◆ Human Brain Mapping 5:124–132(1997) ◆

Striatal Recruitment During an Implicit Sequence Learning Task as Measured by Functional Magnetic Resonance Imaging

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Abstract: Prior research has repeatedly implicated the striatum in implicit sequence learning; however, imaging findings have been inconclusive with respect to the sub-territories and laterality involved. Using functional magnetic resonance imaging (fMRI), we studied brain activation profiles associated with performance of the serial reaction time task (SRT) in 10 normal right-handed males. Behavioral results indicate that significant implicit learning occurred, uncontaminated by significant explicit knowledge. Concatenated fMRI data from the entire cohort revealed significant right-lateralized activation in both the caudate and putamen. Analysis of fMRI data from individual subjects showed inter-individual variability as to the precise territories involved, including right as well as left caudate and putamen. Interestingly, all seven subjects who manifested robust learning effects exhibited significant activation within the putamen. Moreover, among those seven subjects, the magnitude of signal intensity change within the putamen correlated significantly with the magnitude of reaction time advantage achieved. These findings demonstrate right-sided striatal activation across subjects during implicit sequence learning, but also highlight interindividual variability with respect to the laterality and striatal subterritories involved. In particular, results from individual subjects suggest that, during the SRT, the reaction time advantage garnered via implicit sequence learning might be predominantly associated with activity within the putamen. *Hum. Brain Mapping 5:124–132, 1997.*

Key words: putamen; caudate nucleus; procedural learning; memory

INTRODUCTION

The serial reaction time task (SRT) provides a measure of implicit sequence learning [Nissen and Bullemer, 1987]. A growing body of data suggests that the basal ganglia play a critical role in this type of learning [see Curran, 1995]. For instance, patients with basal ganglia disorders (e.g., Huntington's or Parkinson's

Contract Grant sponsor: Tourette Syndrome Association, Inc.; Contract Grant sponsor: NIMH; Contract Grant numbers: MH01215 and MH01230; Contract Grant sponsor: David Judah Research Fund.

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Received for publication 22 October 1996; accepted 11 March 1997

disease) exhibit impaired performance on the SRT [Willingham and Koroshetz, 1993; Knopman and Nissen, 1991]. Furthermore, a series of recent imaging studies employing positron emission tomography (PET) have shown striatal activation when normal subjects are engaged in implicit sequence learning [Rauch et al., 1995; Grafton et al., 1995; Doyon et al., 1996]. In the current study, we adapted the SRT for use in conjunction with functional magnetic resonance imaging (fMRI). The purpose of this project was both to replicate previous PET findings and to validate the fMRI-SRT paradigm, as well as to better delineate the intersubject variability in striatal activation patterns associated with implicit sequence learning.

The SRT [Nissen and Bullemer, 1987] entails serial presentation of visual cues at one of four positions on a computer monitor. The subject is instructed to respond to each cue by pressing one of four buttons on a keypad, where each button corresponds to one of the possible cue positions. In this sense, to the subject, the SRT resembles a simple continuous performance task with attentional, visuospatial, and motor demands. However, unbeknownst to the subject, for some series of stimulus presentations the cues appear in a pseudo-random order and during other series the cues follow a repeating sequence. During blocks of repeating sequence trials the subject is afforded an opportunity to develop a reaction time (RT) advantage by virtue of learning information about the sequence. After the performance trials have been completed, debriefing procedures can be used to determine whether subjects were consciously aware that a repeating sequence was present [Reed and Johnson, 1994; Reber and Squire, 1994; Rauch et al., 1995], such as by testing whether or not subjects are able to consciously recall elements of the sequence [Reber and Squire, 1994; Rauch et al., 1995]. Hence, when subjects are unable to perform better than chance on the recall task, it can be inferred that learning was implicit rather than explicit in nature [Reber and Squire, 1994; Rauch et al., 1995].

Using PET, a 12-item sequence, and bimanual responding, we previously found right inferior striatal activation when contrasting relative regional cerebral blood flow (rCBF) values during blocks of sequence exposure vs. the pseudo-random baseline condition [Rauch et al., 1995]. Nearly the identical locus of activation was identified by Doyon and colleagues [1996], during a ''highly learned phase'' of performance in the context of a similar PET paradigm. Moreover, we have replicated our findings in a second cohort of normal subjects, although in addition to right inferior striatum, activations were found in left caudate and left inferior lenticulate as well [Rauch et al., 1996]. In contrast, Grafton and colleagues [1995] have generated somewhat disparate results in the context of a different paradigm. They used PET, right-handed responding, and a six-item sequence with simpler structural characteristics than Rauch and colleagues' 12-item sequence [for a review of how sequence structure affects learning, see Curran, in press]. To protect against subjects developing explicit knowledge about the sequence, Grafton et al. [1995] employed a distraction task (counting of tones), so that subjects could first be studied with attentional interference, and subsequently (using a different sequence and no distraction task) without attentional interference. They studied subjects during multiple blocks of each condition and looked for monotonic increases in rCBF. As anticipated, in their study the learning curve was substantially steeper during the condition without attentional interference, and seven of 12 subjects reported explicit awareness of the six-item sequence after completing that task. Grafton et al. [1995] found activation in bilateral putamen during the condition with attentional interference whereas striatal activation was confined to right inferior putamen / accumbens during the condition without attentional interference. They interpreted their results as reflecting the mediating anatomy of implicit and explicit sequence learning respectively.

We previously suggested that one parsimonious interpretation of these findings is that right inferior striatum might be preferentially involved during implicit sequence learning and that the dislocation of activation to bilateral dorsal putamen in Grafton and colleagues' study could be viewed as a consequence of divided attentional demands which fundamentally alter the task [Rauch et al., 1995; Corbetta et al., 1991]. An alternative explanation for the discrepant findings is that each of these striatal sub-territories can be involved in the implicit learning process and that previous inconsistent results simply reflect inter-individual differences combined with the high risk of type II error in the face of limited statistical power, which is exacerbated by threshold adjustments for multiple comparisons. Of note, PET data from several different studies speak against the notion that right inferior striatum is involved in the process of explicit sequence learning per se [Rauch et al., 1995; Doyon et al., 1996; Grafton et al., 1995].

We have proposed that the SRT in conjunction with neuroimaging might serve as a useful probe of striatal function in neuropsychiatric disorders [Rauch et al.,

1995, 1996]. Since fMRI offers potential benefits in terms of spatial and temporal resolution and the capacity to perform meaningful statistical analyses in individual subjects, we sought to develop a modified version of the SRT for use with fMRI. The goals of this project included further delineation of the pattern of striatal activation associated with implicit sequence learning, as well as determining the consistency of this pattern among individual subjects.

METHODS

Subjects

This investigation was conducted in accordance with the guidelines of the Subcommittee on Human Studies of the Massachusetts General Hospital; all subjects gave written informed consent. The study sample comprised 10 healthy, right-handed [Oldfield, 1971], adult males (20–35 years of age), who were recruited through advertisement and participated as paid volunteers. A single gender cohort was studied to minimize heterogeneity thereby improving statistical power. In this case, males were chosen in preparation for a subsequent study of Tourette syndrome, a disorder occurring predominantly in males. By history, all subjects were without significant psychiatric, neurologic, or medical illness. None of the subjects were taking psychotropic or cardiovascular medications at the time of study nor during the preceding 4 weeks.

SRT paradigm

The SRT involved presentation of an asterisk, appearing serially in each of four boxes which were arranged horizontally. The stimuli were projected onto a viewing screen within the magnet bore. Subjects were instructed to press one of four keys; each key corresponded to one of the boxes and each key press was performed with a separate finger for each key (first two fingers on each hand). For each trial, asterisks were programmed to appear in one of the four boxes for a fixed duration (1.0 second), followed by a fixed period with no asterisk projected (0.2 second), followed by reappearance of the asterisk in one of the three other boxes, and so on. RT and the accuracy of response were measured for each presentation. In the Implicit Learning conditions, the stimuli followed a 12-item sequence (position: 1-2-1-4-2-3-4-1-3-2-4-3) that repeated six times for a total of 72 trials. The baseline conditions included 24 stimuli in which stimulus locations were pseudo-randomly determined, with the constraint that no location was immediately repeated. Each subject performed an initial practice run (2 minutes of pseudo-random stimuli) followed by two experimental runs of approximately 6 minutes and 15 seconds each. Each experimental run consisted of contiguous alternating baseline (B) and implicit learning (IL) conditions arranged in the following order: B-IL-B-IL-B-IL-B. The successive runs were separated by rest periods of approximately 5 minutes duration.

It should be noted that an earlier version of this paradigm was piloted using B and IL epochs of equal length (i.e., 48 trials each), however, with those parameters, subjects failed to exhibit an RT advantage. Consequently, the current version of the paradigm, with unequal B and IL epochs, was prompted by behavioral performance considerations.

Immediately following the scanning session, subjects completed a debriefing procedure which was administered in an automated fashion via computer [as previously described; Rauch et al., 1995]. First, subjects were asked a series of multiple choice questions regarding the stimuli. Next, they were informed that a sequence had been present and were asked to attempt to recall the sequence by making a series of 15 key presses. The recall task was scored based on the longest consecutive string of correct responses. Subjects' performance on the recall task was then compared with a chance distribution as an index of significant explicit knowledge.

Imaging protocol

Each subject spent a total of ~75–90 minutes within the scanner. Images were obtained with a quadrature head-coil and a 1.5T MR scanner (General Electric, Milwaukee, WI) modified for echo-planar imaging (Advanced NMR Systems, Wilmington, MA) according to the following protocol: 1) a sagittal localizer scan was performed to orient, for subsequent acquisitions, 15 contiguous, 8 mm thick, transaxial slices parallel to the intercommissural plane; 2) an automated shimming technique was used to optimize B_0 homogeneity [Reese et al., 1995]; 3) a spoiled gradient recall (SPGR) T1-weighted flow-compensated scan (resolution = 1.6 mm x 1.6 mm x 8 mm) was obtained for use as an angiogram; 4) a T1-weighted echo-planar spin echo sequence was used to obtain high resolution structural images; 5) an asymmetric spin echo T2*-weighted sequence (TR = 2750 msec; TE = 70 msec; refocusing pulse offset by -25 msec) was used to obtain functional images [i.e., reflecting local increases in blood flow and oxygenation; Kwong et al., 1992; Ogawa et al., 1992;

Bandettini et al., 1992]. Data analysis entailed movement correction [Jiang et al., 1995], coronal reslicing, Talairach transformation [Breiter et al., 1995; Talairach and Tournoux, 1988], and construction of statistical nonparametric maps using the Kolmogorov-Smirnov (KS) statistic. For each fMRI run, 136 time points were acquired; 40 corresponded with the B condition, 90 corresponded with the IL condition, and six were excluded as transitional points overlapping consecutive epochs. KS maps contrasting the IL vs. B conditions were generated for each individual subject, as well as for concatenated data from the entire cohort.

Based on earlier PET-SRT findings [Rauch et al., 1995; Grafton et al., 1995; Doyon et al., 1996] and reflecting our programmatic research focus, we sought to test the a priori hypothesis that significant signal intensity increases would be identified within striatum for the IL vs. B contrast. A threshold of $P < 2.0 \times 10^{-4}$ was applied for group data, corresponding to a conservative Bonferroni-type correction in the context of an a priori hypothesis pertaining to the striatal search volume (~250 voxels). A more liberal threshold (i.e., $P < .005$ uncorrected) was applied in the context of a secondary analysis to localize sites of maximal activation within striatal sub-territories in individual subjects.

RESULTS

Behavioral results

Error rates were < 8% for every subject (mean ± SD = 2.0 ± 2.3%). All subjects exhibited a decrease in mean RT between the B and IL conditions reflecting learning. Although the group exhibited a significant RT advantage for the IL vs. B condition (mean median RT ± SD = 403.9 ± 50.9 msec vs. 437.9 ± 64.1 msec; t = 5.89, df = 9, $P < .0002$), there was considerable intersubject variability in the magnitude of RT advantage achieved (range = 1.8% to 10.7%). In fact, there was an obvious split in terms of behavioral performance, whereby seven subjects manifested a robust RT advantage (8.2–10.7%) and the other three subjects manifested only a marginal RT advantage (1.8–3.5%). The results of the debriefing task, which assessed subjects' ability to explicitly recall the sequence [Rauch et al., 1995] confirmed nonsignificant explicit knowledge across the cohort (mean maximum consecutive correct responses ± SD = 3.10 ± 1.19; chance performance = 3.71) as well as in each individual case (all ≤ 4; chance performance = 3.71 ± 1.26, such that individual scores of ≥ 6 are suggestive of significant explicit knowledge).

FMRI results

Foci of significant striatal activation associated with the concatenated group IL vs. B contrast were found within right caudate and an inferior region of the right putamen (see Table I and Figure 1). Foci of maximal activation within the left caudate (uncorrected $P = 3.2 \times 10^{-4}$) and left putamen (uncorrected $P = 2.4 \times 10^{-3}$) did not achieve the threshold for statistical significance, due to strict adjustment for multiple comparisons. Sites of activation occurring outside the a priori striatal search volume that met the same statistical threshold (i.e., $P < 2.0 \times 10^{-4}$) included: Right anterior cingulate gyrus (BA 24/32), left prefrontal cortex (BA 9 and 46), left premotor cortex (BA 6), left inferior parietal cortex (BA 40), left visual cortex (BA 17/18), and left cerebellum (see Table I). Although these extra-striatal loci are reported, to obviate bias, it must be appreciated that the statistical threshold used was exceedingly liberal for surveying the whole brain; the Bonferroni-type adjusted statistical threshold corresponding to the whole brain search volume is $\sim P < 10^{-7}$.

Inspection of KS-maps for individual subjects revealed inter-individual differences regarding the specific striatal sub-territories involved (see Table II). Of interest, the seven subjects who developed a substantial RT advantage all exhibited activation loci within putamen, whereas the three subjects who manifested only a marginal RT advantage all exhibited striatal activation that was confined to the caudate nucleus. To follow-up on the suggestion that putamen activation is associated with RT advantage, we performed a Pearson product moment correlation analysis of % RT difference and % signal intensity change; signal intensity values were obtained from the point corresponding to the KS-peak within either putamen for each of the seven subjects (i.e., all of the subjects who demonstrated a local maximum of $P < .005$). This analysis demonstrated a statistically significant positive relationship between % RT advantage and % signal intensity change within the putamen ($r = .85$, $df = 5$, $P < .05$; see Figure 2).

DISCUSSION

In the current study, employing a modified version of the SRT in conjunction with fMRI, significant striatal activation was detected during implicit sequence learning. Right caudate and right inferior putamen activations were evidenced in an overall analysis of concatenated runs across the entire cohort. Concatenated runs from each individual subject indicated some

TABLE I. Regional brain activations from concatenated group data

Brain region (BA)	*P* value	% Δ signal	Coordinates[a]		
			x	y	z
Striatum					
Right caudate	1.0×10^{-4}	.21	19	9	13
Right putamen	7.8×10^{-5}	.21	25	6	0
Outside striatal search volume					
Right anterior cingulate (A24/32)	7.5×10^{-6}	.44	3	36	13
Left inferior frontal cortex (A46)	2.7×10^{-5}	.73	−44	36	6
Left middle frontal cortex (A9)	8.1×10^{-5}	.25	−38	15	28
Left premotor cortex (A6)	5.7×10^{-5}	.73	−56	−3	13
Left inferior parietal cortex (A40)	6.2×10^{-5}	.30	−50	−24	19
Left inferior parietal cortex (A40)	6.6×10^{-5}	.27	−41	−51	41
Left visual cortex (A17/18)	3.5×10^{-5}	.29	−9	−69	13
Left cerebellum	1.8×10^{-5}	.29	−3	−57	6

[a] Coordinates are presented according to the convention of Talairach and Tournoux [1988], in millimeter units; the origin is the anterior commissure at the midsagittal plane, with $x > 0$ corresponding to right of midsagittal, $y > 0$ corresponding to anterior, and $z > 0$ corresponding to superior.

intersubject variability regarding the striatal subterritories involved. Upon examination of the behavioral data together with imaging data from individuals, it was apparent that a pattern existed whereby subjects with the most robust RT advantage exhibited putamen activation whereas subjects who showed marginal RT advantage exhibited striatal activation limited to the caudate nucleus. Moreover, among subjects who displayed robust learning effects, the magnitude of activation within putamen was positively correlated with the magnitude of RT advantage achieved.

The hypothesis-driven nature of this study, placing a priori emphasis upon the striatal search volume, enhanced statistical power by allowing a more modest adjustment for multiple comparisons. It should be emphasized, however, that all foci of comparable activation identified outside the striatum were quite consistent with previous reports of cortical territories implicated in implicit sequence learning [Rauch et al., 1995; Grafton et al., 1995]. In particular, prefrontal cortex (e.g., A9/46), parietal cortex (e.g., A40), and visual cortex (e.g., A18), are known to project to the caudate nucleus and constitute a brain system that is purported to mediate cognitive and visuospatial functions [see Alexander et al., 1990]; premotor cortex (e.g., A6) is known to project to the putamen and together with cerebellum these regions constitute a brain system that is purported to mediate motor functions [see Alexander et al., 1990].

The current striatal findings, detected via fMRI, converge with those of previous PET-SRT studies. Each of the four previous PET-SRT experiments [Rauch et al., 1995, 1996; Doyon et al., 1996; Grafton et al., 1995] have yielded significant striatal activation foci. Taken together, these data argue strongly that the striatum plays a critical role in implicit sequence learning. Indeed, striatal spiny neurons appear to be ideally suited for subserving this type of learning, since they recognize or preferentially respond to cortical input constellations, exhibit plasticity in developing such response preferences, and ultimately influence gating at the level of the thalamus [see Houk et al., 1995].

The variability among previous findings with respect to the precise striatal subterritories involved in implicit sequence learning seems best explained in the context of intersubject differences observed in the current study. The striatal elements that participate in implicit sequence learning appear to reflect activity of multiple segregated parallel processing systems [Reber, 1989, 1992; Reber and Squire, 1994; Alexander et al., 1990]. For instance, the topographic arrangement of striatal subterritories provides a scheme for dissociable involvement of putamen (which receives projections from premotor cortex) and caudate nucleus (which participates in the cognitive arm of the corticostriatal system, receiving projections from prefrontal as well as parietal and visual cortex) [Alexander et al., 1990]. In fact, the nature of the SRT is such that the observed RT advantage could develop as a consequence of motor learning, visuospatial learning, or some combination of or interaction between the two [Keele et al., 1995; Mayr, 1996; Willingham et al., 1989; for review see

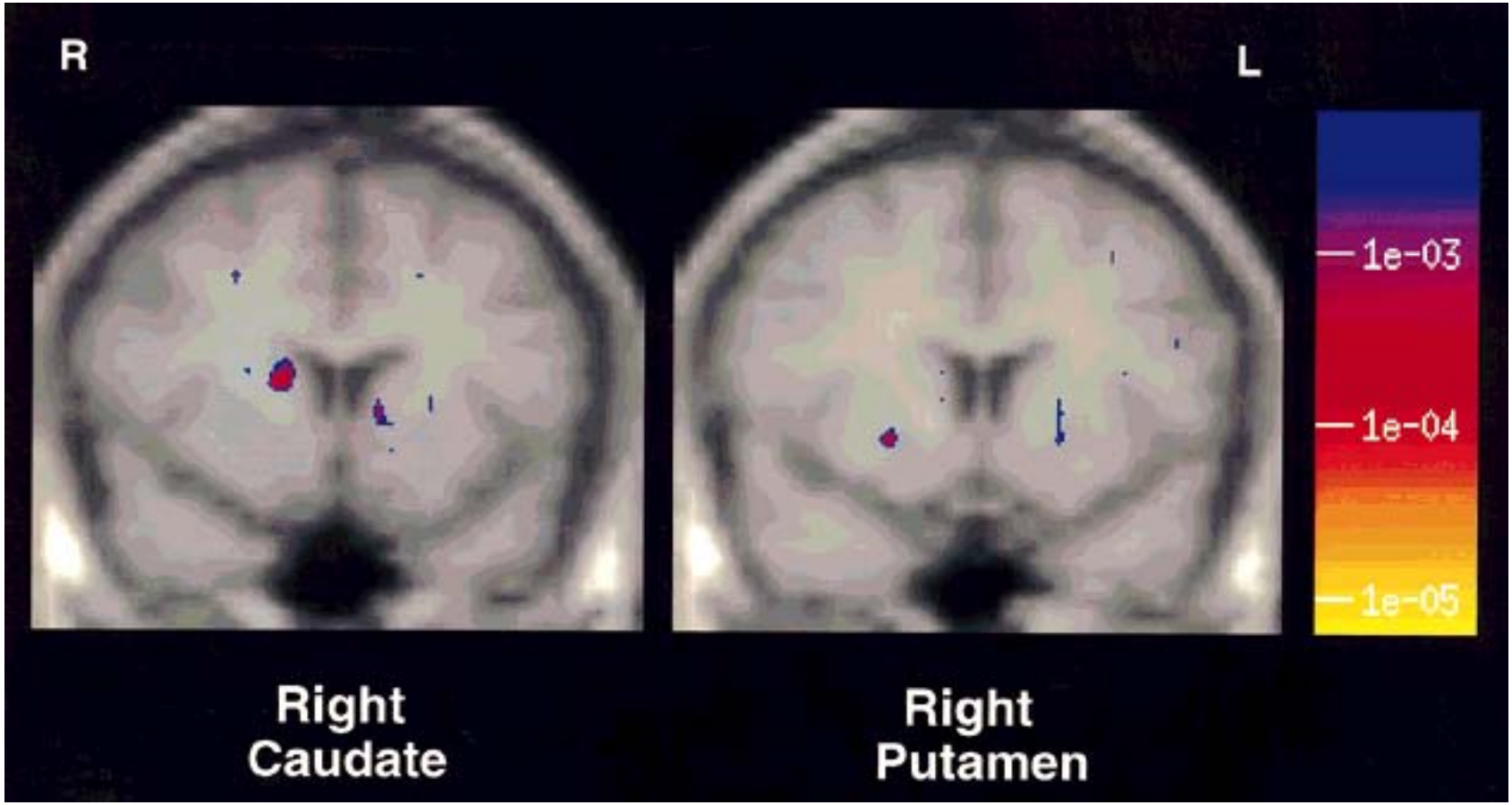

Figure 1.

KS-maps depicting significant right-sided striatal activation ($P < 2 \times 10^{-4}$) from the concatenated IL vs. B contrast for the entire cohort . The KS statistical color maps are superimposed over T1-weighted high resolution coronal images that have been averaged for the 10 subjects. All data have been Talairach transformed [Talairach and Tournoux, 1988; Breiter et al., 1995].

TABLE II. Percent reaction time advantage and location of striatal activation during implicit sequence learning in individual subjects

		Loci of activation within striatum[a]			
Subject #	RT % Δ	R-Putamen	L-Putamen	R-Caudate	L-Caudate
2	10.7	X			X
8	10.4	X	X		
9	9.4	X	X	X	X
6	8.9	X	X		
4	8.9		X	X	
7	8.7	X	X	X	
5	8.2	X	X		
3	3.5			X	
1	2.6			X	
10	1.8				X

[a] Local maxima exceeding uncorrected $P < .005$.

Curran, in press]—-a factor which initially motivated our selection of this paradigm as a candidate panstriatal activation task. Learning information regarding the series of finger movements to accomplish key presses corresponding to the sequence represents motor learning. The motor cortico-striatal circuits have the putamen as their principal striatal component. Learning information regarding the sequence of visual target locations or the spatial sequence of keys to be pressed represents cognitive-visuospatial learning. The prefrontal cortico-striatal circuits which are purported to mediate such cognitive-visuospatial functions have the caudate nucleus as their principal striatal component. It is also worth noting that learning information about the sequence of eye movements consititutes a kind of oculomotor learning [Mayr, 1996]. Although the mediating anatomy of learned eye movements has been studied [e.g., Hikosaka et al., 1989], we are not aware of previous imaging studies that have specifically looked at the neural substrates of implicitly learned sequences of saccades. Nonetheless, the oculomotor cortico-striatal circuit also has the caudate nucleus as its principal striatal component. With the above scheme in mind, the current results suggest that the motor learning system (as evidenced by putamen acivation) might be principally responsible for the observed RT advantage.

Analysis of the group data from the present study suggests that striatal mediation of implicit sequence learning is right-lateralized. However, data from the individual subjects indicate that lateralization of striatal function for this task is not complete or uniform. Of the four previous PET-SRT experiments employing single task conditions [Rauch et al., 1995, 1996; Doyon et al., 1996; Grafton et al., 1995], all found right inferior striatal activation, and three yielded right-lateralized findings [Rauch et al., 1995; Doyon et al., 1996; Grafton et al., 1995]. This pattern of results may be confounded by the gender composition of the study cohorts; the one earlier report of bilateral striatal activation involved an all female cohort [Rauch et al., 1996]; the current sample was all male. Still, the preponderance of findings may reflect genuine laterality for implicit sequence learning, perhaps related to the right hemisphere's dominant role in mediating nonverbal functions [Lezak, 1995]. In the literature pertaining to explicit learning and memory, several laterality distinctions have been proposed. For instance, in analogous fashion, it has been suggested that prefrontal involvement in explicit working memory may be lateralized such that the right side preferentially processes spatial

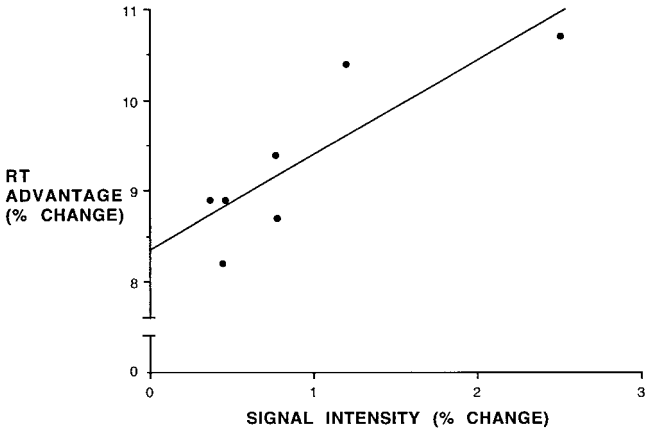

Figure 2.
Graph depicting the relationship between % RT difference and % signal intensity change ($r = .85$, $df = 5$, $P < .05$).

information while the left side processes object identifying information [Smith et al., 1995].

Yet, one striking feature of our current findings is the preponderance of left-sided cortical activation in the face of right-lateralized striatal activation. Such a pattern of complementary cortical vs. striatal laterality was also observed in our most recent PET-SRT study [Rauch et al., 1996]. It raises the intriguing possibility that normally functioning striatal elements literally relieve corresponding cortical territories of their computational load as implicit learning transpires. Consequently, in an adaptive sense, these cortical regions may be liberated to subserve other functions, including explicit information processing. Conversely, disorders characterized by dysfunctional striatal elements might be associated with hyperactivity in corresponding cortical projection zones [Rauch et al., 1996]. Of note, however, the current pattern of complementary cortical and striatal activation was not observed in our original PET-SRT study, where primarily right-sided cortical as well as striatal activations were found [Rauch et al., 1995]. Hence, just as with the inconsistency of results with respect to striatal subterritories, it is likely that the apparent lateralization of cortical findings is incomplete, and possible that the inconsistency in cortical laterality is attributable to intersubject variability, type II error, or the temporal window sampled.

This study provides further evidence delineating the role of striatum in implicit sequence learning. In addition, these initial results—-documenting the capacity for showing brain correlates of individual behavioral differences—-offer encouragement that the fMRI-SRT might be a suitable probe for assessing striatal function in neuropsychiatric diseases such as obsessive-compulsive disorder, attention deficit disorder, or Tourette syndrome [Rauch et al., 1996]. Beyond replication and extension to a female cohort, future research will seek to further delineate the brain systems which mediate the potentially dissociable motor and visuospatial learning components of the SRT. Finally, ongoing studies expressly designed to enhance statistical power in the context of learning multiple different sequences should help to elaborate brain activation correlates of behavioral performance, characterize test-retest reliability of the fMRI-SRT, and explore the temporal dimension as well as inter-regional relationships associated with implicit sequence learning.

ACKNOWLEDGMENTS

Support was provided by the Tourette Syndrome Association, Inc., NIMH (grants MH01215 and MH01230), and the David Judah Research Fund. Paul Whalen was supported in part as a Fellow in the Clinical Research Training Program of Harvard Medical School. We acknowledge Terry Campbell, Mary Foley, Linda Leahy, Michael Lee, and Mike Vevea for their technical assistance, as well as Randy Buckner and Robert Weisskoff for their expert advise. We also thank Thomas Brady and Michael Jenike for their mentorship.

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