0.10$ in all cases) were significant. Therefore, data from the left and right hemispheres were analyzed separately. For the right putamen, there was a significant main effect of Sequence Structure, $F(1, 21)=5.54$, $p<0.05$, and the main effect of S–R compatibility, $F(1, 21)=4.06$, $p=0.06$, approached significance. The S–R compatibility by Sequence Structure interaction $F(1, 21)=1.40$, $p=0.25$, was not significant. For the left putamen, the main effect of S–R compatibility approached significance, $F(1, 21)=3.87$, $p=0.06$. Neither the main effect of Sequence Structure, $F(1, 21)=2.78$, $p=0.11$, nor the interaction, $F(1, 21)=2.28$, $p=0.15$, was significant; however, trends in the main effect data are similar for the left and right putamen.

2.2.1.5. Caudate (Left: x=−20, y=7, z=19; Right: x=20, y=2, z=22). Bilateral activity was evident in the caudate and there were no significant or interacting effects of Hemisphere ($p>0.83$ in all cases) so data were combined across the hemispheres. There was a significant main effect of S–R compatibility, $F(1, 21)=8.42$, $p<0.01$. The main effect of Sequence Structure, $F(1, 21)=3.06$, $p<0.10$, and the interacting effect, $F(1, 21)=3.15$, $p<0.10$ approached significance.

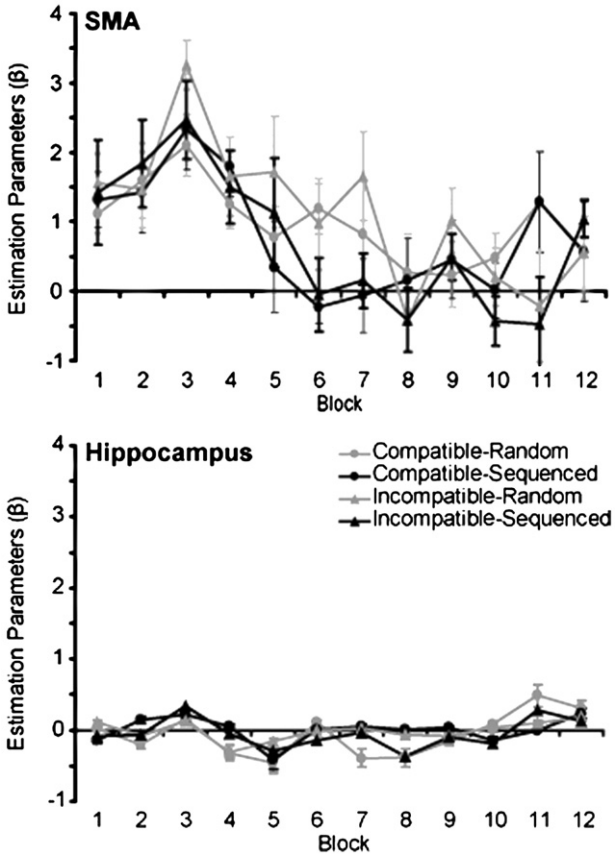

Fig. 3 – Mean activity and standard errors for compatible-random, compatible-sequenced, incompatible-random and incompatible-sequenced conditions relative to the fixation baseline in the SMA and hippocampus.

2.2.2. *Regions mediating spatial response-selection only*

2.2.2.1. Right dorsal prefrontal cortex (x=36, y=39, z=31). The main effect of S–R compatibility, $F(1, 21)=24.19$, $p<0.001$, was the only significant effect. Neither the main effect of Sequence Structure, $F(1, 21)=0.05$, $p=0.83$, nor the S–R compatibility by Sequence Structure interaction, $F(1, 21)=0.70$, $p=0.41$, was significant.

2.2.3. *Additional regions-of-interest*

2.2.3.1. Hippocampus. Bilateral activity was evident in the hippocampus and there were no significant or interacting effects of Hemisphere ($p>0.42$ in all cases), therefore the data from the left and right hemispheres were combined. Neither the main effect of S–R compatibility, $F(1, 21)=1.05$, $p=0.32$, the main effect of Sequence Structure, $F(1, 21)=0.29$, $p=0.59$, nor the interaction, $F(1, 21)=2.02$, $p=0.17$, was significant.

As with the SMA results, an additional ANOVA on the unpracticed group was conducted with Block, Sequence Structure and S–R compatibility as factors. As shown in Fig. 3, no significant main or interacting effects were found ($p>0.23$ in all cases).

3. Discussion

The present study orthogonally manipulated spatial response-selection difficulty and spatial sequence learning to investigate the underlying neural mechanisms for these cognitive processes. Each factor significantly affected mean RTs. Although the mean RT interaction was not significant ($p=0.13$), the results were clearly not additive (the interaction was 45% the size of the main effect of sequence structure). The trend was for an underadditive effect in this interaction (i.e., a larger effect of compatibility on sequenced than random blocks). These data are thus consistent with the interpretation that both sequence structure and S–R compatibility affected at least one processing stage in common (Sternberg, 1969, 2001).

Consistent with the behavioral data, most ROIs showed significant main effects of both factors and a nonsignificant trend for an underadditive interaction. These results suggest that sequence structure and S–R compatibility may rely on the same underlying neurocognitive processes (viz., response selection). However, one region, the right dPFC, which has previously been implicated in spatial response selection (Iacoboni et al., 1996; Jiang and Kanwisher, 2003; Schumacher et al., 2003), showed a selective influence of S–R compatibility. This may suggest that this region mediates a cognitive subprocesses of response selection — distinct from the other regions mediating response selection (viz., dPMC and SPC) (Curtis and D'Esposito, 2003; Miller and Cohen, 2001; Rowe et al., 2000; Schumacher et al., 2007). The lack of regions selectively influenced by sequence learning suggests that the

locus of sequence learning may lie solely in processes affected by S–R compatibility. Finally, the current results failed to find evidence for hippocampal involvement in sequence learning.

We can be confident that the effect of S–R compatibility on activation in right dPFC, dPMC, and SPC reflects spatial response selection because these same regions have previously been affected by similar parametric manipulations of spatial response selection difficulty (Schumacher et al., 2003). It is possible that the other regions affected here by the S–R compatibility manipulation (i.e., SMA and striatum) also mediate spatial response selection. However, it is also possible that they mediate other processes affected by S–R compatibility (e.g., changes in arousal, general effects of task difficulty, etc.). This uncertainty is not critical for the interpretations of the data outlined here. Stimulus–response compatibility is known to affect response selection (Duncan, 1977; Fitts and Seeger, 1953; Kornblum et al., 1990; Schumacher et al., 1999), and compatibility affected activity in regions known to mediate response selection (Schumacher et al., 2003). In fact, both factors affected activity in all ROIs (except right dPFC and hippocampus). Therefore, we conclude that S–R compatibility and Sequence Structure affect at least one process in common (viz., response selection).

3.1. *Regions of common activation*

Neural correlates of both response selection and sequence learning were found in bilateral dPMC and SPC regions as well as SMA and the striatum. As discussed earlier, these regions (except the SMA) have been previously implicated in both the sequence learning and the response selection literature (e.g., Bischoff-Grethe et al., 2004; Dassonville et al., 2001; Grafton et al., 1995, 2001, 2002; Honda et al., 1998; Iacoboni et al., 1996; Jenkins et al., 1994; Jiang and Kanwisher, 2003; Peigneux et al., 2000; Rauch et al., 1997b; Schendan et al., 2003; Schumacher et al., 2003; Tanji, 2001). However, the activation cluster sizes reported as well as the coordinates of peak activation often varied greatly among studies. Therefore, the common activation revealed in the current study provides direct support for the hypothesis that spatial response selection plays an important role in successful spatial sequence learning (e.g., Deroost and Soetens, 2006; Hazeltine, 2002; Schumacher and Schwarb, 2008; Schwarb, 2008).

Some evidence for the mechanism by which dPMC and SPC may mediate spatial sequence learning comes from studies suggesting these regions maintain spatial S–R rules in working memory (Rowe et al., 2000; Schumacher et al., 2007). Greater activation is expected in incompatible conditions in which many S–R rules must remain active compared to compatible conditions, which require relatively few rules (Duncan, 1977). Furthermore, the present results suggest that knowledge about the underlying sequence may prime the upcoming S–R rules across the experimental trials (or adjust the activation threshold for choosing a response); thus making the choice easier and thereby reducing the activity for sequenced relative to random blocks (especially for the compatible mapping).

The current striatal results are also consistent with previous findings and demonstrate the importance of the striatum in higher-order sequence learning and the utilization of the learned sequence to speed performance (e.g., Destrebecqz et al., 2005; Grafton et al., 1992; Peigneux et al., 2000; Rauch et al., 1995, 1997a, 1998). Generally the striatum is thought to be important for motor skill learning and the execution of sequential movements (Laforce, 2001, 2002); the application of the appropriate motor program in a given context (Laforce, 2002); and/or ensuring the correct execution of motor programs (Peigneux et al., 2000). We, therefore, suggest that the striatum is not only engaged in the learning of the appropriate S–R rules required to successfully perform the task in the current study, but also monitoring the sequential order of said rules thus facilitating sequence learning.

Supplementary motor area is frequently activated in studies of spatial sequence learning, but not in studies that manipulate response selection difficulty. However, there are premotor regions reported in the response selection literature that are quite close to or even included in the large SMA region-of-interest used in the present study (e.g., Schumacher et al., 2003). It is generally believed that the SMA is involved in motor planning and the programming movements (viz., Tanji, 2001). More generally, it is hypothesized that the premotor areas are responsible for programming visually guided movements (Tanji, 2001) or movements based on external cues (di Pellegrino and Wise, 1993; Passingham, 1993; Wise et al., 1997). Passingham and colleagues have also suggested that the SMA may mediate movements based on internal cues while other premotor areas mediate movements based on external cues (e.g., di Pellegrino and Wise, 1993; Jenkins et al., 1994; but see Jahanshahi et al., 1995). It is perhaps, then, unsurprising that the SMA would be engaged in the performance of complicated S–R mappings requiring careful motor planning. Furthermore, it has been suggested that the SMA may mediate the temporal ordering of response representations (Bischoff-Grethe et al., 2004; Grafton et al., 2002). Therefore it may be that sequence knowledge primes the upcoming responses leading to increased dPMC, SPC and SMA activity, and that the SMA further organizes or otherwise ensures those responses occur in the correct order.

The direction of the activation in the SMA ROI deserves further consideration. In this ROI (as well as most of the others), the activation patterns generally followed the RT effects (i.e., longer under incompatible than compatible conditions and under random compared to sequenced conditions). The incompatibility effect is commonly reported in studies of response selection (e.g., Jiang and Kanwisher, 2003; Schumacher et al., 2003). The Sequence Structure activation patterns, however, are somewhat surprising. Although greater activation for random compared to sequenced trials has been previously reported in the literature (Olson et al., 2006), many studies report sequence related increases compared to random trials in SMA (e.g., Grafton et al., 1995, 2002; Hazeltine et al., 1997) — opposite of the sequence related decreases reported here. Not all studies, however, report sequence related increases by comparing sequenced trials to random trials. Some report sequence related activation by comparing sequenced blocks to activity during a resting baseline in which no task is being performed (e.g., Bischoff-Grethe et al., 2004; Jenkins et al., 1994; Olson et al., 2006). The current data are consistent with such comparisons: sequence related increases compared to fixation are apparent in all regions affected by sequence structure. Furthermore, some studies do not report sequence-related activity in SMA at all (Eliassen et al., 2001; Rauch et al., 1995, 1997b; Seidler et al., 2002). Thus, the effect of

spatial sequence learning on SMA activity is not consistent in the literature. Further research is necessary before we can truly understand the underlying neural mechanisms in SMA mediating spatial sequence learning.

Still, it is not clear why we found the reverse of the more standard effect of sequence learning on SMA activity. Our SMA ROI overlaps with the regions that have previously shown sequence-related increases so it does not appear that we are investigating a different area of SMA than other studies. Some researchers suggest that SMA activity reflects processes required to learn the sequence, and not to perform it (e.g., Grafton et al., 1998, 2002; Seitz et al., 1990). Therefore, we might expect to find increases in SMA activity in the early phases of the experiment. However, as previously noted, others have suggested that the SMA is important for making internally generated movements (e.g., Mushiake et al., 1991; Tanji, 2001), thus we might expect to find sustained activity in the SMA.

As shown in Fig. 3, although the data are somewhat noisy, activity in SMA decreased across blocks and there was no evidence that sequenced blocks were greater than random at any point during the experiment. In fact, activity in the random blocks was significantly more active than in sequenced blocks across the experiment. This cross-block analysis is not consistent with a role for SMA in learning and/or performance of the sequenced trials specifically. One additional factor that may have had an effect on the current results is that our study used two sequences and two S–R mappings. This may have changed participant strategy, which might account for the discrepant results. However, other studies have used similar procedures and produced sequence-related increases in SMA (e.g., Bischoff-Grethe et al., 2004), so a procedural modification is unlikely to completely explain the activation differences in SMA. Thus it may be that SMA is not always involved in processing sequenced tasks, and the activity here is related to response processing, more generally.

3.2. *Regions of differential activation*

Although the current data suggest that most of the regions investigated were affected by both sequence structure and S–R compatibility (dPMC, SPC, SMA and striatum); and thus these factors rely on the same underlying processes, the right dPFC showed a selective influence of S–R compatibility. This region has repeatedly been implicated in response selection (e.g., Rowe et al., 2000; Rowe and Passingham, 2001; Schumacher et al., 2003, 2005, 2007). Our current data indicate that subprocesses within spatial response selection may be dissociable. This dissociation within the frontal-parietal network for response selection is consistent with previous research showing a dissociation between selection related activity in dPFC and working memory maintenance (Rowe et al., 2000; c.f., Schumacher et al., 2007). The current results suggest that when sequence knowledge primes the upcoming S–R rules (mediated by SPC and dPMC), the right dPFC performs and additional selection process, perhaps related to gating the execution, or double checking the accuracy, of the selected response on a trial-by-trial basis.

Finally, sequence-related activation in the hippocampus has been inconsistently reported in the literature, with some studies reporting significant activity (e.g., Grafton et al., 1995, 2002; Schendan et al., 2003), and others failing to report hippocampal activity (e.g., Hazeltine et al., 1997; Peigneux et al., 2000; van der Graaf et al., 2006). Whether sequence learning affects the hippocampus is an important question because there are theoretical reasons to expect activation there. Cohen and Eichenbaum (1993) suggest that the hippocampus is involved in the obligatory binding of convergent inputs. According to this theory, when an individual is exposed to sequenced stimuli, the hippocampus automatically begins binding together temporally neighboring stimuli (Cohen and Eichenbaum, 1993; Fortin et al., 2002). Therefore, over time a given stimulus is no longer represented as an individual stimulus, but rather as a portion of the greater sequence of stimuli that is repeated throughout the duration of the task.

In light of the support for this view of hippocampal binding of sequences from human and non-human neurophysiology (e.g., Cohen and Eichenbaum, 1993), it is possible that this and other neuroimaging studies (e.g., Grafton et al., 2001; Hazeltine et al., 1997; Peigneux et al., 2000; Rauch et al., 1995; van der Graaf et al., 2006) failed to identify sequence learning related hippocampal activity because the hippocampus is only active during the acquisition of sequence knowledge — not once the knowledge is acquired. Under this scenario, similar to SMA, hippocampal activity may disappear when data are averaged across experimental phases during which the sequence is learned and after it has been acquired. By this account, hippocampal activation should decrease across time when binding is no longer necessary. This decrease in hippocampal activity with sequence learning has been reported in the literature (Grafton et al., 1995, 2002; Schendan et al., 2003).

As with the SMA results, to test if significant hippocampal activity was present during the learning of the spatial sequences we reanalyzed the data from the unpracticed group separately for each block. As shown in Fig. 3, there was no evidence for practice-related changes in hippocampal activity. In fact, there was little or no activity in any of the four conditions across the entire experiment. These results indicate that, at least in our current study, there was little or no sequence related activity in the hippocampus throughout the experiment.[2]

[2] To ensure that this null finding for activity in the hippocampus does not reflect our choice of baseline (Stark and Squire, 2001), partial volume effects resulting from the pulse sequence used (Strauss et al., 1995), or simply a failure of our scanner to record medial temporal lobe activity, a control study was performed with four naïve participants. These participants completed the same experimental procedure as the unpracticed group participants; however, they were explicitly instructed that a sequence was present and that they should try to learn it. Behavioral data showed an effect of both S-R compatibility and sequence structure ($p<0.05$, in both cases), as well as a marginally significant interaction ($p=0.05$). Functional MRI results revealed that three of the four (75%) participants demonstrated significant sequence-related activity in the hippocampus compared to eight of the twenty-four (33%) participants in the primary experiment. We therefore conclude that the failure to find significant hippocampal activation in the primary experiment was related to a lack of consistent task related activity and not to a lack of sensitivity of our MR procedure.

3.3. Conclusion

A possible limitation of this study is the concurrent use of two S–R mappings. This might produce response competition, and thus complicate the interpretation of the current findings. We do not, however, believe that response competition plays a prominent role in the procedure used here. The stimulus colors indicating compatible or incompatible mapping were constant across the experiment. This likely minimized the amount of interference between the two tasks. Furthermore, response competition is associated with activity in anterior cingulate cortex (ACC; Botvinick et al., 2001, 2004). And no significant effect of S–R compatibility was found in ACC in this study, or in other studies using identical or similar S–R compatibility manipulations (Jiang and Kanwisher, 2003; Schumacher et al., 2003). We therefore think it is unlikely that response competition plays a large role in the activity reported here.

The present findings indicate that spatial sequence learning relies on many of the same neural processors as spatial response selection (bilateral dPMC, SPC, as well as SMA and striatum). These regions may mediate a process in which sequence knowledge primes upcoming S–R rules. These data are consistent with theories that localize the effect of sequence learning in response selection (Deroost and Soetens, 2006; Hazeltine, 2002; Schumacher and Schwarb, 2008; Schwarb, 2008; Willingham et al., 1989). These data also demonstrate a dissociation in the frontal-parietal network for spatial response selection (viz., right dDPFC was selectively influenced by S–R compatibility). This dissociation provides support for the idea that that these regions may mediate distinct cognitive subprocesses for spatial response selection (c.f., Bracewell et al., 1996; Curtis and D'Esposito, 2003; Mazzoni et al., 1996; Miller and Cohen, 2001; Mushiake et al., 1991; Rowe et al., 2000; Rowe and Passingham, 2001; Schumacher et al., 2007; Wise et al., 1997). Lastly, although it has been suggested that the hippocampus might be involved in implicit sequence learning, the present results provide no support for this hypothesis.

4. Experimental procedures

4.1. Participants

Twenty-four naïve volunteers (ages 18–25, 9 women) recruited from the Georgia Institute of Technology community participated in this study. Participation was either in partial fulfillment of a course requirement or for pay ($10/h). Participants gave informed consent prior to the experiment and were treated in accordance to American Psychological Association approved guidelines (American Psychological Association, 1992).

4.2. Behavioral procedure

Participants were randomly assigned to one of two groups (practiced and unpracticed). The practiced group completed a one-hour practice session prior to fMRI scanning and the unpracticed group completed only the fMRI scanning session.

4.3. fMRI scanning session

4.3.1. Apparatus

Participants lay supine in an MR scanner and stimuli were projected onto a screen through a mirror that was mounted on the head radio-frequency (RF) coil. Stimuli presentation was controlled with a HP L2000 notebook personal computer using Eprime (Schneider et al., 2002). Participants made responses with their index and middle fingers of each hand using an in-line four-button response pad positioned comfortably across their lap (Current Designs, Inc.).

4.3.2. Design and procedure

4.3.2.1. SRT task. All participants performed a four-choice SRT task using two different S–R mappings. Four evenly spaced annuli and a centrally located fixation cross were presented horizontally in the center of a black background (Fig. 1). The diameter of each annulus subtended 3.5° visual angle and the fixation cross subtended 1.0° by 1.0° visual angle. The inner annuli and the fixation cross were separated by 3.0° visual angle, then inner and outer annuli were separated by 3.0° visual angle. The entire horizontal display subtended 28.0° visual angle horizontally and 3.5° visual angle vertically.

The annuli and fixation cross were blue, green, red or yellow depending on the task condition. At the beginning of each trial, a disk (in the color consistent with the condition) replaced one of the annuli. This disk served as the target stimulus for that trial. On half of the blocks of trials, participants responded using compatible key presses (Fig. 1) to the location of the targets from left to right. On the other half of the trials, participants responded using incompatible key presses (Fig. 1) to the targets from left to right. Participants were informed which S–R mapping to use prior to the start of each block.

4.3.2.2. Stimulus sequences. Two second-order conditional sequences that followed the statistical rules outlined by Reed and Johnson (1994) were used in the SRT task. For half of the participants Sequence 1 was presented during the compatible S–R mapping blocks and Sequence 2 was presented during the incompatible S–R mapping blocks. For the remaining participants, the sequences and mappings were switched.

4.3.2.3. Runs and blocks. Sequence structure (sequenced and random) and S–R compatibility (compatible and incompatible) were varied orthogonally across blocks (i.e., compatible-random, compatible-sequenced, incompatible-random, incompatible-sequenced). A fixation block, in which participants focused on a centrally presented fixation cross, was also included to get a baseline measure of brain activity. Participants completed each of the five block types in each of twelve fMRI runs. Block order was fixed for each participant and randomized across participants. Except for the fixation block, each block was composed of 36 trials.

4.3.2.4. Trials. Each fMRI run began with the fixation display (four annuli and the fixation cross on a black background) for approximately 2000 ms. At the start of each trial, the visual

stimulus (shaded disk) then appeared in one of the four possible target locations and remained on the screen for 100 ms. The target then disappeared and the fixation display remained on the screen for 900 ms before the next trial began. In each block, the targets followed either one of the sequences described above or were randomized.

4.3.2.5. *Instructions and feedback*. Participants were instructed to respond to the targets with the appropriate response mapping as quickly and accurately as possible. They were always informed of which mapping was to be used before the start of the block. Additionally, before the start of the experiment all participants were told that a "+" fixation cross indicated compatible mapping and an "X" fixation cross indicated incompatible mapping; the cross served as a reminder of the mapping and remained constant throughout any given block. Participants were *not* informed about the sequence structure of the blocks. Each fMRI run ended after all five block-types were completed. Following each run, a screen appeared displaying the mean RT and accuracy rate for each of the five blocks. At this time participants were encouraged to respond as quickly and accurately as possible on the upcoming blocks.

4.3.2.6. *Practice*. Before the experiment, participants completed several SRT task practice blocks using both compatible and incompatible mapping. These practice blocks were methodologically identical to the experimental blocks except that the cue order was always random and RT and accuracy feedback was given following each trial as well as at the end of the block. Compatible blocks consisted of 12 trials each and incompatible blocks consisted of 20 trials each. Participants completed a minimum of two blocks with each mapping until 85% accuracy or higher was achieved; participants completed an average of 2 blocks with the compatible mapping and 5 blocks with the incompatible mapping.

4.3.2.7. *Explicit knowledge questionnaire*. After fMRI scanning was complete, participants were removed from the scanner and completed a paper recognition questionnaire to assess their overall level of awareness. This questionnaire was modeled after similar questionnaires used by Frensch et al., (1999). Twenty-four groups of three trials (triplets) were presented for each of the two S–R mappings for a total of forty-eight triplets; 12 triplets represented part of Sequence 1, 12 triplets represented part of Sequence 2 and the other 24 were novel. Participants were instructed to respond by circling only those triplets that they recognized from the experiment. All participants were encouraged to complete the recognition questionnaire as best they could even if they insisted that they knew nothing of the sequence.

4.4. *Practice session*

The practiced group completed a practice session in a mock MR scanner no more than three days prior to the experimental session. The mock scanner recreated the physical enclosure, table, ambient sounds and head coil of the MRI scanner. Participants completed 20 blocks of trials. All aspects of the practice procedure were identical to the scanning session except that the inter-stimulus-interval was 1500 ms instead of 1000 ms on Blocks 1–8.

4.5. *Functional MRI procedure*

Images were acquired using a Siemens Magnetom Trio 3T whole body MRI scanner. A standard RF head coil was used and foam padding was used to restrict head motion. A gradient-echo, echoplanar imaging (EPI) sequence (TR=2000 ms, TE=30 ms, flip angle=90°, FOV=220 mm) was used to acquire data sensitive to the blood oxygen level dependent (BOLD) signal. Each functional volume contained 33 3.4 mm axial slices. Each run lasted 3 min and 10 s (95 volumes/run). A high-resolution 3D MPRAGE (TI=1100 ms, flip angle=8°) structural scan (1 mm isotropic voxels) was acquired at the beginning of the fMRI session.

4.5.1. *fMRI data processing and analysis*

Data reconstruction, processing, and analyses for each participant were performed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). After reconstruction, head-motion artifacts were corrected to the first functional scan with a least squares approach using a six-parameter, rigid-body transformation algorithm (Friston et al., 1995). Slice acquisition timing differences then were corrected and the data were smoothed with a Gaussian filter (FWHM=6 mm). Next, data were analyzed using a modified General Linear Model (Worsley and Friston, 1995). For each participant a design matrix was created with the four covariates of interest (viz., compatible-random, compatible-sequenced, incompatible-random, incompatible-sequenced) convolved with an idealized hemodynamic response function. A high-pass filter removed frequencies below 0.0078 Hz.

For each participant, contrast images were computed for each of the four covariates of interest vs. the fixation baseline condition. These contrast images were then normalized to the Montreal Neurological Institute reference brain. Statistical parametric maps of β-values for each of these covariates were calculated for each participant. These β-values were then submitted to both a 3-way Structure (sequence and random) by S–R compatibility (compatible and incompatible) by Group (practiced and unpracticed) Analysis of Variance (ANOVA) as well as a 2-way Structure by Response-Selection Difficulty ANOVA (collapsing across group).

The effect of sequence learning in both the SMA and hippocampus was further investigated via block-wise analyses in an attempt to identify changes in these regions as the sequence was learned. Only data from the unpracticed group were used these analyses because we were interested specifically in activation mediating early exposure to the spatial sequence. Statistical parametric maps of β-values were calculated separately for each condition for each block of trials for the unpracticed group participants. These β-values were then submitted to an ANOVA comparing activation in these regions across the twelve experimental blocks.

4.6. *Regions-of-interest (ROI) analysis*

In order to characterize the effects of these contrasts on regions specifically related to spatial response selection and

spatial sequence learning we conducted a whole-brain statistical analysis comparing activity in all task blocks combined relative to fixation. Regions-of-interest were functionally defined by identifying sites of peak activity and contiguous voxels with a *t*-value corresponding to $p<0.001$, uncorrected in regions previously implicated in spatial response selection and/or spatial sequence learning in the literature (e.g., Grafton et al., 1995; Peigneux et al., 2000; Rauch et al., 1998; Schendan et al., 2003; Schumacher et al., 2003). The sites of peak activation and their extent are shown in Fig. 2 and Table 1.

Additional ROIs were also included based on other findings in the literature. An ROI for right dPFC was created because it has previously shown to mediate spatial response selection (Schumacher et al., 2003). This region was based on the whole-brain statistical analysis conducted in that study, including the site of peak activity and contiguous voxels with a *t*-value corresponding to $p<0.01$, uncorrected. Finally we created ROIs for the left and right hippocampus. To create these ROIs, we combined four (left hemisphere) and six (right hemisphere) 2-mm spheres centered on the hippocampal regions significantly activated for spatial sequence learning in Schendan et al. (2003).

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