Evidence of Developmental Differences in Implicit Sequence Learning: An fMRI Study of Children and Adults

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Abstract

■ Prevailing theories of implicit or unaware learning propose a developmental invariance model, with implicit function maturing early in infancy or childhood despite prolonged improvements in explicit or intentional learning and memory systems across childhood. Neuroimaging studies of adult visuomotor sequence learning have associated fronto-striatal brain regions with implicit learning of spatial sequences. Given evidence of continued development in these brain regions during childhood, we compare implicit sequence learning in adults and 7- to 11-year-old children to examine potential developmental differences in the recruitment of fronto-striatal circuitry during implicit learning. Participants performed a standard serial reaction time task. Stimuli alternately followed a fixed 10-step sequence of locations or were presented in a pseudorandom order of locations. Adults outperformed children, achieving a significantly larger sequence learning effect and showing learning more quickly than children. Age-related differences in activity were observed in the premotor cortex, putamen, hippocampus, inferotemporal cortex, and parietal cortex. We observed differential recruitment of cortical and subcortical motor systems between groups, presumably reflecting age differences in motor response execution. Adults showed greater hippocampal activity for sequence trials, whereas children demonstrated greater signal during random trials. Activity in the right caudate correlated significantly with behavioral measures of implicit learning for both age groups, although adults showed greater signal change than children overall, as would be expected given developmental differences in sequence learning magnitude. These results challenge the idea of developmental invariance in implicit learning and instead support a view of parallel developments in implicit and explicit learning systems. ■

INTRODUCTION

Behavioral, functional neuroimaging and neuropsychological studies provide converging evidence for the existence of multiple forms of learning and memory in adulthood. Although opinions differ as to how best to describe these differences, most theories agree that learning can occur both intentionally, as in declarative or explicit learning of facts or knowledge, and unintentionally, outside of any conscious awareness that learning has occurred. This unaware learning, termed implicit or procedural learning, tends to occur over an extended period of exposure or practice and is characterized by the acquisition of rules or procedures rather than the rapid, single-trial learning of facts characteristic of declarative memory. These forms of learning have been dissociated from one another behaviorally in healthy adults, but even more strikingly in neuropsychological populations. Patients with global amnesia associated with medial temporal lobe lesions show significant impairments in explicit or declarative learning, but demonstrate sparing of implicit or procedural functions (Nissen & Bullemer, 1987; Cohen & Squire, 1980). In contrast, patients with motor system impairments such as Parkinson's disease or cerebellar degeneration evidence impaired procedural skill learning with relatively spared declarative learning and memory (Gabrieli, Stebbins, Singh, Willingham, & Goetz, 1997; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Pascual-Leone et al., 1993; Heindel, Salmon, Shults, Walicke, & Butters, 1989). Similar dissociations have been reported in functional neuroimaging studies of implicit and explicit learning (Rauch et al., 1997; Grafton, Hazeltine, & Ivry, 1995). Although some contradictions remain, sufficient evidence is mounting to suggest that learning often occurs outside of conscious awareness, and that such implicit learning may rely on different neural systems than explicit learning.

One of the most frequently studied procedural or implicit learning paradigms is the serial reaction time (SRT) task. In the classic SRT task, participants are asked to map the spatial location of a visual target stimulus to a corresponding response button. A visual stimulus appears in one of four horizontal locations and participants press the button directly below the stimulus position on

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each trial. On the surface, this task requires simple visuomotor response mapping. However, unknown to the participant, the locations sometimes follow a repeating pattern or a set of rules. With practice, participants show greater reaction time improvements during sequenced trials than random trials, providing evidence of sequence-specific skill learning. Importantly, participants often demonstrate sequence-specific learning effects without any awareness of the sequence or of their own learning. Neuroimaging studies have demonstrated that implicit learning on the SRT task recruits a network of brain regions including the premotor and motor cortices, cortical–striatal circuits, the cerebellum, and the parietal cortex (Daselaar, Rombouts, Veltman, Raaijmakers, & Jonker, 2003; Doyon, Penhune, & Ungerleider, 2003; Curran, 1997; Rauch et al., 1997; Grafton et al., 1995). In addition, more recent results suggest that medial temporal lobe regions including the hippocampus may be involved in both implicit and explicit learning of visuomotor sequences (Schendan, Searl, Melrose, & Stern, 2003).

A number of theories have been proposed to address the role of implicit learning in the broader context of learning and memory functions, including considerable debate regarding the degree of overlap between implicit and explicit processes (Perruchet & Amorim, 1992). Implicit learning has frequently been proposed as a form of neuronal plasticity, a fine tuning of the perceptual–motor system based on experience (Ungerleider, Doyon, & Karni, 2002; Willingham, Salidis, & Gabrieli, 2002; Karni et al., 1995). This idea is consistent with the learning-related changes observed in functional neuroimaging studies but also presents intriguing questions regarding more global issues of plasticity. Neuropsychological studies suggest that specific brain insults can disrupt this form of plasticity in adulthood (Vakil, Kahan, Huberman, & Osimani, 2000; Haaland, Harrington, O'Brien, & Hermanowicz, 1997; Jackson et al., 1995; Heindel et al., 1989). However, significantly less attention has been devoted to investigating the ontogenetic expression of implicit learning and memory function. An important question for understanding both the integration and dissociability of implicit and explicit learning in adulthood is the degree to which these functions show developmental dissociations, and the plasticity of the implicit learning system in response to developmental brain insults compared with adult neurological insults.

Perhaps surprisingly, given a relative lack of pediatric implicit learning research, this developmental question is not new. Reber theorized over a decade ago that procedural or implicit learning, which appears to recruit evolutionarily primitive brain regions such as the basal ganglia and cerebellum, should therefore demonstrate early ontogenetic maturation and be relatively robust in the face of neurological insults (Reber, 1993). However, data supporting or refuting these ideas are difficult to find. The neuropsychological literature discussed above suggests that implicit learning is not invulnerable to neurological insult. However, whereas medial temporal lobe insults routinely impair explicit but not implicit functions, cases of implicit impairment and explicit sparing following basal ganglia insults have been less consistent (Pascual-Leone et al., 1993; Harrington, Haaland, Yeo, & Marder, 1990; Heindel et al., 1989), providing partial support for Reber's (1993) notion of robustness.

The developmental invariance hypothesis has also proven difficult to test. Studies of infant learning and memory demonstrate clearly that implicit learning mechanisms are available very early in infancy (Clohessy, Posner, & Rothbart, 2001; Canfield, Smith, Brezsnyak, & Snow, 1997; Smith, Loboschefski, Davidson, & Dixon, 1997; Saffran, Aslin, & Newport, 1996; Haith, Wentworth, & Canfield, 1993; Haith & McCarty, 1990). However, ''explicit'' learning and memory systems also appear to be available quite early in infancy, although these systems are unlikely to be the equivalent of adult systems, which tend to involve verbal mediation (Bauer, Burch, & Kleinknecht, 2002; Bauer, Kroupina, Schwade, Dropik, & Wewerka, 1998; Nelson, 1998). Although such explicit learning systems demonstrate clear developmental and age-related improvements across infancy and well into childhood (Schneider & Pressley, 1997; Parkin & Streete, 1988), no such consensus exists regarding the development of implicit functions. Studies of implicit memory (perceptual priming) tend to favor a lack of developmental differences, suggesting very early maturation of this system (Meulemans, Van der Linden, & Perruchet, 1998; Drummey & Newcombe, 1995; DiGiulio, Seidenberg, O'Leary, & Raz, 1994; Naito, 1990; Greenbaum & Graf, 1989; Parkin & Streete, 1988). Results from procedural or implicit learning tasks are more divided. Some find no evidence of developmental effects on learning (Vinter & Perruchet, 2000; Meulemans et al., 1998), whereas others report subtle age (Clohessy et al., 2001; Thomas & Nelson, 2001) or developmental (Fletcher, Maybery, & Bennett, 2000; Maybery, Taylor, & O'Brien-Malone, 1995) differences in learning, with older or more cognitively advanced children demonstrating larger or more consistent learning effects than younger children.

Although pediatric neuropsychological populations have not been examined extensively for implicit learning, recent literature indicates that some childhood behavioral disorders may be associated with deficits in implicit learning, including autism, dyslexia, and attention-deficit hyperactivity disorder (Vicari, Marotta, Menghini, Molinari, & Petrosini, 2003; Kell, Griffiths, & Frith, 2002; Mostofsky, Goldberg, Landa, & Denckla, 2000; Thomas et al., 1998). Further evidence will be required to disentangle the role of motor and attentional problems in these more general deficits. However, these preliminary reports support the notion that implicit learning systems may be sensitive to developmental changes and may show long-term vulnerability to early

insult. Given pediatric neuroimaging evidence over the past 10 years indicating continued structural brain development into middle childhood and adolescence (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Giedd et al., 1996, 1999), further investigation is warranted into the development and neural correlates of implicit learning in childhood. In the current study, we used functional magnetic resonance imaging (fMRI) to explore the brain regions recruited during implicit learning of an SRT task in children compared with adults. This study used a variant of a published behavioral paradigm previously used with 6- and 10-year-old children (Meulemans et al., 1998). In that study, no participants developed explicit awareness of the sequence during the course of the learning session, and children were able to adequately perform the task.

Adults and 7- to 11-year-old children performed a visuomotor SRT task with four spatial locations arranged horizontally on the computer screen. Similar to a previous developmental study in our laboratory (Thomas & Nelson, 2001), on each trial, a bitmap stimulus of a dog appeared in one of the four locations. Participants were instructed to match the location of the stimulus to its corresponding response key as quickly as possible while maintaining a high accuracy rate. Responses were made using the index and middle fingers of each hand. Participants were not informed that the location of the stimulus sometimes followed a predictable sequence. A 10-step sequence of locations was presented opposite brief periods of randomly ordered locations in an alternating fashion. In this design, the sequence never repeated immediately. Random trials were constrained to ensure equal overall frequencies of each location in the random and sequence conditions. From this paradigm, we were able to examine behavioral and functional brain imaging effects of sequence-specific learning as a function of age group (children and adults), and as a function of the stage of learning (early in the session compared to late in the session). Given previous behavioral data on this task, we expected children and adults to demonstrate equivalent sequence-specific learning. We hypothesized that children and adults may differentially activate cortical–striatal circuits given the continued structural and functional development of these brain regions across childhood and adolescence. Alternatively, a lack of developmental differences would support the developmental invariance theory proposed by Reber (1993), suggesting that implicit learning relies on an early maturing brain system that already has reached adult levels by middle childhood.

RESULTS

Behavioral Results

No participants, either adults or children, showed evidence of any explicit awareness following the reaction time trials. When questioned, most participants believed they had improved their reaction time across trials. In addition, three participants indicated that they noticed a pattern. In two cases, the individuals (1 adult, 1 child) described an increased probability of location 3 compared to other locations. This pattern is present in the task, but does not differ across random and sequence trials, and is therefore unrelated to sequence-specific learning measures. Two additional adults reported short chunks of locations, none of which were actually present in the fixed 10-step sequence. Therefore, although these participants endorsed some awareness, they were not in fact explicitly aware of the sequence.

One child's behavioral data were lost due to a technical problem with the response box; therefore, behavioral results are reported for nine children. Both adults and children showed a high level of accuracy on the task, although adults were significantly more accurate than children [98% vs. 87%; $t(18) = 3.47$, $p < .005$]. Accuracy did not differ by block [$F(4,72) = 0.393$, *ns*] but was marginally better for sequence trials compared with random trials [94% vs. 92%; $t(18) = -2.07$, $p = .053$]. Response accuracy was not significantly correlated with the magnitude of the learning effect, either for each age group independently or across all participants in a combined analysis [$r = .31$, $t(18) = 1.35$, *ns*].

Adults responded more quickly overall than children [411 msec vs. 575 msec; $t(17) = -5.61$, $p < .001$]. Both age groups showed general reaction time improvements with time on task. To assess the degree of sequence specific learning, each individual's data were *z*-normalized using individual mean reaction time. Sequence-specific learning was measured as a difference between *Z*-score reaction time for random and sequence trials. Figure 1A and B illustrates the *Z*-score reaction times for random and sequence trials for adults and children, respectively, across runs. Learning is evidenced by significant separation between random and sequence reaction times. Adults demonstrated significant sequence-specific learning in all runs. In contrast, children did not show significant sequence learning in run 1 but did show effects in later runs. The overall learning effect was smaller for children than for adults [0.10 vs. 0.26; $t(17) = -2.62$, $p < .05$; Figure 1C], reflecting in part the differential performance in run 1. However, children continued to demonstrate a significantly smaller learning effect than adults throughout the session, even by the end of run 5 [0.16 vs. 0.31; $t(17) = 2.12$, $p < .05$]. A correlation analysis indicated a trend towards a relationship between overall reaction time and the magnitude of the sequence-specific learning effect [$r = -.40$, $t(17) = -1.80$, $p = .09$]. However, this effect resulted from the fact that all children were slower than adults overall, and that all children showed smaller sequence learning effects than adults. When examined within each age group, no significant relationship was observed between

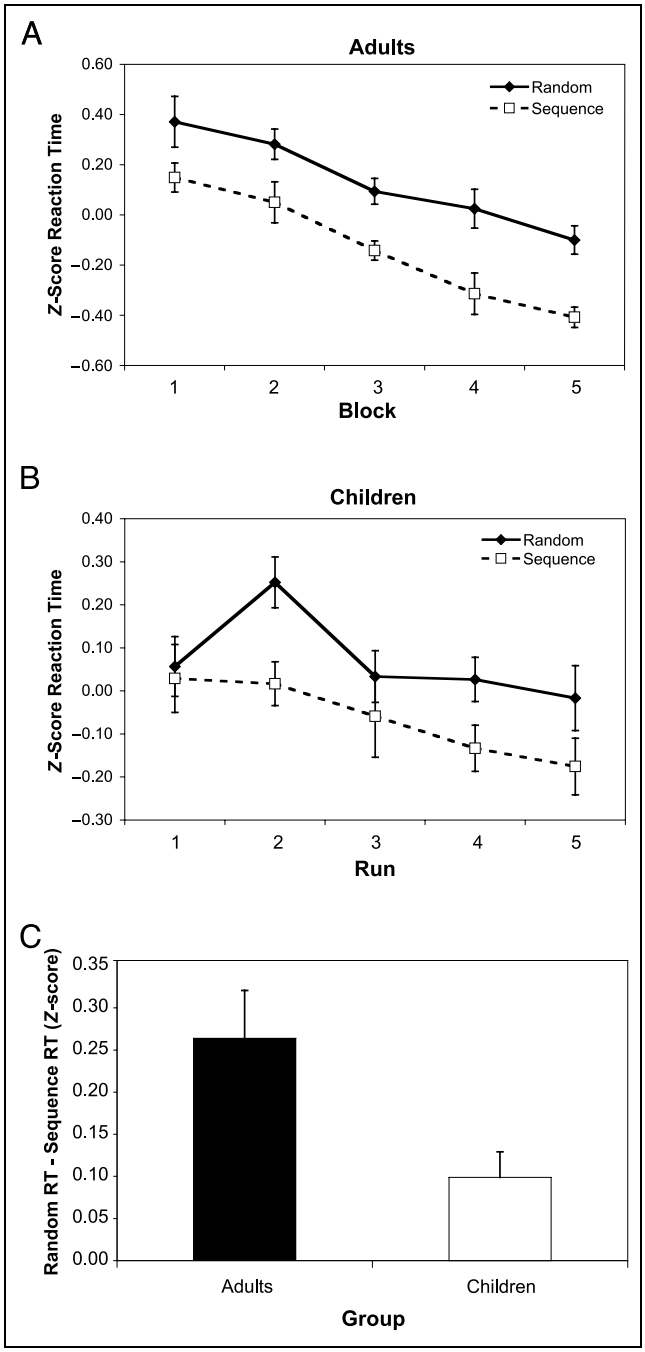

Figure 1. Behavioral learning effects. (A) *Z*-score normalized reaction times for adult participants for random and sequence trials across five runs; (B) *Z*-score normalized reaction times for child participants for random and sequence trials across five runs; (C) Sequence-specific learning effects for adult and child participants.

overall reaction time and the degree of sequence-specific learning.

Imaging Results

A 20 (subjects) × 2 (age groups) × 2 (runs) × 2 (conditions) voxelwise analysis of variance (ANOVA) was conducted to assess main effects of group, run, and condition, as well as interactions among these factors. Given our interest in comparing early and late learning effects, we included only data from runs 1 and 5 in our analysis. Although the overall statistical effects were somewhat reduced in magnitude given the reduced power in this ANOVA, similar regions were observed for the effects of group, condition, and Group × Condition when all five runs were included. Here, we report only data from the reduced analysis to highlight learning-related effects in brain activity. Given the difficulties inherent in disentangling main effects of run (or time) from confounding factors such as scanner drift, we restrict our analysis of this factor to interactions with within-subject factors (i.e., Run × Condition, Group × Run × Condition).

Developmental Differences

Main effects of age group were observed for activity in the bilateral putamen, left premotor/inferior frontal cortex, and right inferotemporal cortex (parahippocampal, fusiform, and lingual gyri). Adults showed greater activity in cortical regions (BA 6/9/44, 19, 30), whereas children showed greater activity in the bilateral putamen (Table 1; Figure 2A). These effects were not moderated by any significant interactions with condition or run. These effects appear to reflect an overall motor performance difference between adults and children and does not differ by trial type. Children recruit predominantly subcortical regions to complete this motor mapping task, whereas adults demonstrate greater recruitment of cortical regions. A similar result has been observed in other developmental studies of eye movement control, attention and motor inhibition (Casey, Thomas, Davidson, Kunz, & Franzen, 2002; Casey, Tottenham, & Fossella, 2002; Luna et al., 2001). In fact, activity in the premotor cortex was negatively correlated with activity in the putamen [$r = -.78$, $t(17) = -5.06$, $p < .0001$], suggesting a possible tradeoff in recruitment of these regions. This effect appeared to be carried predominantly by the child group [$r = -0.81$, $t(7) = -3.68$, $p < .01$], although adults showed a trend in the same direction [$r = -0.49$, $t(8) = -1.59$, $p = .15$]. Premotor activity was also negatively correlated with overall reaction time for adult participants. For child participants, overall reaction time did not correlate significantly with activity in either the premotor cortex or the putamen.

Inferotemporal cortical activity was significantly negatively correlated with overall reaction time across all participants (Figure 2A). However, a closer examination reveals that this correlation was driven by the child age group. Children showed a significant increase in activity in the fusiform gyrus as reaction times improved [$r = -.77$, $t(7) = -3.15$, $p < .05$], approaching adult levels of activation as reaction times approached the adult range. In contrast, adults appeared to be at ceiling activity in

Table 1. Regions of Significant Activity for the Main Effects and Interactions of Age Group, Condition, and Run

Effect	*Hemisphere*	*Anatomical Region*	*Brodmann's Area*	*Talairach Coordinates*			*Max F*	*Volume (mm^3)*
				x	*y*	*z*		
Group	Left	Precentral gyrus	4/6	50	−7	29	26.4	8008
	Left	Putamen/Globus pallidus	na	23	−9	8	19.59	2539
	Right	Putamen/Globus pallidus	na	−25	−10	5	20.71	1758
	Right	Parahippocampal gyrus/ Lingual gyrus	9/30	−16	−47	−3	22.11	3789
	Right	Lingual gyrus	19	−16	−75	1	15.16	1055
Condition	Left	Middle frontal gyrus	9	22	29	34	13.12	313
	Right	Middle frontal gyrus	9/46	−30	34	27	19.9	1094
	Right	Cingulate gyrus	24	−7	1	47	19.97	703
	Right	Caudate	na	−5	13	14	22.4	1523
	Left	Globus pallidus/Putamen	na	13	2	7	29.18	4141
	Left	Thalamus	na	22	−16	15	32.06	1133
	Left	Thalamus	na	7	−25	17	24.28	2188
	Left	Anterior insula	40	35	4	19	38.43	5820
	Left	Superior temporal gyrus/Insula	42	44	−36	20	33.88	4102
	Left	Middle temporal gyrus	21/37	46	−53	0	16.89	1250
	Right	Insula	na	−34	6	5	14.04	469
	Left	Inferior parietal lobule	40	30	−33	46	37.91	5781
	Right	Inferior parietal lobule	40	−56	−40	23	22.05	2266
	Left	Cuneus	17/18	10	−71	6	46.98	6992
	Right	Cuneus/Lingual gyrus	17/18/31	−14	−78	8	43.5	4766
Group × Condition	Left	Medial/Superior temporal gyrus	21/22	46	−28	−1	24.32	1875
	Right	Superior temporal gyrus	22	−61	−35	5	40.56	2188
	Right	Hippocampus	na	−29	−31	−4	18.86	977
	Right	Superior parietal lobule	7	−17	−77	36	27.03	1133
Run × Condition	Right	Middle frontal gyrus	6	−24	41	1	15.73	742
	Right	Inferior frontal gyrus/Insula	44	−34	13	23	19.65	1602
	Left	Caudate	na	11	12	8	14.56	391
	Right	Posterior caudate	na	−23	−32	16	23.2	859
	Right	Superior temporal gyrus	22	−49	−49	13	12.48	273
	Right	Angular gyrus/Supramarginal gyrus	39/40	−32	−52	31	24.76	1484
	Left	Occipital gyrus	19	35	−77	27	16.63	703
Group × Run × Condition	Left	Superior frontal gyrus	99/46	31	49	28	13.74	469
	Left	Middle frontal gyrus		34	25	7	17.08	664
	Right	Middle frontal gyrus	10/46	−41	47	21	17.63	1211
	Right	Caudate	na	−14	19	16	15.5	352
	Right	Cingulate gyrus	23	−11	−14	29	25.62	586
	Right	Middle temporal gyrus	21	−60	−29	−9	18.42	234
	Left	Inferior Parietal Lobule	40	27	−56	37	14.83	625

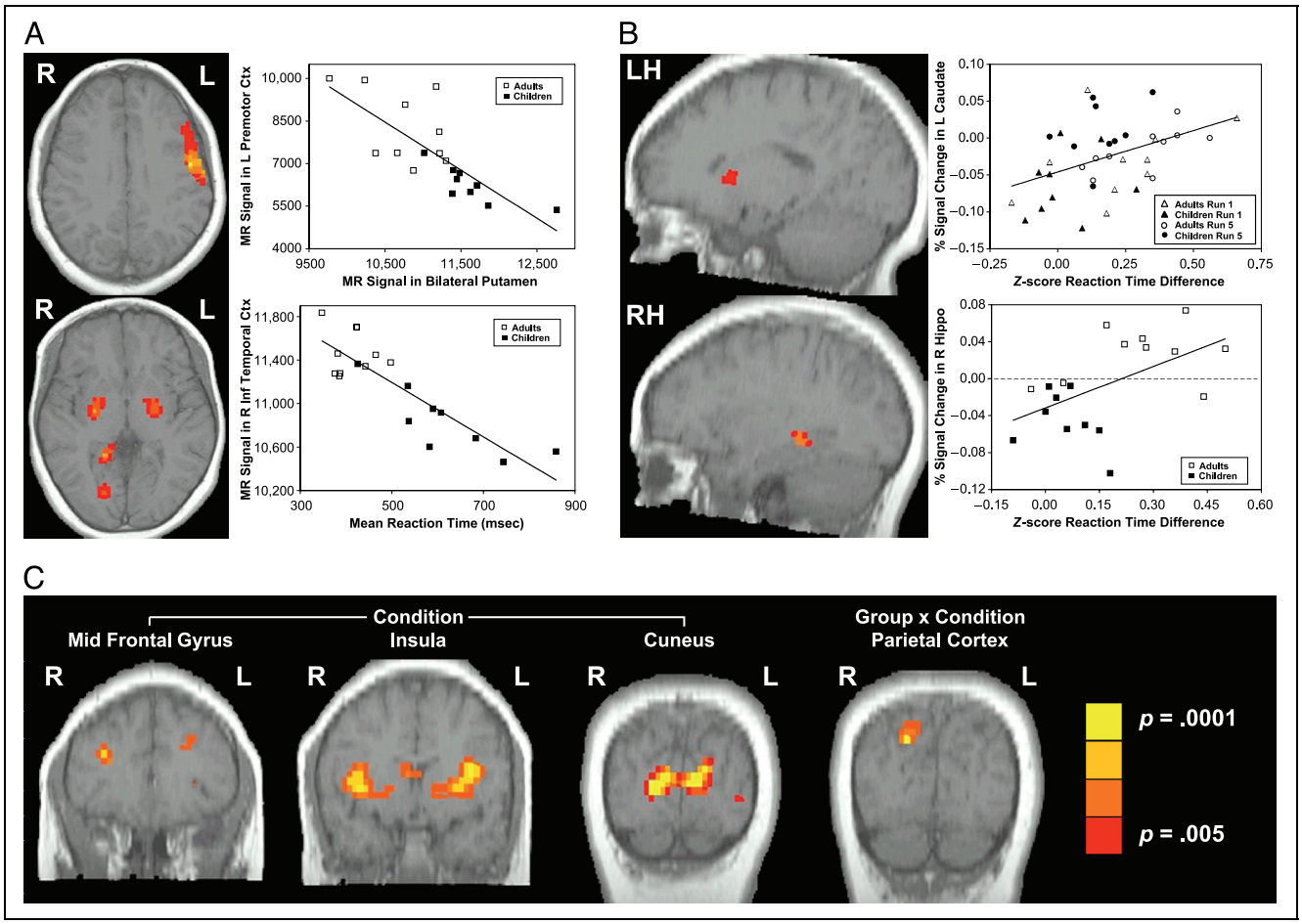

Figure 2. Imaging results. (A) Main effects of age group. Adults show greater activity in the left premotor cortex (upper left); children show greater activity in the bilateral putamen and adults show greater activity in the right inferotemporal cortex (lower left). Activity in the premotor cortex was negatively correlated with activity in the putamen (upper right); activity in the inferotemporal cortex was negatively correlated with overall reaction time (lower right). (B) Interaction effects. Activity in the left caudate showed a significant Run × Condition interaction (upper left); this activity difference correlated positively with the sequence-specific learning effect (RT difference) (upper right). Activity in the right hippocampus showed a Group × Condition interaction (lower left); an apparent correlation between activity and sequence-specific learning (RT difference) was accounted for largely by age-related differences in both factors (lower right). (C) Other effects. MR signal was larger for random trials than sequence trials in the bilateral middle frontal gyrus, insula, and cuneus (left three images). A Group × Condition interaction revealed age-related differences in right parietal activity; children showed greater signal for sequence trials while adults showed greater signal for random trials (right image).

these regions, showing no correlation between activity and overall reaction time [$r = .10$, $t(8) = 0.30$, *ns*]. It is unclear to what extent these differences reflect developmental as compared to performance differences as both are present in the current sample.

Learning Effects

Significant differences were observed between random and sequence trials in the bilateral cuneus and lingual gyrus (BA 18/19), portions of the left superior temporal gyrus (BA 42), bilateral insula, bilateral inferior parietal lobule (BA 40), bilateral middle frontal gyrus (BA 9/46), left putamen and thalamus, right cingulate gyrus (BA 24), and right caudate (Figure 2B and C). Random trials elicited greater activity in these regions than sequence trials. Similar effects have been reported previously and have variously been termed a repetition suppression effect (Buckner, Koutstaal, Schacter, & Rosen, 2000; Buckner et al., 1998; Gabrieli, 1998; Petersen, van Mier, Fiez, & Raichle, 1998), category fluency effect (Reber, Gitelman, Parrish, & Mesulam, 2003), or visual priming effect (Gabrieli, 1998). In all cases, repeated exposure to the same stimuli or same category of stimuli results in a decrease in cortical activity in regions such as the extrastriate cortex (Reber et al., 2003). In this case, we observed a decrease in extrastriate activity for a repeating pattern of stimulus locations compared to a random pattern of the same locations. This effect was not differentiated across age groups. Although we observed a main effect of age group (adults activated the extrastriate cortex more strongly than children), the interaction of these factors was not significant, suggesting that this extrastriate activity is not related to the

sequence learning differences observed between adults and children in the behavioral reaction time data.

Regions in the insula, superior temporal cortex, and caudate all showed similar effects of decreased activity for sequence trials compared to random. However, a significant interaction between condition and run mediated effects in the left caudate nucleus and right insula/inferior frontal cortex (BA 44). Early in learning (run 1), activity in these regions was greater for random trials compared to sequence trials. However, later in learning (block 5), there was little or no difference in activity by condition (Figure 2B). These interaction effects were significant only in one hemisphere. Dropping the threshold to $\alpha = .01$ did not produce a bilateral response. This pattern of interaction was also significant in the right parietal cortex (angular and supramarginal gyri, BA 40). Although all of these regions have been observed in previous studies of SRT learning with adult participants, the effects have typically been greater for sequence than for random trials (Bischoff-Grethe, Martin, Mao, & Berns, 2001; Grafton et al., 1995). In fact, the anatomical regions observed here for random trials compared to the implicitly learned sequence are strikingly similar to locations reported by Willingham et al. (2002). Although our results are in the opposite direction overall, activity in the left caudate nucleus (Condition × Run interaction) was significantly positively correlated with the magnitude of the sequence-specific learning effect [$r = .44$, $t(36) = 2.97$, $p < .005$]. That is, the percent change in MR signal for sequence trials compared to random trials increased proportionally to the difference in behavioral measures of learning (Figure 2B). This correlation was significant for both adult and child data. This relationship was stronger early in learning (run 1). The percent change in signal between sequence and random trials was more positive in run 5 than in run 1. Overall, activity was greater for random compared to sequence trials, but most (although not all) participants showed a reduction in this effect in run 5 compared to run 1 (i.e., a reduction in activity to random trials or an increase in activity to sequence trials with practice).

Finally, medial temporal lobe regions showed condition effects that differed by age group. Activity in the right hippocampus was greater for sequence trials than random trials for adult participants. However, children showed the opposite effect, showing greater right hippocampal activity for random trials compared to sequence trials. This effect did not vary significantly across runs 1 and 5. A significant correlation was observed between percent change in signal for sequence compared to random trials and the magnitude of the learning effect (Figure 2B). However, this effect occurred as a result of overwhelming group differences in signal change and learning. No significant correlation was observed between percent change in MR signal in the hippocampus and magnitude of the learning effect within either the adult or child age groups, suggesting little or no relationship with the degree of behavioral learning in these small samples.

Additional interactions between age group and condition were observed in the lateral regions of the bilateral temporal cortex (BA 21/22) and in the right superior parietal cortex (BA 7) (Figure 2C). Similar to hippocampal activations, children showed greater bilateral superior temporal cortex activity for random trials than sequence trials while adults showed the opposite effect. However, in the superior parietal cortex, this pattern was reversed with children showing greater activity for sequence than random trials and adults demonstrating more parietal activity in response to random trials compared to sequence (Figure 2C). This sequence-related effect for adults is consistent with previous data suggesting decreases in superior parietal activation with increases in stimulus predictability (Bischoff-Grethe et al., 2001), although we observe this activity in the right hemisphere as opposed to the previously reported left hemisphere activation.

DISCUSSION

In the current study, we tested behavioral and functional neuroimaging differences in implicit learning on a visuomotor SRT task between adults and 7- to 11-year-old children. Previously proposed theories suggest developmental invariance in implicit learning across the lifespan despite substantial age-related improvements in explicit learning. Behavioral and neuroimaging results from the current sample highlight age-related improvements in implicit learning as well as differential recruitment of neural systems previously associated with visuomotor sequence learning.

The behavioral findings presented here provide clear evidence that, although children showed significant implicit sequence learning on this task, the magnitude of this effect was not equivalent to adult performance. Children showed slower overall reaction time and somewhat lower mean accuracy than adults during this visuomotor task. Importantly, adults showed faster reaction times for sequence trials than random trials within the first behavioral run, but children did not demonstrate this learning until sometime in the second run, suggesting that a longer period of exposure or acquisition may be necessary for the child age group. In addition, the magnitude of the learning effect was not equivalent between adults and children even in the final run of trials. One possibility is that the overall performance differences of the child participants led to smaller learning effects for this group. However, follow-up analyses showed no significant correlation between the size of the learning effect and overall response accuracy for either age group independently, or when the two groups were combined. Both adults and children were less accurate in the current study than the Meulemans

et al. (1998) study from which the paradigm was modeled. This result is not entirely surprising as both adults and children are expected to have a more difficult time correctly mapping the visual locations to response buttons when they cannot see their hands, as is the case in the MRI scanner. Overall reaction time also was not significantly correlated with the magnitude of the learning effect within age groups, suggesting that implicit learning on this task shows developmental differences over and above simple motor performance effects.

These data conflict with previous reports of developmental invariance in implicit sequence learning (Meulemans et al., 1998; Reber, 1993). In our own work, we previously observed no significant differences in sequence learning magnitude between 4-, 7-, and 10-year-old children and adults despite group differences in overall reaction time and error rates (Thomas & Nelson, 2001). However, our previous data did indicate developmental trends. In that study, although children and adults learned to the same extent, the number of individuals demonstrating ''any'' significant learning decreased with age, such that fewer 4-year-olds showed learning than 7-year-olds, and fewer 7-year-olds showed learning than 10-year-olds or adults. In the current sample, no group differences were observed in the number or percentage of nonlearners although the small sample size makes such analyses difficult to interpret. The sequence-specific learning differences observed in the current study may reflect differences in the current behavioral paradigm. The constant interruption of the repeating sequence as well as the specific sequence used may be candidate factors in understanding why a developmental effect emerged in this case. In particular, the sequence used in the current study differed slightly from that used by Meulemans et al. (1998). The current sequence included two completely ambiguous positions (1 and 3), meaning these locations were followed equally often by all other locations. The previously used sequence included only one completely ambiguous position, whereas the remaining locations were more predictable. This increase in sequence complexity may elicit age-related differences in implicit learning not observed in other studies. Adult behavioral paradigms have indicated that completely ambiguous sequences are more difficult to learn (Reed, 1994; Curran & Keele, 1993). A similar age-related effect has been reported in infant behavioral studies. For example, Clohessy et al. (2001) reported that 18- to 24-month-old infants were able to learn a sequence with one ambiguous element (i.e., 1–2–1–3), whereas younger infants showed learning only for a sequence with unique pairwise probabilities (i.e., 1–2–3). Importantly, none of the participants in the current study had any awareness of the nature of the sequence. Therefore, developmental differences in learning reflect differences in implicit as opposed to explicit cognition.

Functional MRI data from this SRT paradigm provide evidence of both learning-related changes in activity as well as group differences in activation, despite significant overlap in the neural systems recruited by adults and children. Developmental differences were observed in the recruitment of motor systems. Children showed relatively greater recruitment of subcortical motor structures (specifically, the putamen) during this manual button press task than adults did. In contrast, adults evidenced greater recruitment of cortical regions including the premotor cortex compared to children. This effect was driven solely by age group and was not mediated by trial type or the stage of learning (early vs. late). Signal intensity in these regions was significantly correlated with overall mean reaction time, suggesting that these effects reflect overall differences in motor response execution between adults and children. Activity was not correlated with response accuracy for either age group, however, reducing the possibility that these effects arise due to error detection or attempts at error correction. Developmental differences in subcortical compared to cortical brain regions have been observed in previous pediatric imaging studies addressing the development of attentional control and response inhibition (Casey, Thomas, et al., 2002; Casey, Tottenham, et al., 2002; Luna et al., 2001). In the current work, we saw evidence of a possible tradeoff in recruitment of subcortical versus cortical brain regions as activity in the left premotor cortex was negatively correlated with activity in the bilateral putamen. Premotor activity was also related to overall reaction time, at least for the adult participants in this sample, with faster response times corresponding to greater signal strength in the premotor cortex. These data support a developmental shift in recruitment of motor subsystems during performance of this visuomotor response task, from a heavily subcortical contribution early in childhood to a more cortically driven system in adulthood.

Age-related differences were also observed in regions of the inferotemporal cortex (parahippocampal and lingual gyri) with adults showing greater activity overall than children. However, further examination of this effect in relation to overt behavior demonstrates that this response may be related to behavioral efficiency or speed of processing. Activity in these regions was correlated with overall reaction time such that individuals with faster responses showed stronger signal. This effect was observed primarily for the child group, perhaps due to their broader range of overall reaction times. This correlation suggests a second developmental trend towards increasing activity in the inferotemporal cortex with improvements in response efficiency. Children approach adult levels of activation in these areas as their reaction times approach the adult range. Activity in medial inferotemporal and occipital regions may index the efficiency or ease with which the basic stimulus–response mapping

is completed as this effect is age-related rather than learning-related.

Implicit learning of the visuomotor sequence yielded significant activation in many of the same regions identified in previous adult imaging studies (Daselaar et al., 2003; Doyon et al., 2003; Reber et al., 2003; Schendan et al., 2003; Muller, Kleinhans, Pierce, Kemmotsu, & Courchesne, 2002; Willingham et al., 2002; Bischoff-Grethe et al., 2001; Ghilardi et al., 2000; Grafton et al., 1995; Grafton, Hazeltine, & Ivry, 1998; Rauch et al., 1995, 1997; Karni et al., 1995). Differences between random and sequence trials were observed for both adults and children in the extrastriate cortex, superior temporal/insular cortex, basal ganglia, middle frontal gyrus, and anterior cingulate cortex. However, our results show greater activity in these regions during random trials compared to sequence trials. This effect is consistent with published data suggesting decreased activation in the visual extrastriate cortex following repeated exposure to the same stimuli or task, presumably reflecting priming or increased processing efficiency for previously encountered information. These repetition suppression effects (reduced activity for sequence trials relative to random) did not differ by age group, although adults did show greater signal magnitude in extrastriate regions than children in general. These results support the general notion that priming functions may be equivalent in adults and children.

In contrast to the visual cortex, other brain regions are not traditionally associated with greater activity during random trials. For example, previous studies have reported signal ''increases'' in the insular cortex with repeated practice on a task (Petersen et al., 1998; Raichle et al., 1994), as well as increases in caudate activity with sequence learning (Schendan et al., 2003; Rauch et al., 1997). An examination of the behavioral learning data from the current study may help to resolve this apparent conflict regarding the role of these regions in implicit sequence learning. Although our ANOVA model showed greater activity in the caudate nucleus for random trials, this difference was significantly related to behavioral measures of learning. As learning increases, the relative MR signal for sequence trials increases. That is, the MR signal difference shifts from random-greater-than-sequence toward sequence-greater-than-random with increasing evidence of learning, even though activity for random trials is greater overall. This correlation suggests that, like other reports, we observed increased activity in the caudate as a function of sequence learning. However, we cannot determine from the current dataset whether this reflects an increase in activity to the sequence trials or a decreased response to the random trials. Previous studies have reported caudate sensitivity to low stimulus predictability or novelty (Bischoff-Grethe et al., 2001; Berns, Cohen, & Mintun, 1997). Although this result is consistent with our finding of stronger activation for random trials overall, it is unclear why this response to novelty would diminish with learning. If caudate activity reflects novelty, one would expect increasing activity to random trials with learning because the relative novelty of random trials would increase as the sequence became more familiar. The relative response to random trials decreased across runs, perhaps reflecting an early bias towards novelty detection and an increased sensitivity to the sequence over time. Importantly for the current work, activity differences in the caudate were associated with differences in sequence learning rather than age per se. Of course, the child age group showed smaller sequence learning effects than adults in general, therefore these effects are at least partially confounded.

Learning-related developmental differences in activation were also observed in the right hippocampus. Adults showed greater hippocampal activation during sequence trials than during random trials, whereas children demonstrated the inverse pattern, with random trials eliciting a greater hippocampal response. The signal difference was significantly correlated with the overall magnitude of the behavioral learning effect such that larger learning effects were associated with hippocampal activity for sequence trials compared to random. However, as indicated in Figure 2B, the two age groups show little or no overlap in either signal change or learning. In fact, unlike the findings in the caudate, there is no significant correlation between learning and hippocampal activity for either age group separately. This clustering effect suggests that hippocampal activity is not related to sequence learning, but alternatively may reflect age-related or maturational differences in recruitment of this region during stimulus–response mapping. Casey, Thomas, et al. (2002) reported similar age-related effects during explicit stimulus–response association learning. Children showed greater hippocampal activity than adults during performance of a new stimulus–response mapping relative to a well-learned mapping (Casey, Thomas, et al., 2002). In contrast, adults demonstrate clear evidence of sequence related signal in the hippocampus during both implicit and explicit SRT tasks (Schendan et al., 2003) suggesting age-related differences in hippocampal function.

These effects were not limited to the hippocampus, as superior temporal regions showed similar patterns of activity. However, only one region, the superior parietal cortex, showed the opposite pattern of activity. Adults showed greater parietal activity for random trials than sequence trials. This finding is consistent with reports suggesting that parietal regions are sensitive to stimulus predictability (Bischoff-Grethe et al., 2001). These authors found increased activity in the parietal cortex for adults with decreases in stimulus predictability. Given the role of the parietal cortex in visual attention and spatial orienting, increased activity may reflect a greater demand on an attentional orienting system. In the context of implicit sequence learning, sequence-specific

learning may effectively reduce attentional demands, resulting in less activity in the parietal cortex. This idea raises the possibility that age-related differences in the parietal cortex are associated with differential attentional demands in the two age groups.

This study provides the first evidence of age-related differences in implicit sequence learning in an SRT task. Adults showed a larger learning effect than children and learned the sequence more quickly, challenging theories proposing developmental invariance in implicit function. We observed both age-related and learning-related changes in brain activity. Functional imaging data reported here are consistent with previous adult data implicating fronto-striatal circuitry, the hippocampus, and parietal and motor cortices in implicit sequence learning. Age-related differences in the recruitment of the premotor cortex and the putamen during response execution likely reflect a developmental shift from subcortical to more cortical motor systems with age. Learning-related differences in caudate activity did not vary with age, despite developmental improvements in behavior. Caudate activity increased for sequence compared to random trials with continued exposure to the fixed stimulus pattern. Contrary to the adult literature, the hippocampus showed greater activity to random than sequence trials for children. Although the current findings cannot differentiate between age-related and learning-related changes, these results suggest developmental differences in the function of the hippocampus. Future developmental studies will be required to assess the nature of these developmental changes in medial temporal lobe function.

METHODS

Subjects

Ten right-handed adults between the ages of 23 and 33 years (5 men, 5 women; $M = 27.9$ years) and 10 right-handed children ages 7–11 years (4 boys, 6 girls; $M = 9.6$ years) were included. Participants were recruited from the New York metropolitan area. Adult participants and parents of child participants gave written consent in accordance with procedures approved by the Institutional Review Board of the Weill Medical College of Cornell University. In addition, children provided both verbal and written assent to participate. Participants were screened for use of psychoactive medication, for neurological or psychiatric diagnosis or learning disability, and for the presence of metal in or on the body.

Behavioral Paradigm

Each participant completed five runs of 192 trials in a visuomotor SRT task. Stimuli consisted of a bitmap image of a golden retriever dog presented in one of four blue square frames arranged horizontally along the vertical midline of a solid black screen (Figure 3). A green fixation cross was positioned at the midpoint of the array, between the second and third stimulus frames. On each trial, the bitmap stimulus appeared in one of the four locations for a duration of 750 msec followed by an interstimulus interval of 750 msec (1500 msec trial duration). The location frames and fixation stimulus stayed on the screen continuously throughout each run. Participants were instructed to ''catch the dog'' as quickly as possible using a corresponding set of four buttons split between left-hand and right-hand response pads. The left two stimulus locations corresponded to the left middle and index fingers, respectively, while the right visual locations corresponded to the right index and middle fingers. Accuracy and response times were collected for each trial. Following the design of Meulemans et al. (1998), trials occurred in short, alternating blocks of sequence and random trials. Sequence blocks consisted of 10 trials

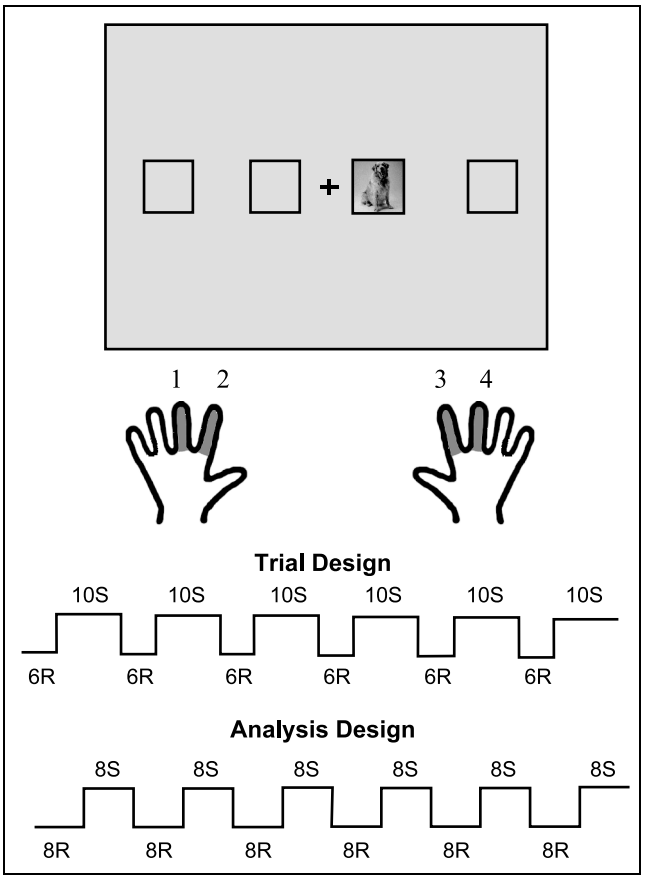

Figure 3. Task design. Participants pressed buttons to indicate the location of the dog on the screen. Responses were bimanual, using the index and middle fingers of each hand. A fixed 10-item sequence of stimulus locations (10S) alternated with 6-item pseudorandom strings (6R). Given the structure of the 10-item sequence, the third item was the first location that could be predicted accurately. Therefore, responses to the first two locations in the fixed sequence were treated as random. The resulting analysis was a boxcar function with alternating periods of eight predictable locations (8S) and eight unpredictable locations (8R).

following a fixed 10-step sequence (3–4–1–3–2–1–4–3–1–2, where numbers indicate the stimulus locations from left to right). Random blocks consisted of six trials without any fixed pattern. Random trials were constrained to prevent immediate repeats of individual locations and to match the individual location probabilities presented in the sequence block (i.e., 1 and 3 more frequent than 2 and 4). Faster reaction times during sequence trials are assumed to reflect sequence learning and anticipatory response preparation. In the sequence used here, participants must know at least two preceding locations in order to accurately predict the current location. Learning of simple pairwise associations would be insufficient given the complexity of the sequence. Therefore, during data analysis, the first two sequence trials of each block were analyzed as though they were random (as they were unpredictable), resulting in an analysis comparing blocks of eight random trials to blocks of eight sequence trials (Figure 3). All participants were queried for explicit awareness of the sequence at the end of the learning trials. Questioning began very open-ended (''Do you think you got faster at catching the dog?'') and became more specific (''Did you ever think you could tell where the dog would go next?''). Finally, all participants were told that the stimulus sometimes followed a repeating pattern and were encouraged to indicate or ''guess'' the sequence using their response buttons or by pointing to sequential locations on the stimulus display. Participants were considered to have at least partial explicit awareness if they correctly indicated a string of five sequential locations.

Prior to the learning trials, participants received a brief 2-min practice session in which all stimulus locations were equally probable. To ensure that children could correctly map the stimulus locations to the correct buttons, the practice session used response contingent stimulus presentation. That is, stimuli remained on the screen until the participant pressed the correct response button. Pilot testing suggested that this procedure significantly improved the reaction time and accuracy of child participants during the forced pace learning trials presented during the actual scan. Adults completed the practice session in the scanner during structural scanning. Children completed a practice session in an MRI simulator at a date prior to the actual scan session, and completed a second practice session during structural scanning.

Image Acquisition

Child participants were first acclimated to the scanning environment in an MRI simulator. Imaging was conducted using a 1.5 T Signa scanner (GE Medical Systems, Milwaukee, WI) with functional imaging capabilities. A standard radio-frequency (RF) head coil was used with foam padding to restrict head movement. Visual presentation and response collection was accomplished using IFIS-SA (MRI Devices, Waukesha, WI) equipment. Whole-brain T1-weighted images were collected for anatomical localization. Functional images were collected in five runs using a gradient-echo, echo-planar imaging sequence (TR = 2000 msec, TE = 40 msec, 90° flip angle). In-plane resolution was 3.125 × 3.125 mm with a 4-mm slice thickness. Data were collected from 24 transverse slice locations covering the majority of the cerebral cortex ($\sim z$ = +65 to −30) for a total of 144 volumes per run. An additional four volumes were included at the start of each run to allow for steady-state tissue magnetization.

Data Preprocessing and Statistical Analysis

Individual data were corrected for motion using AIR software (Automated Image Registration, version 3.08) with a six-parameter rigid body model (Woods, Cherry, & Mazziotta, 1992). Individuals with mean in-plane motion greater than 0.5 voxels across the session were excluded from further analysis. All images were registered to a representative anatomical reference brain, intensity normalized and spatially smoothed (8 mm FWHM) using AIR software. The anatomical reference brain was selected from the pool of actual participants and reflects the median brain across 20 participants in overall size in x, y, and z dimensions. Voxelwise ANOVAs were conducted on these pooled data using normalized signal intensity as the dependent measure (NeuroImaging Software, University of Pittsburgh, Pittsburgh, PA).

Random and sequence trials were modeled in a block design using a boxcar function assuming a 4-sec hemodynamic lag at the start of each run. One functional volume was discarded at the end of each random and sequence block as they reflect a transition state between conditions. The entire dataset was first examined in a 20 × 2 × 5 × 2 ANOVA comparing age group (2), run (5), and condition (2) in a random-effects analysis across 20 subjects. Significant regions were defined as $\alpha = .005$ with a minimum contiguity threshold of six voxels (three voxels in-plane). A second random-effects analysis was conducted using the same parameters comparing data from only the first and last runs (20 ×2 × 2 × 2) to better address early and late learning effects on this task. In both cases, the resulting pooled functional activations were transformed into standardized Talairach space (Talairach & Tournoux, 1988) for visualization using AFNI software (Cox, 1996). Tables list the number of activated voxels for each region and the standardized Talairach coordinates for the point of maximal activation in that region. Figures show significant activations in Talairach space.

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The data reported in this experiment have been deposited in the fMRI Data Center (http://www.fmridc.org). The accession number is 2-2004-116H9.

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