NeuroImage 50 (2010) 1303–1312

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Activation in striatum and medial temporal lobe during sequence learning in younger and older adults: Relations to performance

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ARTICLE INFO

Article history:
Received 28 August 2009
Revised 24 November 2009
Accepted 7 January 2010
Available online 15 January 2010

ABSTRACT

The striatum and connected cortical areas have been implicated in sequence learning (SL) tasks, in which performance increments are gradual and learning typically occurs in the absence of awareness. It has recently been shown that increasing striatal activation during SL may be accompanied by decreasing activation in the medial temporal lobe (MTL) across time, but the specific contribution of the MTL to SL remains unclear. In the current age-comparative fMRI study, we show that gradual SL in the serial reaction time task is associated with activation increases in the striatum and activation decreases in the MTL across time in younger adults. However, in older adults, SL is positively related to activation increases in both the striatum and the MTL. The results are discussed in terms of the functional role of the MTL in SL, and offer a novel explanation of the fact that SL is little affected in aging.

Animal and human research suggests that the striatum and the medial temporal lobe (MTL) may support different cognitive functions (e.g., Rauch et al., 1995, 1997a; Knowlton et al., 1996; Packard and McGaugh, 1996; Gabrieli, 1998). Evidence indicates that the MTL is more generally involved in forming rapid associations between previously unrelated temporally or spatially distributed events, which are stored as flexible representations (Knowlton et al., 1996; Reber et al., 1996; Cohen et al., 1997; Curran 1997a; Eichenbaum, 2000). By contrast, the striatum is typically recruited for simpler incremental stimulus-response binding, based on statistical likelihoods of stimulus occurrence over time. With practice, this form of learning leads to automatic behavior, but representations are likely inflexible and confined to the context of learning (see Packard and Knowlton, 2002; Shohamy et al., 2008 for reviews). Because striatal-dependent learning does not require conscious awareness of the to-be-learned information, it is often also referred to as implicit (Reber, 1967; Seger, 1994). However, it has been suggested that the striatal and MTL systems may be dissociated by the demands imposed by the to-be-learned material, rather than by awareness or lack thereof (e.g., Cohen and Eichenbaum, 1993, Curran, 1997a; Cohen et al., 1999; Poldrack et al., 2001; Rose et al., 2002; Schendan et al., 2003).

During the last decade, evidence has emerged that the striatal and MTL systems do not work in isolation during cognitive task performance. For example, imaging studies in younger adults show that sequence learning (SL) in a serial reaction time task (SRTT; Nissen and Bullemer, 1987) depends on a subcortical–cortical network, with the striatum being a key component (Grafton et al., 1995; Rauch et al., 1995, 1997a; Doyon et al., 1996; Hazeltine et al., 1997; Peigneux et al., 2000; Daselaar et al., 2003; Reiss et al., 2005), but also that learning may be accompanied by early hippocampal activation that decreases across time (Grafton et al., 1995; Schendan et al., 2003; Fletcher et al., 2005; Albouy et al., 2008). The SRTT is presented as a motor task but, often unbeknownst to the participant, the motor actions are not always random but occasionally follow a certain sequence. Increasing speed during sequential over random trials is taken as evidence for SL (e.g., Nissen and Bullemer, 1987; Seger, 1994; Robertson, 2007). The finding that recruitment of the striatal system is accompanied by relative disengagement of the MTL system has been demonstrated using other striatal-dependent cognitive tasks, which has led to the more general idea of "competing" brain systems (e.g., Poldrack et al., 2001; Rose et al., 2002; Poldrack and Packard, 2003; Foerde et al., 2006; Frank et al., 2006; Seger and Cincotta, 2006; Atallah et al., 2008).

A more "cooperative" relationship between these brain systems has been observed in the presence of striatal pathology (e.g., Parkinson's disease). Specifically, in patient groups, spared performance on SL tasks normally relying on the striatum was associated with increased MTL activation (Rauch et al., 1997b, 2007; Dagher et al., 2001; Moody et al., 2004; Beauchamp et al., 2008).

There are, however, also studies reporting no MTL activation or deactivation during the SRTT (e.g., Rauch et al., 1997a; Willingham et al., 2002; Daselaar et al., 2003). Daselaar et al. (2003) included groups of both younger and older adults, and found no age differences in the SRTT, either in terms of performance or neural correlates. This is surprising, as studies have reported age-related volumetric decreases

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doi:10.1016/j.neuroimage.2010.01.015

in striatum between 5% and 10% per decade from early to late adulthood (e.g., Raz et al., 2003, 2005). These figures may be compared to corresponding age-related volume losses in the MTL, which have been estimated to be around 3% per decade or less during adulthood (e.g., Raz et al., 2004, 2005). Moreover, molecular imaging studies in humans indicate that striatal contributions to SL are modulated by dopamine (Badgaiyan et al., 2007; Garraux et al., 2007). Research has consistently found age-related losses of dopamine, with various pre- and postsynaptic biomarkers exhibiting decreases of around 10% per decade across the adult life span (for reviews, see Reeves et al., 2005; Bäckman et al., 2006, in press). Given these patterns of age-related brain changes, one might have expected an increased reliance on the MTL in the older sample used by Daselaar et al. to account for their preserved SRTT performance. A possible explanation for conflicting results with regard to striatal–MTL interactions during the SRTT is the presence of individual differences within age groups in this interaction. SRTT studies with younger adults have shown that the RT advantage for repeating over random sequences can vary considerably (typically between no advantage up to 12%), and that striatal activation is associated with better learning (Rauch et al., 1997a; Peigneux et al., 2000; Reiss et al., 2005; Garraux et al., 2007). Recently, Albouy et al. (2008) demonstrated that, during training of an oculomotor sequence learning task, both striatum and MTL were involved in learning a repeating sequence, and that an increase in striatal activation across sessions was accompanied by a decrease in MTL activation. However, this pattern was only true for those who showed the fastest eye movements to sequential patterns after five blocks of training. By contrast, slower learners showed an increase in MTL activation across sessions.

The present study used functional magnetic resonance imaging (fMRI) to investigate patterns of activation increases and decreases in the whole brain as a function of SRTT performance in healthy younger and older adults. For younger adults, we predicted that, as learning progresses across the experimental run, striatal activation increases and MTL deactivation are related to degree of SL. Such an outcome would be consistent with the notion of competing brain systems. We further predicted a change in this pattern among older adults given the marked striatal alterations in aging. Specifically, for older adults we expected that SRTT performance increments across time are related not only to greater striatal recruitment, but also to increased MTL activation, reflecting compensatory processes in older adults.

Materials and methods

Participants

Fourteen younger (M = 24.71 years, SD = 3.12, 10 female) and 13 older (M = 68.08 years, SD = 2.90, 8 female) right-handed adults participated in the study. All participants were recruited through a newspaper advertisement. Participants reported no history of psychiatric disorders or neurological insult and were screened for current use of psychoactive and blood thinning medication. Older adults were examined for brain lesions. Vision was either unimpaired or corrected using MRI-compatible glasses or contact lenses.

A cognitive test battery was administered to all participants, which included two computerized measures of perceptual speed (letter and pattern comparison), a computerized measure of working memory (WM; verbal n-back), two paper and pencil measures of episodic memory (free recall and paired-associate learning), and a paper and pencil measure of vocabulary (synonym task). Results were age-typical (e.g., Lindenberger and Baltes, 1997; Bäckman et al., 2001), with younger adults generally outperforming older adults on the fluid measures, but not on the vocabulary test (Table 1). The study was approved by the regional ethics committee (Regionala Etikprövningsnämnden in Stockholm) and written consent was obtained from all participants prior to the start of the experiment.

Table 1
Sample characteristics.

	Young	Old	
n	14	13	
Age (mean, SD)	24.71 (3.12)	68.08 (2.90)	
Sex	10 female	8 female	
Education (mean years, SD)	15.65 (1.72)	13.35 (3.01)	
Cognitive test battery	Mean score (SD)		*t*
Letter comparison (max. 20)	10.14 (3.00)	7.81 (3.30)	1.93
Pattern comparison (max. 30)	21.86 (2.23)	16.23 (3.13)	5.40*
Working memory			
2-back (max.10)	9.02 (0.89)	7.13 (1.64)	3.78*
3-back (max.9)	7.02 (1.10)	4.90 (2.53)	2.80*
Episodic memory			
Paired associates (max. 18)	13.14 (3.80)	8.31 (3.15)	3.59*
Free recall (max. 16)	10.86 (2.58)	7.31 (2.72)	3.30*
Vocabulary (max. 30)	24.86 (3.04)	26.92 (2.60)	−1.89

* $p<0.05$.

Task design

In the SRTT, four circles were presented on a horizontal line in the center of a computer screen. The stimuli subtended a visual angle of approximately 18° (width) × 1.5° (height). Each circle's position corresponded to one of four buttons, in order from left to right. Participants were instructed to press the corresponding buttons using the index and middle finger of each hand as quickly and as accurately as possible when a circle changed color from white to gray. Reaction times (RTs) and response accuracy were recorded.

The task was administered in a blocked design. Each trial lasted for 700 ms with a 300 ms inter-stimulus interval. Thirty-six trials formed a block and participants completed 16 blocks with six seconds of rest between blocks.

Unbeknownst to the participants, in every other block the trials followed a second order 12-item fixed sequence (1-2-1-4-2-3-4-1-3-2-4-3-…; e.g., Schendan et al., 2003), from here on referred to as SEQUENCE blocks. In the remaining blocks, trials were presented in pseudo-random order, with the constraint that two consecutive trials were not the same (from here on referred to as BASELINE blocks).

Finally, following the experiment proper, participants filled in a questionnaire designed to assess awareness of the repeating sequences (cf. Seger, 1997). An "awareness score" (max 8) was derived from questions about the participants' experience of (a) the non-random nature of the trials ("I believe the gray circles occurred in random locations, I did not notice a pattern" (0pt), "I think the locations of the gray circles could have followed a pattern, but I am unsure" (1pt), "I am pretty sure the locations of the gray circles were not random, but I am not sure what the pattern was" (2pt), " I am pretty sure the locations of the gray circles were not random, and I think I know what pattern they followed" (3pt), " I am sure the locations of the gray circles were not random, and I am sure I know what pattern they followed"(4pt)); (b) the description of the regularity across blocks ("A sequence of circles was repeated over and over again" (1pt), "A sequence of trials was occasionally repeated" (2pt), "Some locations occurred more often than others"/ "other" (0 pt)); and (c) the ability to reproduce consecutive items of the sequence (< 4 items (0pt), 4 items (1pt), > 4 items (2pt)).

Procedure

Data from three occasions, separated by approximately 1 week, were used. On the first occasion, the cognitive test battery was administered. On the second occasion, the SRTT data collection took place and on the third occasion structural images were acquired. Participants were paid 1500 SEK after completion of all sessions. Before entering the MRI scanner, participants were told that they

were to perform a motor task, and no reference was made to the nature of the repeating sequence or to the post-test questionnaire. Each participant trained on 96 random trials outside the scanner. If accuracy was lower than 80%, the training continued until the 80% accuracy criterion was attained.

Stimuli were presented using E-prime (Psychology Software Tools) and responses were recorded from the index and middle finger of both hands using custom-built response pads on both hands (MAG Design & Engineering, Sunnyvale, California). Stimuli were projected via a Philips LCD projector (Philips Corp., Netherlands) onto a mirror mounted on top of the brain coil and in good view for the participants. Immediately after the end of the SRTT, participants left the scanner and were asked to complete the awareness questionnaire.

MRI protocol

All images were acquired on a 1.5 Tesla MRI system (Signa Excite HD Twinspeed, General Electrics Medical Systems, USA), with an 8-channel high-resolution brain coil.

Functional scan

Blood-oxygen-level-dependent (BOLD) fMR images were generated with a gradient-echo echo-planar imaging (EPI) pulse sequence (TR/TE = 2500/40 ms, flip angle = 90°, matrix = 64 × 64, FOV = 22 cm × 22 cm, 32 slices, slice thickness 4 mm, 0.5 mm interslice spacing), that yielded 3.44 × 3.44 × 4 mm^3 voxels. Slices were acquired interleaved, in axial orientation. Total scanning time was 11 min and 22 s, which resulted in 272 volumes of which the first four were discarded as "dummy scans".

Structural scans

A T1-weighted image (TR/TE = 24/6 ms, flip angle = 35°, FOV = 22 cm × 22 cm, slice thickness 1.5 mm) was used to co-register with the functional scan. For the older adults only, a coronal fluid-attenuated inversion-recovery (FLAIR) image, and an axial T2-weighted fast spin-echo image were acquired, which were screened by a radiologist to rule out any brain lesions.

Data analysis

Behavioral variables

Mean latencies for correct responses were calculated for BASELINE and SEQUENCE blocks. In order to assess SL across time, the experimental run was separated into halves (Fig. 1), and for each half, the % RT decrease for the SEQUENCE blocks compared to BASELINE blocks $((M_{RT-BASELINE} - M_{RT-SEQUENCE})/(M_{RT-BASELINE}/100))$ was used as a measure of SL (from hereon referred to as *SL half 1* and *SL half 2*, where a positive score denotes better SL).

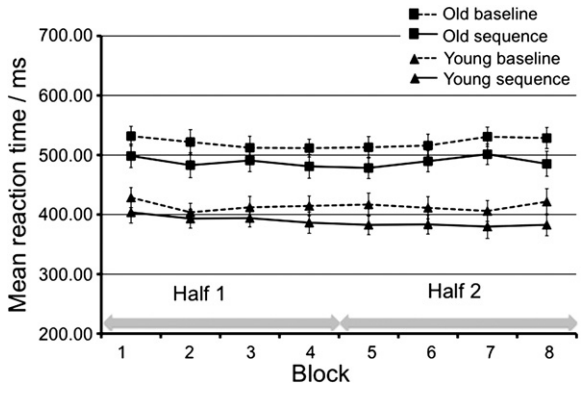

Fig. 1. Mean RT during sequence learning by block, block type and age group. Error bars are standard errors around the means.

A difference score (*SL half 2* − *SL half 1*) was calculated to denote SL change across time (Fig. 1, from hereon referred to as *SL change*). Post-test questionnaires yielded a score between 0 and 8, where a higher score indicated greater subjective awareness of the repeating sequence.

Imaging data

All imaging data were analyzed using FEAT (FMRIBs Expert Analysis Tool Version 5.92), available as part of FSL (FMRIBs Software Library; Smith et al., 2004).

Pre-processing

Before images were subjected to pre-processing, BET (Brain Extraction Tool; Smith, 2002) was used to strip away the skull and other non-brain parts of the image. Images were motion-corrected using rigid body transformations as implemented in MCFLIRT (Motion Correction using FMRIBs Linear Image Registration Tool; Jenkinson et al., 2002), and smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM). A 100 s high-pass temporal filter was applied to remove low-frequency noise.

Statistical modeling

Statistical analyses were based on voxel-wise general linear modeling (GLM). In the first-level individual analysis, parameter estimates for BASELINE blocks were subtracted from SEQUENCE blocks (divided by the pooled standard error) in order to estimate BOLD signal response for SEQUENCE blocks. Autocorrelations in the data were removed using FILM (FMRIBs Improved Linear Modeling) pre-whitening, as implemented in FEAT. The first and second half of the experiment were modeled separately using four explanatory variables (First Half SEQUENCE, First Half BASELINE, Second Half SEQUENCE, and Second Half BASELINE). The hemodynamic response was convolved using a gamma function. FLIRT was used to register functional images to the respective high-resolution structural images and then to the MNI152 standard brain for anatomical reference of the group results.

In a second-level individual analysis, the resulting contrasts from the first-level analysis were compared to each other using fixed effects to estimate activation changes across time (first half [SEQUENCE > BASELINE] > second half [SEQUENCE > BASELINE] = activation decreases over time; second half [SEQUENCE > BASELINE] > first half [SEQUENCE > BASELINE] = activation increases over time).

In order to assess where the BOLD signal varied as a function of successful learning within and across age groups, individual performance scores were included as regressors in the group analyses using FMRIBs Local Analysis of Mixed Effects (FLAME; Beckman et al., 2003). Because there was a negative relationship ($r_{young} = -.53$; $r_{old} = -.71$) between *SL change* and *SL half 1* (individuals who improved most across halves also started off with low *SL half 1* scores), *SL change* scores were orthogonalized with respect to *SL half 1* scores (according to the Gram Schmidt process as implemented in FEAT), when included as a regressor. This procedure ensures that the contrast identifies those voxels at which the signal contains variance that is explained by *SL change*, after accounting for variance in the BOLD signal as a function of *SL half 1* scores. In addition, for all higher-level analyses, awareness scores were included as a covariate in the group analyses in order to account for signal changes related to awareness rather than SL.

Region of interest (ROI) analyses were conducted to illustrate BOLD–behavior relationships. ROIs were created in MNI152 space as a 10 mm sphere around the respective group's peak activations. FEATQUERY as implemented in FEAT was used to extract percent signal change for SEQUENCE blocks (> BASELINE) from the first and second half of the experimental run for each participant. The difference in signal change between halves was plotted against individual *SL change* scores, and linear trends were fitted separately

for younger and older adults. Signal change values that were more than 2 SD away from the mean were treated as outliers. According to these criteria, one younger individual was an outlier for both MTL and striatal signal change, and one older individual was an outlier for MTL signal change. Lastly, mean percent signal change and standard deviations (SD) across voxels were calculated separately for half 1 and half 2 for each ROI and plotted as bar graphs.

Post-processing

All contrasts were thresholded cluster-based at $Z>1.6$ (equivalent to $p<.05$, corrected for multiple comparisons based on Gaussian Random Field Theory), with a minimum cluster extent of 25 voxels, unless otherwise indicated.

Results

Behavioral data

Mean RTs for correct responses by block and age group are shown in Fig. 1.

A 2 (age: young, old) × 2 (block type: RANDOM, SEQUENCE) × 2 (half: first, second) ANOVA, with mean RT as the dependent variable showed reliable main effects of age ($F(1, 25)=20.80$, $p<.001$, $\eta_p^2=.45$), and of block type ($F(1, 25)=77.51$, $p<.001$, $\eta_p^2=.76$), but not of half ($F<1$). Importantly, there was no age × block type interaction ($F<1$), indicating similar rates of SL in both age groups (Fig. 2a).

Most individuals showed a decrease in RT for repeated over random trials in the first half (*SL half 1*: $M_{young}=5.01\%$, $SD=4.32$; $M_{old}=6.30\%$, $SD=5.58$). However, there were large individual differences in how SL progressed across the two halves (*SL change*: $M_{young}=2.60$, $SD=4.45$; $M_{old}=0.21$, $SD=5.30$; Fig. 2b). Neither *SL half 1* nor *SL change* differed between age groups ($ts(25)<1$). There was a negative relationship between *SL half 1* and *SL change* ($r_{young}=-.53$; $r_{old}=-.71$), indicating that those individuals that showed low SL in the first half improved the most in the second half.

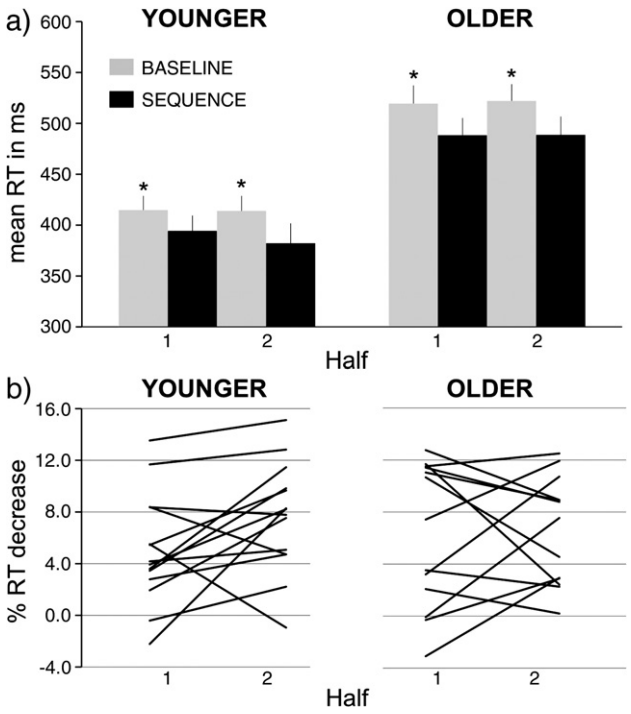

Fig. 2. (a) Mean RT for BASELINE and SEQUENCE blocks by half and age group. *$p<.05$. (b) Individual differences in % RT decrease for SEQUENCE blocks compared to BASELINE blocks by half.

The size of the SL effects and the large between-person variability observed are in excellent agreement with previous research (e.g., Rauch et al., 1997a; Peigneux et al., 2000; Reiss et al., 2005).

Overall, the results from the post-test questionnaire indicate that learning was largely implicit ($M_{young}=1.93$, $SD=1.64$; $M_{old}=2.69$, $SD=1.84$) and there was no significant difference between groups ($t(25)<1$). Nine participants (3 younger and 6 older) had scores higher than 3, indicating that they believed that the trials occurred in non-random order, and that certain sequences were repeated occasionally. However, when asked to reproduce the repeating sequence, all participants failed to reproduce more than 4 out of 12 items (Rauch et al., 1997a; Seger, 1997), indicating poor awareness of the repeated sequences. Substantiating this point, there was no significant relationship between awareness score and any measure of SL (*SL half 1*, *SL half 2*, *SL change*) in either age group (*ps* >.20).

Imaging data

In order to investigate BOLD–behavior relationships across time, we compared SEQUENCE (> BASELINE) contrasts between halves with *SL change* as a regressor (and awareness scores as a covariate). Results therefore reflect areas where increases (Half 2 > Half 1) or decreases (Half 2 < Half 1) in BOLD signal are related to SL improvement over time.

Younger adults

SL change-related BOLD signal increases in younger adults were observed bilaterally in the striatum as well as in the thalamus, the insular cortex, the left parietal cortex (laterally in angular and supramarginal gyri, and medially in precuneus), the cerebellum, and the right brain stem (Table 2).

SL change-related decreases in BOLD signal across halves were observed in the anterior and posterior temporal lobe, posterior MTL as well as in superior and anterior portions of the fontal lobe including the anterior cingulate, the medial prefrontal cortex (PFC), and the orbitofrontal cortex (Table 3).

This pattern shows that improvement of SL across time was accompanied by an increase in striatal activation and a decrease in MTL activation. ROI analyses were performed to elucidate this pattern (Fig. 3). Scatterplots illustrate the correlations between BOLD signal change and *SL change*. A BOLD signal decrease from half 1 to half 2 in right MTL was related to greater *SL change* ($r=-.50$, 1 outlier removed), although this correlation just failed to attain conventional significance ($p=.08$). For the striatum, there was a significant correlation between signal change increase and *SL change* ($r=.78$, $p<.01$, 1 outlier removed). The correlation between signal change in striatum and MTL was non-significant ($r=-.12$; $p>.50$). However, after removal of one case there was a trend toward a negative correlation ($r=-.41$, $p=.18$). Bar graphs in Fig. 3 indicate that *SL change*-related MTL decreases reflect positive BOLD signal change in the first half and negative BOLD signal change in the second half, whereas caudate increases reflect a negative signal change in half 1 and a positive signal change in half 2, consistent with the notion of competing brain systems.

The observation that striatal activation increases and MTL activation decreases are beneficial to performance was substantiated by activations for SEQUENCE blocks (> BASELINE) in Half 1 only with *SL half 1* as a regressor (again with awareness as a covariate). In the first half, better SL was positively related to striatal activation (left caudate, $x=-10$, $y=12$, $z=10$; $Z=1.81$, <25 voxels) and negatively related to right MTL activation (right parahippocampal gyrus, $x=28$, $y=-6$, $z=-26$; $Z=-2.42$, Fig. 4). This analysis shows that SL-related effects generalize to those participants who show very good SL already in the first half, but then exhibit little additional learning gains across halves.

Table 2
Performance-related activation increases from half 1 to half 2.

Brain area	Young				Young > Old				Old				Old > Young			
	x	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*
R Caudate	14	4	10	1.8					12	4	20	2.2				
L	−14	−2	20	2.8					−12	24	0	2.3				
R Putamen	24	−2	−6	2.7	26	−2	−6	2.2								
L	−28	−16	−4	2.1												
R Thalamus	14	−14	4	2.6	0	−22	12	2.5	22	−28	−2	2.2				
L	−4	−6	8	3.0												
R Lat. Par	42	−44	28	3.6	44	−46	26	2.5	32	−74	42	2.4				
L	−34	−38	30	2.4	−36	−38	28	2.4	−46	−56	40	2.0				
R Med. Par	12	−74	48	3.6	4	−76	52	2.1								
L	−2	−26	50	2.8	−4	−28	50	2.1								
R Insula	36	16	16	2.9	32	−8	22	3.0*								
L	−36	14	−2	2.2	−36	−12	10	2.1								
R ACC	2	−8	36	3.2	0	−12	34	2.4	12	34	4	2.0	12	32	6	2.2
L									−6	28	16	2.0	−20	36	2	1.9
R Lat. PFC	48	34	0	2.1					46	48	−8	2.5	38	60	2	2.2
L									−44	24	26	2.7	−42	48	−16	2.4*
R Sup. Fr									6	40	36	2.8	8	44	32	2.4
L																
R Inf. Fr									50	14	10	2.7				
R Orbito Fr	36	22	−6	2.5												
L									−24	42	−18	1.9	−18	14	−20	2.1
R Motor C	44	−16	34	3.0	4	−18	64	2.0								
L	−38	−6	40	2.5	−4	−28	50	2.1	−24	−4	44	2.4	−18	−2	62	1.8
R Ant. Temp	34	16	−28	2.4												
L									−42	0	−40	2.1	−46	0	40	2.5*
R Sup. Temp													42	4	−18	2.2*
L	−56	−12	0	2.0												
R MTL									42	−14	−24	2.1	44	−24	−20	1.8*†
L									−38	4	−22	2.0				
R Brain stem	10	−20	−10	3.0	0	−20	−10	2.2*	12	−20	−22	2.3	10	−16	−24	1.9
L									−14	−28	−30	2.1	−10	−18	−24	2.6*
R Occipital lobe	10	−78	10	2.9	20	−68	0	2.3	58	−58	−4	1.9				
L	−46	−70	2	2.5					−46	−70	−12	2.0				
Cerebellum	8	−70	−18	2.9	0	−62	−32	1.8	26	−70	−38	2.3				
	−30	−60	−54	2.1	−18	−62	−22	2.2								

All age group comparisons are driven by significant activations ($Z>1.6$) of the group in the preceding column unless indicated otherwise. Coordinates *x*, *y*, and *z* are reported in MNI space. Abbreviations: R = right, L = left, Sup = superior, Inf = inferior, Ant = anterior, Pos = posterior, Med = medial, Lat = lateral, Par = parietal lobe, Fr = frontal lobe, Temp = temporal lobe, ACC = anterior cingulate cortex, PFC = prefrontal cortex, MTL = medial temporal lobe.

* The corresponding Z statistic reflects both increases in one group and decreases in the other.

† Cluster extent <25 voxels.

Table 3
Performance-related activation decreases from half 1 to half 2.

Brain area	Young				Young > Old				Old				Old > Young			
	x	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*
L Lat. Par									−36	−32	28	2.0				
									−62	−52	20	2.2				
R Insula									50	−16	8	2.0	32	−8	22	3.1*
R ACC	−12	44	6	2.3												
L Lat. PFC					−42	48	−16	2.5*								
R Med. PFC	20	56	16	2.7												
L	−6	68	−12	2.4												
R Sup. Fr	12	32	52	2.9												
R Orbito Fr	20	24	−20	2.1	18	24	−18	2.0								
L	−42	32	−12	2.4												
R Ant. Temp	44	−2	−44	2.8	42	4	−18	2.2*								
L	−46	−6	−44	2.7	−46	0	−40	2.5*								
L Pos. Temp	−52	−20	−14	2.5	−58	−48	−12	2.4	−60	−10	−20	2.1				
L Sup. Temp													−48	−30	6	2.3*
R MTL	34	−28	−16	2.1	44	−24	−20	1.8*†								
L	−30	−38	−18	2.3	−30	−38	−20	1.8	−40	−28	−10	2.1				
R Brain stem									0	−20	−12	2.1	0	−20	−10	2.2*

All age group comparisons are driven by significant activations ($Z>1.6$) of the group in the preceding column unless indicated otherwise. Coordinates *x*, *y*, and *z* are reported in MNI space. Abbreviations: R = right, L = left, Sup = superior, Ant = anterior, Pos = posterior, Med = medial, Lat = lateral, Par = parietal lobe, Fr = frontal lobe, Temp = temporal lobe, ACC = anterior cingulate cortex, PFC = prefrontal cortex, MTL = medial temporal lobe.

* *The corresponding Z statistic reflects both increases in one group and decreases in the other.

† Cluster extent <25 voxels.

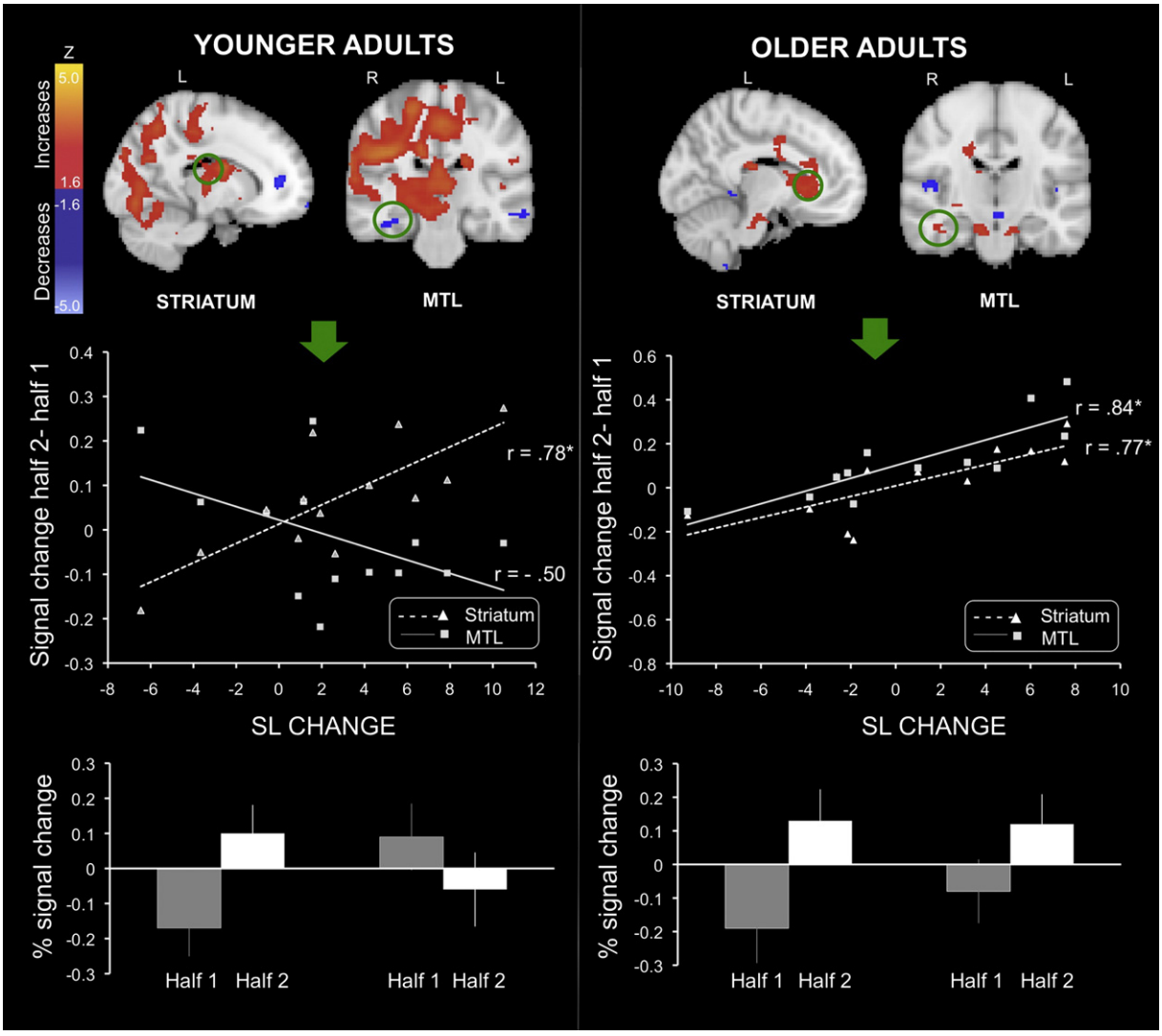

Fig. 3. Sequence learning *(SL) change*-related activation differences over time by age group. Activations reflect voxels where an improvement in SL from half 1 to half 2 (*SL change*) is correlated with BOLD signal changes from half 1 to half 2 (Half 2 [SEQUENCE>BASELINE] > Half 1 [SEQUENCE>BASELINE]) in striatum and MTL. These correlations are illustrated in scatterplots by extracting mean percent BOLD signal change for each subject from a 10 mm spheric ROI around peak voxels (younger adults/striatum: $x=-14$, $y=-2$, $z=20$; younger adults/MTL: $x=34$, $y=-28$, $z=-16$; older adults/striatum: $x=-12$, $y=24$, $z=0$; older adults/MTL: $x=42$, $y=-14$, $z=-24$); $^*p<.05$. Bar graphs show mean signal change across voxels in the same ROIs by half (error bars: ± 1 SD). Anatomical reference is MNI152 space and images are displayed in radiological orientation.

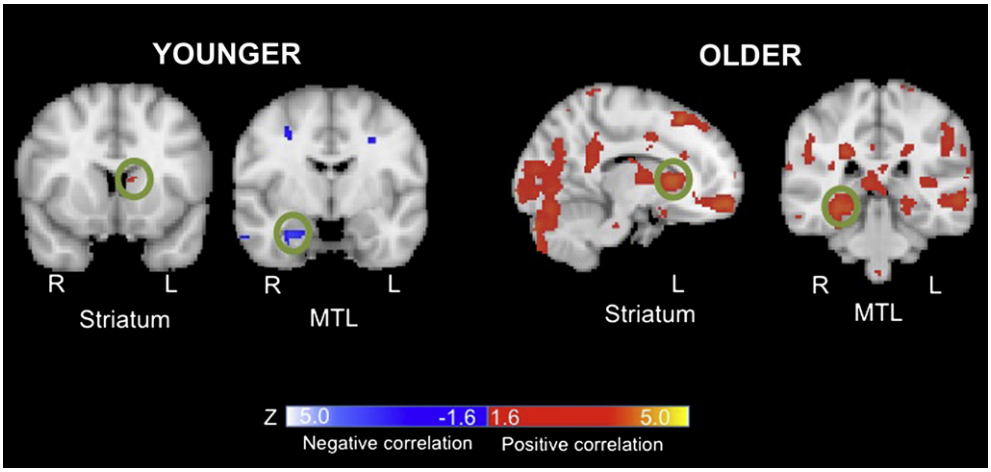

Fig. 4. Sequence learning (SL)-related activations for half 1 of the experimental run. Activations reflect voxels where *SL half 1* is correlated with BOLD signal for SEQUENCE (> BASELINE) blocks. Anatomical reference is MNI152 space and images are displayed in radiological orientation.

Taken together, individuals who performed well already in the first half and then showed little additional SL change across time relied more on the striatum, and less on the MTL in both halves. Conversely, for those individuals who started off with low SL scores in the first half but then improved greatly in the second half, improvement of learning was related to increasing striatal activation and decreasing MTL activation from half 1 to half 2.

Older adults

As with the younger adults, we found *SL change*-related increases from half 1 to half 2 in a subcortical–cortical network comprising the striatum and thalamus as well as bilateral parietal and inferior middle frontal regions (Table 2), and learning-related activation decreases in left MTL (Table 3). However, older adults showed additional activation increases in right MTL, middle temporal gyrus and left inferior temporal gyrus, as well as in lateral and medial PFC, superior frontal gyrus, and orbitofrontal cortex (Table 2). Thus, in older adults SL improvement across time was related to increases in both the striatum and the right MTL (Fig. 3). ROI analyses were used to illustrate this pattern. Scatterplots in Fig. 3 show a significant positive correlation between *SL change* and signal increase across halves in MTL and striatum for older adults ($r_{MTL}=.84$, $p<.01$, 1 outlier removed, $r_{striatum}=.77$, $p<.01$). There was also a significant positive relationship between signal change increases in MTL and striatum ($r=.81$, $p<.01$, 1 outlier removed). Consistent with the hypothesis of "cooperative" brain systems in older adults, bar graphs show a similar pattern for activation increases in striatum and MTL: Negative signal change in the first half, and positive signal change in the second half.

Relatedly, for learning-related activations in the first half with *SL half 1* as a regressor, SL was related to striatal activation (left caudate, $x=-12$, $y=18$, $z=6$; $Z=2.68$) and the MTL (right hippocampus, $x=28$, $y=-34$, $z=-8$; $Z=2.59$, Fig. 4). In summary, successful SL in older adults was related to recruitment of both the striatum and the MTL, regardless of whether SL occurred already early on or developed over the two halves.

Age-group comparisons

SL change-dependent comparisons of halves were contrasted between age groups to delineate voxels where the correlation between BOLD signal change between halves and *SL change* was significantly greater in one age group compared to the other.

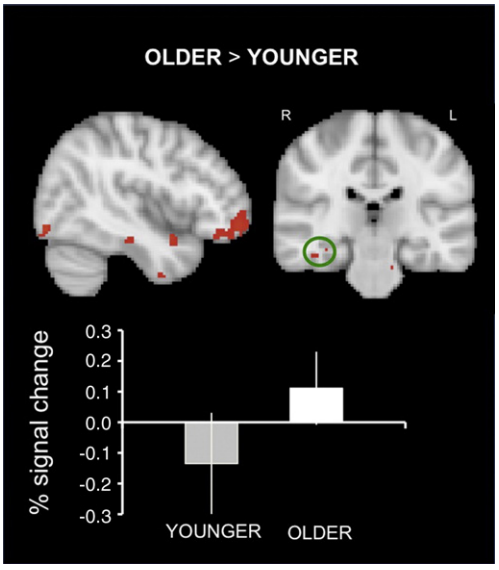

Fig. 5. Direct age-group comparisons in sequence learning (*SL*) *change*-related MTL activation. Bar graphs represent mean percent BOLD signal change in a 10 mm spheric ROI around the peak voxel ($x=44$, $y=-14$, $z=-24$; error bars $=\pm 1$ SD). Anatomical reference is MNI152 space and images are displayed in radiological orientation.

Younger adults showed significantly larger *SL change*-related increases in the striatum, as well as in the thalamus, the parietal, insular and occipital cortex, and the cerebellum. In left angular/supramarginal gyrus and right insular cortex, significant age differences were due to both significant activations in younger adults, and significant deactivations in older adults. *SL change*-related decreases were significantly greater in younger adults in superior frontal and orbitofrontal areas.

Older adults showed significantly greater *SL change*-related increases than younger adults in a number of frontal areas (lateral and medial PFC, superior frontal, and orbitofrontal). Most importantly, significant activation differences in the temporal lobe (right hippocampal complex and middle temporal gyrus) were due to both increases in older adults and decreases in younger adults (Fig. 5, Table 2).

These direct age group comparisons support the age-differential involvement of the MTL in SL: An improvement in SL was accompanied by striatal increases and MTL decreases in younger adults, and by both striatal and MTL increases in older adults.

Discussion

The present study sought to delineate how individual differences in performance and age affect striatal and MTL activations during SL in the SRTT.

Performance-related BOLD changes

Brain activation patterns in the SRTT are sensitive to individual differences in performance. Specifically, studies with younger adults have found that striatal activation is positively related to learning success (Rauch et al., 1997a; Peigneux et al., 2000; Reiss et al., 2005; Garraux et al., 2007). Moreover, when groups of slow and fast learners were compared, only fast learners showed deactivation of the MTL across time (Albouy et al., 2008). Fast versus slow learning in the Albouy et al. study can be compared with high versus low *SL change* scores in the present study. In both studies, an improvement in SL was defined as a decrease in latencies for the sequential pattern across time. As in the Albouy et al. study, our ROI analyses clearly illustrate a positive relationship of learning improvement across time to activation increases in the caudate, as well as to activation decreases in the MTL among younger adults. This implies that both striatal activation increases and concomitant decreases in MTL signify successful SL in early adulthood. Moreover, the fact that participants in the present study received considerably less exposure to the sequence compared to those in Albouy et al. (24 versus 90 repetitions) suggests that MTL and striatal activation dynamics occur already early on in learning, after only a few repetitions of the sequence.

In addition to a positive linear relationship between striatal increases and performance, activation increases in the right MTL across time were related to successful SL in older adults. Because the MTL activation increases in older adults were performance-related, they may be interpreted as compensatory. Thus, whereas disengagement of the MTL across time was beneficial to performance in younger adults, older adults needed to engage both the striatal and the MTL systems in order for successful SL to occur. Importantly, we found similar age-differential patterns regarding SL during the first half: For younger adults, proficient SL in the first half was positively associated with striatal activation, but negatively related to MTL activation; for older adults, good SL in the first half was related to activation in both striatum and MTL. This pattern demonstrates that the differential role of the MTL for SL in early and late adulthood generalizes across different time windows. Moreover, in light of the findings of a negative correlation between *SL half 1* and *SL change* in both age groups, an improvement in learning across halves in younger adults

was related to early MTL activation that decreased across time. By contrast, for older adults, an improvement of learning was related to increasing MTL activation throughout the experiment.

Previous research has not found evidence for compensatory brain activation in older adults during SL that may explain preserved performance despite striatal losses in aging (Daselaar et al., 2003; Aizenstein et al., 2006). Our finding of age-dependent differences in the MTL in relation to performance suggests that the absence of neural compensation in past studies may be related to the fact that individual differences within age groups were not taken into account.

Although this study focused on the striatum and the MTL, we also found performance-dependent BOLD signals outside these structures. Younger adults showed SL-related BOLD increases in a striatal-cortical network, which has previously been associated with SL, including parietal and inferior frontal areas, and cerebellum (e.g., Rauch et al., 1997a; Daselaar et al., 2003; Schendan et al., 2003; Fletcher et al., 2005; Albouy et al., 2008). Moreover, as with the right MTL, activation in the prefrontal areas decreased over time in the young. For older adults, SRTT performance was related to increases in similar striatal and cortical areas, but activation was less widespread. Instead, the older adults showed increasing activation of the bilateral PFC across time, a pattern similar to that observed for the right MTL.

SL and adult age

The current findings of slower motor responses, albeit preserved implicit SL, in old age are in good agreement with the bulk of age-comparative work on the SRTT (e.g., Cherry and Stadler, 1995; Howard and Howard, 1997; Howard and Howard, 2001; Daselaar et al., 2003; Aizenstein et al., 2006), as well as with aging research on other implicit learning tasks such as weather prediction and artificial grammar learning (Fera et al., 2005; Midford and Kirsner, 2005; Price, 2005), which shows that age differences in implicit learning are small in magnitude when contrasted against the pattern for explicit cognition. Our data suggest that one reason why SL is relatively spared in old age, despite alterations in key brain structures such as the striatum (e.g., Raz et al., 2003, 2005; Bäckman et al., 2006, in press), is that good learning is supported by other brain regions, notably the MTL. The present results are in line with research on patients with marked striatal impairments (e.g., Parkinson's patients) indicating that, for comparable SL levels, patients showed reduced striatal activation and increased MTL activation (Rauch et al., 1997b, 2007; Dagher et al., 2001; Moody et al., 2004; Beauchamp et al., 2008). Thus, our findings on normal older adults and the patient work converge in suggesting that MTL recruitment during SL is inversely related to striatal integrity, an instantiation of brain plasticity.

Interactive brain systems

In relation to SL in the SRTT, some researchers have suggested that both striatal increases and MTL decreases distinctively contribute to SL (Curran, 1997a; Schendan et al., 2003; Albouy et al., 2008). On this view, the MTL supports rapid initial acquisition of higher-order associations across several stimuli and, as the novelty of these associations decreases across time, so does MTL activation (Schendan et al., 2003; Doeller et al., 2005; Fletcher et al., 2005). At the same time, the striatum is involved in translating these associations into stimulus-response links across multiple experiences of the repeating sequences. This is evidenced in the relation between decreasing RTs and increasing striatal activation across time. The notion that SL might be partly driven by early MTL-dependent associations is consistent with our data for younger adults, showing that increasing SL from half 1 to half 2 reflected MTL activation in the first half and MTL deactivation in the second half.

However, it is difficult to reconcile the notion that the MTL is critically involved in SL in younger adults with the pattern observed in older adults, who showed parallel learning-related activation increases in both the MTL and the striatum. To the extent that MTL activation decreases are related to successful formation of higher-order associations in complex sequences (e.g., Curran, 1997a; Schendan et al., 2003; Doeller et al., 2005; Fletcher et al., 2005; Albouy et al., 2008), we would have expected faster SL to be associated with MTL decreases across the course of learning also in older adults. One explanation for the differential involvement of the MTL between age groups may be that different processes underlie SL in younger and older adults. Support for the notion of separate processes comes from studies showing little evidence for a relationship between measures of WM and SL in younger adults (e.g., Hayes and Broadbent, 1988; Mathews et al., 1989; Cleeremans and McClelland, 1991; Unsworth and Engle, 2005), although WM capacity and general cognitive ability are related to degree of SL in older adults (Cherry and Stadler, 1995). An alternative interpretation of the current data is that the learning-related disengagement of the MTL in younger adults is not directly implicated in SL, but rather a byproduct of learning-related striatal recruitment (Frank et al., 2006; Brown and Robertson, 2007). In other words, with increasing striatal involvement, the MTL system becomes deactivated or "functionally suppressed," which may be beneficial to learning in younger adults. In older adults, both systems seem to be needed to achieve successful SL. Support for this interpretation comes from studies showing that hampering MTL functions in younger adults by a demanding dual task (Foerde et al., 2006) or neuropharmacological blockage (Frank et al., 2006) during SL tasks had no effect on performance, but increased the reliance on the striatum. Further, Brown and Robertson (2007) showed that an MTL-taxing task in between two SRTT sessions can even lead to performance improvements in the SRTT, supporting the claim that MTL disengagement can be beneficial to SL in early adulthood.

It has been suggested that frontal areas play a role in mediating striatal–MTL interactions (e.g., Poldrack and Rodriguez, 2004; Seger and Cincotta, 2006). Accordingly, both the striatal and the MTL system acquire information about repeating patterns across trials in parallel. When information from the two brain systems is compatible (Atallah et al., 2008), the frontal cortex may preferentially gate learning to the striatal system and disengage the MTL system. In other words, the frontal cortex might be involved in promoting the most efficient processing strategy, which in turn results in a negative relationship between the two systems. On this view, the role of the frontal cortex in selecting appropriate processing strategies is more evident early on in learning. This point relates to our findings that those younger adults who showed successful SL across the course of the experimental run exhibited greater frontal activation early on. In older adults, when the striatal system alone is insufficient to promote successful SL, the frontal cortex might engage both the striatal and MTL systems throughout the experimental run, leading to a positive relation between frontal activation and SL increases.

Traditionally, the striatal and MTL brain systems are dissociated by awareness, where the striatal system is thought to support implicit acquisition of information, whereas the MTL system, along with prefrontal areas, is thought to support explicit cognition (e.g., Knowlton et al., 1996; Squire and Zola, 1996). According to this view, the increasing MTL (and frontal) activation we observe in older, but not younger, adults might signify greater explicit learning of the sequence in the older adults. However, our data, along with those of many others (e.g., Cohen and Eichenbaum, 1993; Curran, 1997a; Cohen et al., 1999; Poldrack et al., 2001; Rose et al., 2002; Schendan et al., 2003; Seger and Cincotta, 2006), indicate that awareness is not a critical determinant of MTL involvement during SL. Our measure of awareness did not differ between age groups and was unrelated to all SL measures. Moreover, awareness scores were entered as a covariate in all higher-level analyses of the fMRI data.

We cannot completely rule out the possibility that there were age-related differences in awareness that our test did not capture, and that contributed to the observed activation patterns. However, in SRTT studies that have used more extensive tests of sequence awareness, including prediction or recognition tasks, age differences are either

non-existent (e.g., Curran, 1997b; Negash et al., 2003; Howard et al., 2008) or show greater awareness in younger than in older adults (e.g., Dennis et al., 2006; Gaillard et al., 2009). Further, to the extent that the MTL recruitment in the older group reflects increased awareness of the repeating sequence, we would have expected MTL increases among older adults to be negatively related to SL, as explicit learning in the SRTT has been shown to affect older adults' performance in a negative manner (Howard and Howard, 2001; Midford and Kirsner, 2005). As noted, the opposite pattern was found. Thus, several lines of evidence make it highly unlikely that the age-related differences in MTL activation observed reflect greater awareness of the repeated sequences among older adults.

Conclusions

We focused on striatal and MTL activation changes across time during SL in younger and older adults. Critically, we related neural activation to individual learning rates and showed that successful SL was related to striatal increases and MTL decreases in activation across time in younger adults. By contrast, in older adults better learning across time was associated with activation increases in both striatal and MTL regions. Because (a) there were no performance decrements in older compared to younger adults, (b) MTL engagement was beneficial to SL in older adults only, and (c) striatal alterations in aging are well documented, we interpret the MTL recruitment in older adults to reflect compensatory brain activation during SL. In this way, we have offered a novel explanation for the common observation of relatively well spared SL in aging, despite marked alterations in task-relevant striatal regions. Moreover, this study has extended work in patients with pronounced striatal impairments, by showing that increased MTL recruitment in the presence of striatal deficiencies is positively related to performance.

It has been proposed that MTL deactivation during SL is related to the formation of higher-order associations of complex sequences (e.g., Schendan et al., 2003; Doeller et al., 2005). On this view, the SL-related increases in the MTL among older adults suggest that different processes underlie SL in older compared to younger adults. We have suggested an alternative interpretation by which the MTL disengagement in the young is driven by increased striatal recruitment. In older adults, however, when the striatum is impaired, both systems need to be engaged in order to promote successful SL. Future research is needed to disentangle the contribution of the MTL to SL in younger and older adults. For example, according to the notion that the MTL is critically important to higher-order associations during SL (Schendan et al., 2003; Fletcher et al., 2005) an MTL-taxing dual task should cause impaired SL in younger adults. However, in line with the idea of MTL disengagement being beneficial to SL in younger, but not older, adults, a concurrent MTL-taxing task should have no or even beneficial effects in younger adults, but impair SL in older adults.

Acknowledgments

This work was supported by grants from the Swedish Research Council and Swedish Brain Power and by an Alexander von Humboldt Research Award to L.B., and by grants from the Swedish Research Council and Konung Gustaf V:s and Drottning Victorias Stifelse to H.F. A.R. was supported by a studentship from the Leverhulme Trust.

We are grateful to Joachim Gavazzeni for help with data collection.

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