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Research Report
Evidence for the importance of basal ganglia output nuclei in semantic event sequencing: An fMRI study
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ABSTRACT

Semantic event sequencing is the ability to plan ahead and order meaningful events chronologically. To investigate the neural systems supporting this ability, an fMRI picture sequencing task was developed. Participants sequenced a series of four pictures presented in random order based on the temporal relationship among them. A control object discrimination task was designed to be comparable to the sequencing task regarding semantic, visuospatial, and motor processing requirements but without sequencing demands. fMRI revealed significant activation in the dorsolateral prefrontal cortex and globus pallidus internal part in the picture sequencing task compared with the control task. The findings suggest that circuits involving the frontal lobe and basal ganglia output nuclei are important for picture sequencing and more generally for the sequential ordering of events. This is consistent with the idea that the basal ganglia output nuclei are critical not only for motor but also for high-level cognitive function, including behaviors involving meaningful information. We suggest that the interaction between the frontal lobes and basal ganglia output nuclei in semantic event sequencing can be generalized to include the sequential ordering of behaviors in which the selective updating of neural representations is the key computation.

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1. Introduction

Meaningful events unfold over time. In describing our personal memories, time is critical. As [Tulving \(1984\)](#) wrote, “The organization of knowledge in the episodic system is temporal. One event precedes, co-occurs, or succeeds another in time.” The temporal relationship between successive events can be learned, abstracted and generalized across

repeated experiences and stored as sequential, high-level knowledge structures ([Schank, 1982, 1999](#)), previously described as scripts ([Schank and Abelson, 1977](#)). Therefore, our general knowledge of concepts and facts, called semantic memory ([Tulving, 1972](#)), can also include a unidirectional temporal component. We know a tadpole will develop into a frog, but a frog never develops into a tadpole. While many functional neuroimaging studies have focused on the

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representation, organization and retrieval of semantic knowledge (for a review see [Thompson-Schill, 2003](#)), active sequencing based on semantic knowledge has not received much attention in neuroimaging research. This study aimed to define the neural systems supporting the ability to organize visual events into a conceptually coherent sequence using semantic memory for the events. We refer to this cognitive ability as semantic event sequencing.

This investigation focused on a specific role for frontal-basal ganglia circuits in semantic event sequencing. The frontal lobes have been implicated in maintenance and manipulation in working memory ([D'Esposito et al., 1998, 1999, 2000](#); [Owen et al., 1998](#); [Petrides et al., 2002](#); [Postle et al., 1999](#); [Stern et al., 2000](#)). A manipulation process varies with the type of stimuli in working memory or with the task goals. For instance, manipulation in working memory can include the re-ordering or reorganization of material held over a delay, whereas in mental rotation tasks, the manipulation involves transformation of visuospatial information. A specific type of manipulation, in this case re-ordering that involves the selective updating of neural representations for response selection from among competing alternatives, is required for semantic event sequencing. In our view, this process is dependent on the basal ganglia, an idea consistent with a computational model suggesting that “the frontal cortex exhibits robust active maintenance, whereas the basal ganglia contribute a selective, dynamic gating function that enables frontal memory representations to be rapidly updated in a task-relevant manner” ([Frank et al., 2001](#)). In this type of manipulation, “the basal ganglia may...[function] by promoting the building up of performance units made up of multiple parts that can be implemented in a particular temporal order. One function of the striatum may be to chunk performance sequences. It may be these chunked representations that are selected and scaled by the output circuits of the basal ganglia” ([Graybiel, 1998](#)).

Neuropsychological research indicates that frontal lobe and basal ganglia structures are necessary for semantic event sequencing. Patients with right frontal damage tend to use a passive approach to the Picture Arrangement subtest of the Wechsler Adult Intelligence Scale ([Wechsler, 1997](#)), moving very few cards from the original layout ([Kaplan et al., 1991](#)). Further, patients with primarily right-sided or left-sided frontotemporal dementia are impaired on Picture Arrangement or word sequencing tasks, respectively ([Boone et al., 1999](#)). Most important for the present work, patients with Parkinson's disease, a neurodegenerative disease that impairs the functional integrity of the frontal-basal ganglia circuits, are specifically impaired on Picture Arrangement ([Beatty and Monson, 1990](#); [Cooper et al., 1991](#); [Sullivan et al., 1989](#)) and on script ordering tasks ([Zalla et al., 1998](#)).

Using neuroimaging, sequencing has been studied using events with little or no semantic content. Both the acquisition and retention of learned and overlearned perceptuomotor sequences of varying complexity have been investigated. Activation has consistently been found in frontostriatal circuits ([Berns et al., 1997](#); [Doyon et al., 2003](#); [Hazeltine et al., 1997](#); [Jenkins et al., 1994](#); [Jueptner et](#)

[al., 1997a,b](#); [Peigneux et al., 2000](#); [Rauch et al., 1997](#); [Schendan et al., 2003](#); [Toni et al., 2002](#); [Willingham et al., 2002](#)).

Frontostriatal circuits have also been implicated in sequencing tasks requiring higher order cognitive processing. In particular, neuroimaging studies of executive function using tasks that require the acquisition and performance of cognitive action sequences (e.g., the Tower of London task) have demonstrated activation in frontostriatal circuits including the dorsolateral prefrontal cortex (DLPFC) and caudate ([Dagher et al., 1999](#); [Rowe et al., 2001](#)). In addition, neuroimaging during a variant of the n-back working memory task with predictable and unpredictable sequences reported activation in anterior medial PFC-ventral striatum and in lateral polar PFC-dorsal striatum circuits, respectively ([Koechlin et al., 2000](#)).

Such prior studies of executive function focused more on planning and working memory. The sequences were abstract, arbitrary and acquired during the experimental session, and the stimuli were highly familiar alphanumeric characters or simple geometric shapes. By contrast, we were interested in event sequencing when both sequences and stimuli are meaningful. Of note, neuroimaging studies of temporal sequence processing using script order tasks have found activation in bilateral prefrontal cortex (Brodmann area (BA) 6, 8) ([Crozier et al., 1999](#); [Knutson et al., 2004](#)) but not in basal ganglia. These script order tasks have highlighted the role of the frontal lobes (BA 6, 8) in the retrieval and maintenance of sequence representations.

We propose that, in the present semantic event sequencing task, not only the frontal lobe (i.e., dorsolateral prefrontal cortex BA 9/46 and 46) but also the basal ganglia should be recruited because of additional requirements for generating an active sequencing output.

To examine semantic event sequencing, a picture sequencing task was developed based on the “Picture Arrangement” subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III) ([Wechsler, 1997](#)). The picture sets used in this study describe simple, familiar meaningful events ([Beatty and Monson, 1990](#)) that are presented simultaneously in a scrambled order. The task requires subjects to study the pictures, determine the correct temporal relationship between each event, and, finally, re-order the pictures ([Groth-Marnat, 1999](#); [Lezak, 1995](#)). An object discrimination control task was devised to involve the same visuospatial, semantic, and motor components as the picture sequencing task. Specifically, subjects evaluated four objects to find the odd item. A saccadic eye movement task was used to control for the oculomotor demands in both experimental and control tasks. We predicted that contrasts between the picture sequencing and control tasks would reveal activation in frontal-basal ganglia circuits.

2. Results

2.1. Performance

During scanning, behavioral responses during the “GO!” response period were recorded. The data reflect performance

of 12 subjects on 60 picture sequencing (PS) and 60 object discrimination control (CON) trials. The median RTs on the PS task was 512 ms (363–753 ms, SE 33), and 507 ms (362–720 ms, SE 34) on the CON task. There was an average of 1.25 errors in the PS task (0–3, SE 0.37) and 0.6 in the CON task (0–3, SE 0.26). The responses were not recorded in an average of 1.7 trials (0–4, SE 0.46) in the PS task, and in 1.3 trials (0–4, SE 0.41) in the CON task, because the subjects either responded too early or too late or did not respond at all. The paired-sample *t* test revealed no significant differences between the median RTs ($P = 0.66$), accuracy ($P = 0.15$) and number of omissions ($P = 0.61$) between the two tasks.

2.2. fMRI

Results of group averaged BOLD data from 12 subjects are reported at $P < 0.05$ level, corrected for multiple voxel-wise comparisons using the False Discovery Rate (FDR) procedure.

2.2.1. Task versus baseline (fixation)

The general activation pattern observed in the picture sequencing (PS) versus baseline and the object discrimination control (CON) versus baseline contrasts was similar. Both contrasts revealed a distributed network of cortical and subcortical regions including occipital, medial and lateral temporal, parietal and frontal cortices, posterior thalamic nuclei (pulvinar and mediodorsal nucleus), striatum and the internal part of the globus pallidus (GPi). Critically, the CON versus baseline contrast showed activation in the right dorsolateral prefrontal cortex (DLPFC) and right GPi, whereas these structures were bilaterally involved in the PS versus baseline contrast (see, Tables 1 and 2 for coordinates, and Figs. 1 and 3 in Supplementary material).

2.2.2. Picture sequencing (PS) task versus object discrimination control (CON) task

The PS and CON tasks were directly compared in order to assess the brain regions important for semantic event sequencing. Most of the areas that were active in the PS versus baseline contrast survived in the PS versus CON contrast, and we observed activation in additional regions. An area located in the lateral posterior temporo-occipital gyri (Brodmann area (BA) 21/37) showed the peak activation of this contrast on the right side. The same area was also active on the left. The GPi demonstrated bilateral activation. In addition to the right DLPFC (Area 9/46 and 46), the left DLPFC (Area 9/46) (Petrides and Pandya, 1999) demonstrated significant activation. BA 8, which is anterior to the frontal eye fields (FEFs), showed bilateral activation (Table 1, Figs. 1a–c).

We evaluated evidence of activity in the left DLPFC and left GPi during the control task by applying small volume correction to the object discrimination control (CON) versus fixation contrast using a sphere of 28 mm centered at the left DLPFC maximal voxel and a sphere of 8 mm centered at the left GPi maximal voxel (Worsley et al., 1996). In the left DLPFC, the corrected region of interest was not significant, and, when no voxel-wise correction was applied, only a few voxels were significant. We are thus confident that there was little or no activation in the left DLPFC during the CON task but clearly

Table 1 – Picture sequencing task versus object discrimination control task contrast

Region	MNI coordinates					
	Side	Brodmann areas	x	y	z	Z score
<i>Occipitotemporal</i>						
Lateral occipital sulcus	R	BA 18/19	30	–90	2	4.38*
	L		–30	–94	2	4.02*
Lateral FG/IT	R	BA 20/37	54	–54	–24	5.53**
	L	BA 20/37	–54	–58	–16	4.58**
Hippocampus/PHG/CoS	L		–22	–34	–6	3.56*
<i>Parietal</i>						
Supramarginal gyrus	R	BA 40	46	–46	44	4.67**
	L		–30	–56	46	4.48**
Inferior parietal lobule	R	BA 39	40	–78	30	5.00**
	L		–28	–74	24	4.21*
Superior parietal gyrus	R	BA 7	–22	–74	52	4.39*
	L		28	–78	44	4.25*
<i>Frontal</i>						
Premotor cortex	R	BA 6	52	8	38	4.26*
	L		–48	4	38	3.20*
Superior frontal gyrus	R	BA 8	28	6	58	4.28*
	L	BA 6/8	–32	0	64	3.94*
Dorsolateral PFC	R	BA 46, 9/46 ^a	50	44	16	4.03*
	L	BA 9/46 ^a	–46	32	30	4.79**
<i>Subcortical nuclei</i>						
Globus pallidus	R		20	–6	–2	3.87*
	L		–14	–2	–6	4.51**

All statistical parametric maps were corrected across the whole brain for multiple voxel-wise comparisons using the false discovery rate (FDR) procedure ($P < 0.05$). Regions that were >4 mm apart and consisted of at least 5 contiguous voxels are shown. R: right; L: left; PFC: prefrontal cortex; FG: fusiform gyrus; IT: inferior temporal gyrus; PHG: parahippocampal gyrus; CoS: collateral sulcus.

^a Dorsolateral PFC areas as described in Petrides and Pandya (1999).

* $P < 0.05$.

** $P \leq 0.005$.

significant activation in the picture sequencing (PS) task. The analysis in the left GPi revealed no activation even when no voxel-wise correction was applied, suggesting that the left GPi activation was specific to the PS task.

2.2.3. Object discrimination control task versus picture sequencing task

This contrast corresponds to the deactivations in the picture sequencing task. At FDR-corrected $P < 0.05$ level, there was no activation in this comparison. At uncorrected $P < 0.05$ level, medial PFC, including orbitofrontal, frontopolar and superior frontal gyri, medial parietal cortex (precuneus), posterior cingulate cortex, retrosplenial cortex, superior, middle and inferior temporal gyri and precentral gyrus showed bilateral activation.

2.2.4. Saccadic eye movement task (SEM) versus fixation

SEM task revealed activation in the occipital and parietal cortices and in the FEFs and supplementary eye fields

Picture Sequencing vs. Object Discrimination

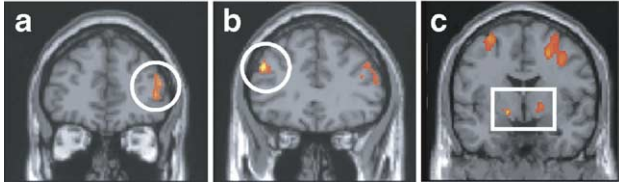


Fig. 1 – Picture Sequencing versus Object Discrimination Control contrast. Group averaged activation patterns ($n = 12$) are displayed on the coronal slices of the canonical MNI305 brain in SPM2. (a) Right dorsolateral prefrontal cortex (DLPFC), (b) Left DLPFC and (c) bilateral globus pallidus internal part. All activation maps are FDR corrected at $P < 0.05$ level. For the coordinates and a detailed description of the active areas, see Table 1.

(SEFs) bilaterally. Subcortically, bilateral GPi (coordinates 20, -10, -6 and -20, -6, 0) and putamen (coordinates 22, 0, 6 and -24, -4, 10) activation were also observed (see Table 3 for coordinates, and Figs. 2 and 3 in Supplementary material).

2.2.5. Masking

We masked the picture sequencing and object discrimination control contrasts with the saccadic eye movement contrast to evaluate the overlaps and differences in activation patterns across three tasks. We focused on the basal ganglia activation in these comparisons. Inclusive masking (overlap) with the saccadic eye movement (SEM) versus fixation contrast revealed activation in bilateral GPi and putamen in the picture sequencing versus fixation contrast and in bilateral putamen and only right GPi in the control versus fixation contrast. After exclusive masking (differences) with the SEM versus fixation contrast, additional activation was observed in bilateral GPi, caudate and left putamen in the picture sequencing versus fixation contrast and in bilateral putamen, left caudate and right GPi in the control versus fixation contrast.

2.2.6. Functional connectivity

To assess the functional connectivity between the basal ganglia and other brain regions, specifically frontal lobes, in the picture sequencing task, we performed a correlation analysis. Results are reported at $P < 0.05$ level, corrected for multiple voxel-wise comparisons using the Family-wise Error (FWE) procedure. Activation in both right and left GPi clusters autocorrelated with itself. Right GPi activation correlated significantly with bilateral putamen, left ventral posterior–medial thalamic nucleus, left lateral geniculate nucleus, left hippocampus, right lingual gyrus, left inferior parietal lobule, right orbitofrontal cortex and right middle frontal gyrus BA 8. Left GPi activation correlated significantly with the right ventral posterior–medial thalamic nucleus, right lateral geniculate nucleus, right hippocampus, right lingual gyrus, right inferior occipital gyrus, left insula, right supramarginal gyrus, left inferior frontal gyrus and right middle frontal gyrus (Area 9/46) (see Tables 4a–b for coordinates in Supplementary material).

3. Discussion

These findings demonstrate that frontal–basal ganglia circuits play an important role in semantic event sequencing. While both picture sequencing and object discrimination control tasks show comparable activation of neural systems for visual knowledge and attention, the picture sequencing task demonstrates robust, bilateral recruitment of a neural network involving the dorsolateral prefrontal cortex (DLPFC) and the globus pallidus (GP).

3.1. Posterior object-related areas and ventral prefrontal cortex: visual knowledge network

High-level visual knowledge representations have been localized to the temporal lobe (Thompson-Schill, 2003). In both picture sequencing and control tasks compared to baseline, bilateral activation was found in occipital and ventral temporal regions, including fusiform and lingual gyri, and medial temporal lobe, including the hippocampus and the parahippocampal gyrus. Activity in these areas has been reported for tasks that require perceiving and categorizing objects and memory for trial unique, complex pictures (Brewer et al., 1998; Hasson et al., 2003; Stern et al., 1996).

In the frontal lobe, the ventrolateral PFC (VLPFC, BA 44/45) and the orbitofrontal cortex (OFC, BA 47/12) showed bilateral activation in both tasks. Neuroanatomical studies in monkeys have demonstrated that the OFC receives projections from inferiotemporal cortical regions that support visual object and scene categorization and discrimination functions (Barbas, 2000). Neuroimaging studies indicate that the VLPFC receives and organizes information from posterior association areas (D'Esposito et al., 2000), and left VLPFC has been implicated in processing verbal items, while right VLPFC processes nonverbal items (Braver et al., 2001; McDermott et al., 1999). Bilateral VLPFC activation herein could be related to the encoding, retrieval and selection of both verbal and visual nonverbal information (Kirchhoff et al., 2000). Our results are consistent with the idea that the occipitotemporal and the ventral prefrontal regions act together in a visual knowledge network.

The parts of this visual knowledge network that support semantic knowledge representation were similarly active in both tasks. In particular, there were no significant differences between picture sequencing and control tasks in the mid-fusiform gyrus (BA 19/37), a posterior region closely related to object categorization processes supporting naming, semantic and response-related functions with visual images (Bar et al., 2001; Grill-Spector et al., 2000).

Differences were noted in the medial temporal lobe (MTL), specifically in the hippocampus and parahippocampal gyrus. The picture sequencing task may activate the MTL more than the control based on the additional requirements for encoding relational or conjunctive features of events (Eichenbaum and Cohen, 2001; Rudy and Sutherland, 1995). An alternative, but not mutually exclusive, interpretation is that the hippocampus may be critical for ordering events, as has been described in both human and animal studies (Fortin et al., 2002; Hopkins et al., 1995, 2004; Kesner et al., 2002; Schendan et al., 2003).

3.2. Frontal eye fields, parietal cortex and thalamus: attentional network

Both picture sequencing and object discrimination control tasks require selective attention and voluntary saccades. Consequently, in picture sequencing and control tasks compared to baseline, we observed activity in the bilateral frontal eye fields (FEFs) and banks of the intraparietal sulcus extending to lateral parietal areas (BA 39, 40, 7) and posterior thalamus. These regions are components of a distributed, large-scale attention network (Gitelman et al., 2002) involved in shifts of attention (Corbetta, 1998) and saccadic eye movements (Gagnon et al., 2002; Luna et al., 1998; Petit et al., 1996). Regarding voluntary saccades in the present study, inclusive masking techniques show that activation in the cortical components of this network, as well as putamen and globus pallidus internal part (GPi), overlap with activation during saccadic eye movements. This finding is consistent with an oculomotor corticobasal ganglionic loop involving FEF and parietal areas which are targets of basal ganglia output (Middleton and Strick, 2000, 2001). However, the activation pattern in picture sequencing and control tasks cannot be explained simply based on oculomotor considerations. The DLPFC and the caudate are key components of the cognitive DLPFC-corticostriatal loop, and both were also activated in the picture sequencing and control tasks, but not in the saccadic eye movement task, which is a challenging motor but simple cognitive task. Thus, we suggest that it is recruitment of the DLPFC-basal ganglia loop that best explains the additional DLPFC and GP activation found in the experimental tasks and, especially, in the picture sequencing task.

Furthermore, while the oculomotor exploratory demands of the picture sequencing task may be higher than for the control task, the picture sequencing versus control contrast shows bilateral activation in dorsolateral prefrontal regions (BA 8, 9/46 and 46) but not in the FEFs. Subcortically, only GPi activity differed; there was no additional striatal or thalamic activation. Moreover, exclusive masking of the experimental tasks with the saccadic eye movement task revealed additional activation (i.e., beyond eye movements) only in the right GPi for the control task (versus fixation) but in bilateral GPi for the picture sequencing task (versus fixation). This finding provides further evidence of a more prominent and bilateral role for GPi in the picture sequencing task. Given the known anatomical connectivity between the DLPFC and basal ganglia output nuclei (Middleton and Strick, 2000, 2001), we propose that the activation in these structures is related to the high level cognitive sequencing requirements of the picture sequencing task.

3.3. DLPFC

Both picture sequencing and object discrimination control tasks produce right DLPFC (Area 9/46 and 46) activation and require not only passive encoding but also elaborative processing of the stimuli, which has been shown to recruit the DLPFC (Buckner and Koutstaal, 1998; Davachi et al., 2001). Activation in DLPFC was more pronounced and bilateral in the picture sequencing task (BA 8, 9/46, 46). This finding was further supported by the small volume correction analysis

that shows that the picture sequencing task strongly recruits the left DLPFC. In the picture sequencing task, the neural representations of the pictures in the array need to be maintained, and their positions need to be cognitively reorganized in order to sequence them. Bilateral activation in BA 8, which is anterior to the FEFs (Luna et al., 1998; Petit et al., 1996; Sweeney et al., 1996), has been reported in tasks requiring maintenance of visuospatial information in working memory (Courtney et al., 1998; Rowe and Passingham, 2001; Rowe et al., 2000), and a role for BA 9/46 and 46 in manipulation processes during working memory tasks is well supported (D'Esposito et al., 1998, 1999, 2000; Owen et al., 1998; Petrides et al., 2002; Postle et al., 1999; Stern et al., 2000).

3.3.1. Basal ganglia

Critically, bilateral caudate and putamen activation was found during both picture sequencing and object discrimination control tasks, whereas only putamen activation was found in the saccadic eye movement task. Caudate activation during the picture sequencing and control tasks but not the saccadic eye movement task is consistent with the dichotomy between motor corticostriatal loops involving the putamen and non-motor loops involving the caudate (Middleton and Strick, 2000). Cognitive (nonmotor) corticostriatal loops are engaged during both picture sequencing and control tasks. Moreover, the small volume correction analysis demonstrates that left GPi activation was specific to the picture sequencing task. Remaining discussion thus focuses on the GPi activation, starting with a review of the anatomical and physiological features of the basal ganglia circuits relevant to the functional role of the GPi in semantic event sequencing (see Fig. 2).

Topographically organized cortical information passes through the successive stages of processing in the basal ganglia, and the GPi, as an output nucleus, is the final stage of processing before information is projected back to the neocortex via the thalamus. Fibers from the striatal direct and indirect pathways and from the subthalamic nucleus (STN) hyperdirect pathway (Levy et al., 1997; Nambu et al., 2002) converge on GPi. STN uniformly excites large neuronal populations in GPi. In contrast, striatal neurons on the direct pathway inhibit distinct subpopulations of pallidal neurons that are driven by the STN. A separate set of striatal neurons on the indirect pathway excites GPi neurons (Parent and Hazrati, 1993, 1995).

In the picture sequencing task, once the meaning of a picture has been derived, and its ordinal position in the sequence determined, the neural representation of this picture becomes relatively task-irrelevant and needs to be suppressed. On the other hand, the neural representations of the remaining pictures need to be facilitated until their ordinal position in the sequence can be determined, and the target representation is selected from among competing alternatives.

We propose that the GPi contributes to processing in the frontal lobes via the thalamus by facilitating the selection of the appropriate response and suppressing the unwanted ones in order to accomplish the picture sequencing task. This idea is supported by the known anatomical connectivity between primate GPi and DLPFC (Middleton and Strick 2000, 2001) and

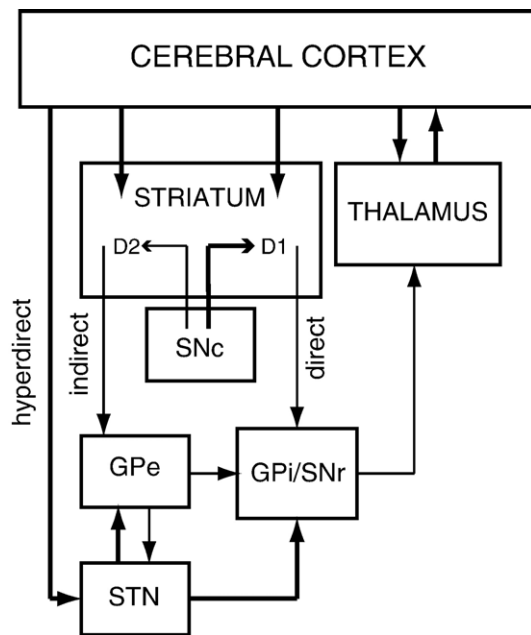


Fig. 2 – Schematic diagram of the basal ganglia–thalamocortical circuits. Excitatory projections (thick arrows) and inhibitory projections (thin arrows) are shown. Topographically organized cortical information enters the input nuclei (striatum and STN), passes through successive stages of information processing and finally projects to the output nuclei (Gpi and SNr). Basal ganglia output is projected back to the neocortex via the thalamus. GPe: globus pallidus external part, Gpi: globus pallidus internal part, STN: subthalamic nucleus, SNc: substantia nigra compacta part, SNr: substantia nigra reticular part; D1, D2: dopaminergic receptors on the direct and indirect pathways, respectively.

our finding of functional connectivity between these structures in the picture sequencing task. It is not possible to determine whether these selection and suppression processes take place simultaneously or sequentially due to the low temporal resolution of fMRI. What is important is that the dynamic interplay between the excitatory and inhibitory influences exerted by the direct, indirect and hyperdirect pathways regulate activation of the GPi neurons, resulting in facilitation or suppression of the activity in the thalamocortical circuits. The more pronounced and bilateral activation of the GPi in the picture sequencing task may be related to the intense synaptic activity in this structure that is produced by the dynamic interplay between the direct and indirect pathways, as synaptic activity correlates with the BOLD signal (Logothetis et al., 2001).

GP activation has been observed in several human neuroimaging and monkey electrophysiology studies of sequencing. In particular, the GP is active during motor sequencing tasks in which past responses need to be monitored in working memory in order to select the most appropriate new response (Boecker et al., 1998; Jueptner et al., 1997a,b; Mushiaké and Strick, 1995) and when the movement representations need to be maintained over a delay in working memory (Menon et al., 2000). In addition, a 2-back spatial working memory task has revealed activation in the GP

(Krasnow et al., 2003). GP activation was also observed in the execution of pre-learned and self-paced saccade sequences (Petit et al., 1996) and when the timing of the saccades was predictable (Gagnon et al., 2002). In addition, activation in the substantia nigra reticular part, the other basal ganglia output nucleus, was shown in monkey electrophysiological studies during saccades to a remembered location but not during spontaneous saccades based on external cues (Hikosaka and Wurtz, 1983a,b,c).

All these tasks require sharp spatiotemporal control of sequential behavior. Previous neuroanatomical and computational modeling studies indicate that the highly segregated parallel organization of the frontal lobe–basal ganglia architecture is well suited for carrying out such a control function (Beiser and Houk, 1998; Frank et al., 2001; Houk, 2001; Parent and Hazrati 1995). The role of GP seems to be particularly important for tasks in which a response selection needs to be made in the face of an ongoing process (e.g., maintenance/monitoring in working memory), as is the case in the picture sequencing task where the visuospatial information is maintained and selectively updated. We propose that GPi may provide part of the neural basis of this process and thereby help the DLPFC in linking the individual elements of the sequence in the picture sequencing task.

3.3.2. Functional connectivity results provide evidence for the importance of cortical–basal ganglia circuits for semantic event sequencing

The functional connectivity results herein provide evidence for the engagement of multiple cortical–basal ganglia circuits in the picture sequencing task. We propose that the additional cortical activation in occipital, parietal, limbic and especially prefrontal regions reflects the differential activation of specific corticostriatal loops during the picture sequencing relative to the control task. Critically, GPi computations are required in order to accomplish semantic sequencing. As the GPi is a basal ganglia output nucleus, it is the pathway from GPi to cortex that modulates the cortical computations in the picture sequencing relative to the control tasks.

3.3.3. Specificity of network activity to semantic event sequencing

Several cortical areas demonstrate greater activation in picture sequencing than control tasks. Information processing demands, including oculomotor exploratory functions, and manipulation requirements may have been higher in the picture sequencing than the control task. One might argue that the additional DLPFC and GPi activations in the picture sequencing task could simply reflect greater task difficulty or greater manipulation demands and not a specific change in neural activity related to sequencing. Task difficulty has been a confounding factor in most working memory studies with monitoring/manipulation components and has been shown to affect lateral PFC activity (Duncan and Owen, 2000).

Several of our findings are not compatible with a simple task difficulty explanation. First, activation in the visual knowledge network is not greater in the picture sequencing

than the control task. Second, additional DLPFC activity has been observed despite a decrease in task difficulty when reorganization and chunking of materials are required (Bor et al., 2003). Third, neuroimaging studies of perceptuomotor sequence learning have shown DLPFC activation, implicating this structure specifically in monitoring the sequence structure in working memory and selecting the future response (Jenkins et al., 1994; Jueptner et al., 1997a,b; Schendan et al., 2003; Toni et al., 1998; Willingham et al., 2002). A recent fMRI study of motor sequencing with varying manipulation demands showed that subcortical structures including the putamen and the cerebellum interact preferentially with the frontoparietal association areas including the DLPFC rather than the motor areas when a high-level control of movement timing and order is required (Garraux et al., 2005). Fourth, similar activation of the striatum and thalamus occurs in both picture sequencing and control tasks. By contrast, left GPi is active uniquely in the picture sequencing task, and right GPi is more active in the picture sequencing task than the control task, suggesting a specific role for the GPi in semantic event sequencing. Finally, the functional connectivity data demonstrate clearly that the additional cortical activation is related to the additional GPi activation in the picture sequencing task and so reflects picture sequencing task-specific engagement of cortical-basal ganglia circuits. As the GPi is the output nucleus of the basal ganglia, it is the differential computations in the GPi and their subsequent influence on cortical computations, especially in left DLPFC, that plays a crucial role in semantic sequencing.

A related issue warranting further discussion concerns manipulation demands. In particular, by design, the picture sequencing task, but not the control task, requires a specific type of manipulation, namely, selective updating of neural representations. Selective updating is a component of any manipulation task that requires the subject to compare or contrast items held in working memory in order to select the correct response from a number of competing elements (Frank et al., 2001). This type of manipulation is also an essential element of semantic sequencing. In the picture sequencing task, the subject must choose between multiple stimuli based on their temporal relationship. Other tasks, such as re-ordering objects based on other semantic criteria, for instance size or number, would also require selective updating, and we would predict GPi activity in these tasks. In the current study, we designed our tasks to differ in this manipulation requirement. The critical comparison was between a task requiring semantic sequencing and one requiring semantic knowledge without sequencing.

In conclusion, this study provides evidence for a role of frontal lobe and basal ganglia output nuclei in semantic event sequencing. The findings support the accumulating body of evidence suggesting that the basal ganglia output nuclei are not only important for motor control but also participate in the decision-making processes in complex cognitive tasks by integrating converging information from a wide range of projections (Middleton and Strick, 2001). Visual knowledge and attentional networks were also found to play an important role in semantic event sequencing. We propose that it is the interaction of these networks with the frontal

lobe-basal ganglia loops that enables us to organize multiple discrete events in our daily lives.

4. Experimental procedure

4.1. Subjects

Twelve healthy volunteers participated (6 females; mean age 21.75 ± 4) with informed consent and approval of Mass General Hospital and Boston University.

4.2. Tasks

All pictures were black and white cartoon-like simple line drawings. At the piloting stage of the study, participants were asked to rate the visual complexity of the pictures. Based on their feedback, pictures that were too complex and sequences that were difficult to comprehend were excluded. The picture sequencing (PS) task required subjects to order a series of four pictures. The nature of the temporal constraints in the series was causal (e.g., banana being eaten, airplane lifting off, bird building a nest etc.), and the time scale of the sequences was diverse. The object discrimination control (CON) task required subjects to find the odd item (living or nonliving) among a set of four objects. The nonliving category included line drawings of every day objects (e.g., tools, furniture, clothes, vehicles etc.), and the living category included line drawings of animals, fruits and vegetables. The CON task served as a control for the visuospatial, semantic and motor components of the PS task and did not include a semantic sequencing component (see Fig. 3 for detailed task descriptions).

Subjects completed 60 trials of both tasks (PsyScope Version 1.2.5 Cohen et al., 1993). The ordinal position of the pictures in the horizontal array was randomized and counterbalanced across trials. Based on pilot behavioral data, subjects were given 8 s to arrange the pictures and find the answer and 2 s to respond. They were instructed not to respond until they saw the "GO!" signal that was illuminated after the 8-s sequencing period. This allowed us to synchronize the motor response component in both PS and CON tasks. By displaying the "GO!" cue on top of the pictures and always having the four pictures available to the subject, we intended to minimize the working memory requirement during the response period in both PS and CON tasks. Subjects responded during both tasks using their right hand. Each subject received a pre-scan behavioral practice session on both tasks.

Each subject performed 4 runs in one experimental session. Each run contained three experimental and three control blocks that were randomized and counterbalanced across subjects. Each block in both PS and CON tasks included five trials. A white fixation-cross at the center of the computer screen indicated the resting period of 30 s in the beginning and 40 s in the end of each run.

4.3. Control experiment: saccadic eye movement task (SEM)

The SEM task served as an additional control for the oculomotor component in both PS and CON tasks. A different group of twelve healthy volunteers participated in the SEM task (mean age 20 ± 1.85). The target was a white dot that was displayed on a black screen. Subjects were instructed to track the moving target with their eyes and fixate it when it remained stationary in the center of the screen. The target stepped 6 and 12° to right and left on the horizontal plane every 500 ms. The direction of the target movement was randomized. Subjects completed two runs of the SEM task. Four

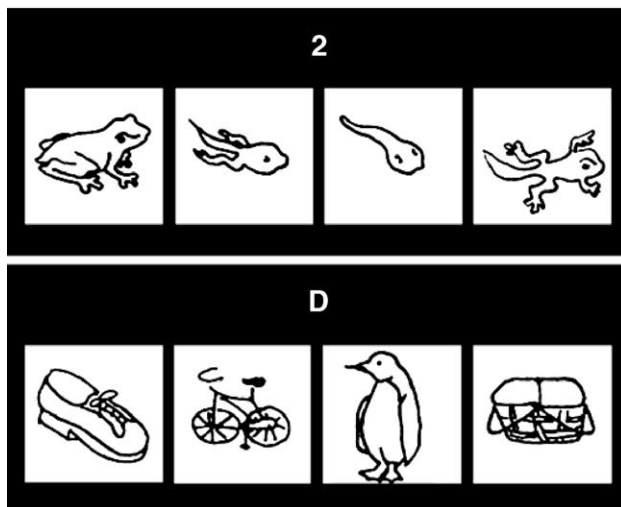


Fig. 3 – (Top) Picture Sequencing (PS) task. On each trial, four pictures were shown that were temporally related. In the example, a tadpole develops into a frog. The pictures were black and white line drawings (3.4 cm × 3.4 cm, resolution 59 pixels/cm, eye-to-screen distance 57 cm) presented simultaneously in a scrambled order at the center of the computer screen. A number cue (2, 3 or 4) centered above the pictures cued subjects to find a specific picture in the sequence. Subjects were given 8 s to order the pictures and identify the target picture. The number cue remained illuminated throughout the 8-s period. Subjects were told not to respond until they saw the “GO!” signal displayed immediately after the 8-s period above the pictures for another 2 s. Subjects indicated the location of the target picture by pressing one of four keys on a response box that had the same spatial array as the pictures. **(Bottom) Object Discrimination Control (CON) task.** Four black and white line drawings of living and nonliving objects were presented simultaneously. Three out of four line drawings were from the same category (i.e., living or nonliving), and one was from a different category. The cue “D” above the pictures instructed the subjects to identify the object from the “different” category. In the example, the penguin is the different object. All other procedures in the CON task were the same as the PS task.

saccade and four fixation blocks alternated in each run. Each block lasted 20 s.

4.3.1. fMRI acquisition and design

Scanning was performed on a 3-T Siemens Allegra MRI system using a whole-head coil. High-resolution T1-weighted scans (MP-RAGE; FOV = 256 × 256 mm, matrix = 192 × 256, TR = 6.6 ms, TI = 300 ms, TE = 2.9 ms, flip angle = 8° thickness = 1.33 mm) for anatomical localization and four T2*-weighted functional BOLD scans (185 images per scan) were collected for each subject. The functional data were acquired using a gradient-echo, echo-planar pulse sequence, 21 AC-PC slices were acquired (slice thickness = 5 mm, distance factor = 20%, 1 mm skip between slices), TR = 2 s, TE = 30 ms, flip angle = 90°, 64 × 64, 3 × 3 × 5 mm³ voxels).

4.3.2. fMRI data analysis

BOLD data were analyzed using SPM2 (Wellcome Department of Cognitive Neurology). All scans were realigned with respect to

the first scan in the fMRI time series using 4th degree B-spline interpolation (Thevenaz et al., 2000) and were unwarped. Unwarping was used to correct for the residual movement-related variance after realignment that is caused by movement-by-field inhomogeneity interactions (Andersson et al., 2001). The scans were then normalized to MNI305 stereotactic space by using trilinear interpolation (interpolating to 2 mm³ voxels; neurological convention) and spatially smoothed with a 4-mm³ Gaussian kernel. Statistical analyses employed the general linear model. Design matrices were modeled in scans convolved with a canonical hemodynamic response function with time derivative. High-pass filtering with a cutoff period of 128 s was applied, but global signal scaling was not used to avoid spurious deactivations.

To assess task-related activation, linear contrasts of picture sequencing (PS) blocks relative to fixation and of object discrimination control (CON) blocks relative to fixation were created in the first experiment. The 2-s response period was included in the analysis. Sequencing-related activation was assessed in linear contrasts of PS relative to CON blocks. Saccade-related activation was assessed in linear contrasts of saccadic eye movement relative to fixation blocks in the second experiment. Contrast images were first created for each subject and were subsequently used in a second-level analysis treating subjects as a random effect (one-sample t test). Group averaged, statistical parametric maps (SPMs) were corrected across the whole brain for multiple voxel-wise comparisons using the false discovery rate (FDR) procedure ($P < 0.05$). FDR is the proportion of false positives among supra-threshold voxels only. FDR correction is less conservative than traditional procedures for multiple hypotheses testing (e.g., Bonferroni or random field correction) and more powerful (Genovese et al., 2002). Extent threshold was always 5 voxels.

4.3.2.1. Functional connectivity analysis. To assess the functional connectivity between the basal ganglia and other brain regions, specifically frontal lobes, in the picture sequencing task, we performed a correlation analysis. We selected the right and left globus pallidus internal part (GPi) as the regions of interest. The right and left GPi masks were created anatomically using the WFU-Pick Atlas tool in SPM2 (Maldjian et al., 2003) and applied to the picture sequencing versus fixation contrast image of each subject. fMRI signal intensity time courses were extracted from the clusters around the peak activation in the GPi masks for each subject using the Volume of Interest (VOI) tool in SPM2 (adjusted for effects of interest). The right and left GPi time courses were used as regressors in a simple correlation analysis at the single subject level. Finally, single subject SPMs were created and entered in a second level analysis using one-sample t test. Group averaged SPMs were corrected across the whole brain for multiple voxel-wise comparisons using the family-wise error (FWE) procedure ($P < 0.05$). Extent threshold was 5 voxels.

4.3.2.2. Masking. In order to further evaluate whether the regions in the basal ganglia correspond to the structures involved in saccadic eye movement, the target group averaged SPMs of the picture sequencing (PS) versus fixation and object discrimination control (CON) versus fixation contrasts were also masked inclusively and exclusively, separately, with the group averaged SPMs of the saccadic eye movement (SEM) versus fixation contrast. The significance level of the mask was uncorrected $P < 0.05$. The resulting SPMs for PS or CON versus fixation were FDR corrected ($P < 0.05$). Exclusive masking eliminates all voxels in the target contrast (e.g., PS versus fixation) that reach the significance level in the masking contrast (i.e., SEM versus fixation). The resulting SPM shows the voxels in the target contrast that are not shared by both the

target contrast and the masking contrast. On the other hand, inclusive masking removes all voxels from the target contrast that do not reach the significance level in the masking contrast. The resulting SPM shows only those voxels that are shared both by the target and masking contrasts.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.brainres.2005.10.057](https://doi.org/10.1016/j.brainres.2005.10.057).

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