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Research report

Dissociation of human caudate nucleus activity in spatial and nonspatial working memory: an event-related fMRI study

Bradley R. Postle *, Mark D'Esposito

Department of Neurology, University of Pennsylvania Medical Center, 3 West Gates, Area 9 3400 Spruce St. Philadelphia, PA 19104 USA

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Abstract

We employed a novel event-related fMRI design and analysis technique to explore caudate nucleus contributions to spatial and nonspatial working memory. The spatial condition of a delayed-response task revealed greater mnemonic activation in four of six subjects when the delay period preceded immediately a probe stimulus requiring an overt motor response, as contrasted with a probe requiring no response. This effect was not seen in frontal or parietal cortical areas, and was seen in the caudate nucleus in a formally identical object condition in just one of six subjects. We hypothesized that this pattern of activity represented spatially dependent motor preparation. A second experiment confirmed this hypothesis: delay-period activity of the caudate nucleus showed greater time dependence in a task that featured spatial and motoric memory demands than in a comparable nonspatial task that featured the same response contingencies. These results suggest an important subcortical locus of the dissociation between spatial and nonspatial working memory, and a role for the human caudate nucleus in the integration of spatially coded mnemonic information with motor preparation to guide behavior.

Keywords: Basal ganglia; Motor preparation; Planning

1. Introduction

A role for the caudate nucleus in spatial working memory has been established through studies of the behavioral effects of lesions to [6,17,18,22,36] and electrical stimulation of [10,28,39] this subcortical structure in monkeys. Despite this evidence, the preponderance of neuroimaging studies of human working memory to date have focused on cortical correlates of working memory function. These studies have established that spatial and nonspatial working memory are differentially reliant on dorsal stream and ventral stream regions, respectively, in posterior cortex [7,12,31,38], whereas the extent of spatial/nonspatial segregation of working memory function in frontal cortex remains a topic of debate [14,31,37,44]. Evidence of a deficit in spatial working memory in patients with Parkinson's disease (PD) [19,41], a disease characterized by reduced supply of dopamine to the striatum, has led to proposals that the caudate nucleus might be a site where spatial and nonspatial mnemonic processing are carried out differentially. Evidence consistent with this model has emerged from demonstrations of a selective impairment of spatial working memory in early PD, despite spared working memory for objects [29,32,33], and of differential patterns of activation of the caudate nucleus in monkeys performing spatial and object working memory tasks [26]. The studies reported here were intended to elucidate the contribution of the caudate nucleus to spatial and nonspatial working memory in humans.

2. Expt 1: 'What'-then-'Where' delayed response

2.1. Introduction

Most experiments designed to study visual working memory do not permit resolution of the theoretically dissociable contributions of sensory memory and motor preparation to delay period activity. Evidence of selectively compromised spatial working memory in PD [29,32,33], for example, may arise from degraded spatial (sensory) memory representations or from disordered motor planning and execution when behavior must be organized with exclu-

* Corresponding author. Fax: +1-215-349-5579; E-mail: postle@mail.med.upenn.edu.

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sively spatial information. Our 'what-then-where' delayed-response task (based on [35]) featured two discrete delay periods during each trial, enabling us to analyze delay-period activity by stimulus material (spatial, object) and by position in the trial (first, second). Importantly, only the second delay period was followed by a motor response (Fig. 1a). This 2×2 design permitted us to unconfound mnemonic and motor contributions to delay-period activity

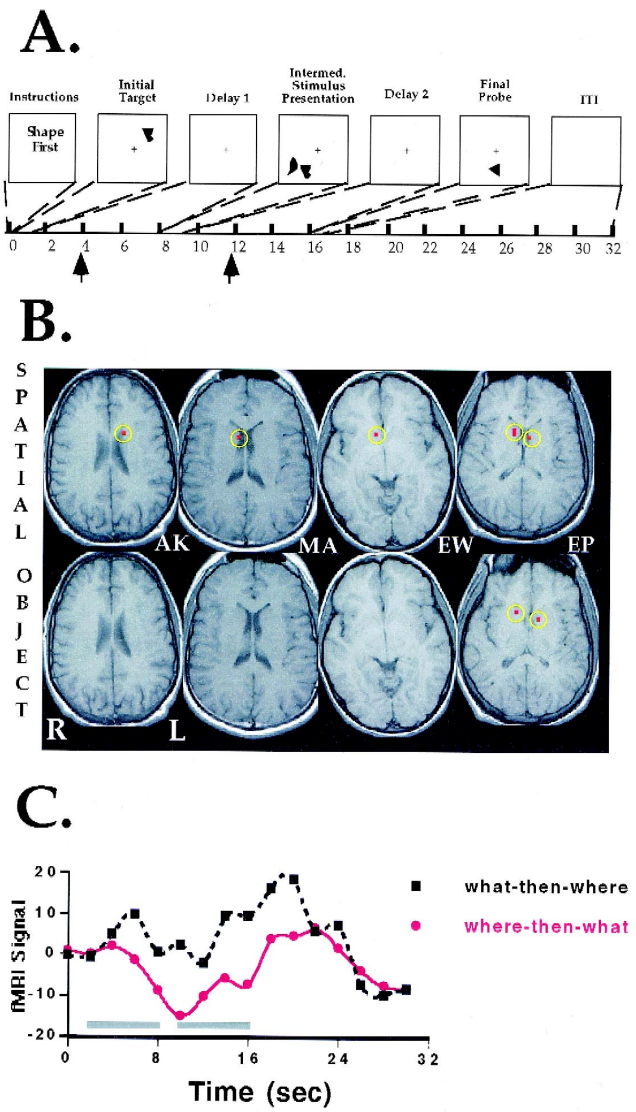

Fig.1

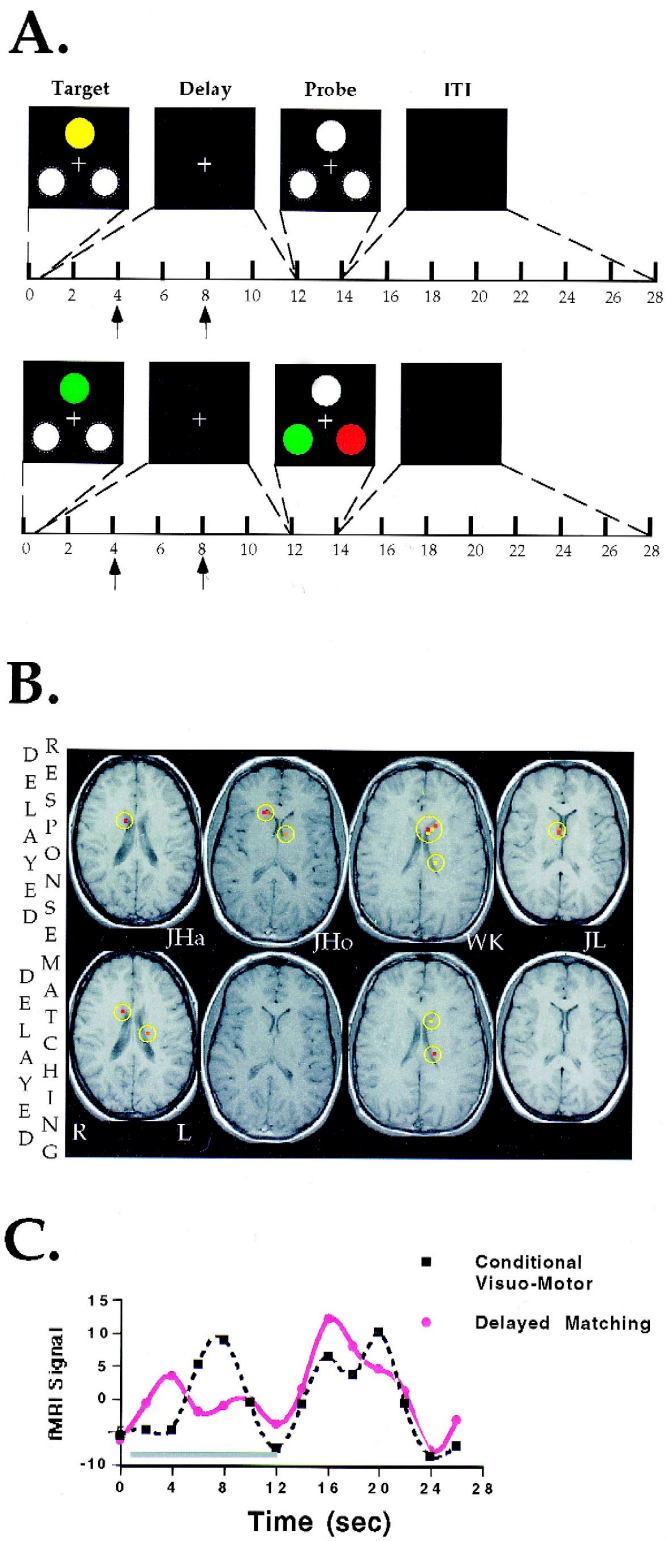

Fig. 2

in the caudate nucleus. We tested two hypotheses about caudate nucleus delay-period activity in a delayed-response task: (i) we would observe a main effect of stimulus condition, such that spatial activity would be greater than nonspatial activity (consistent with the sensory memory hypothesis); or (ii) we would observe an interaction of stimulus condition with position of the delay, such that activity would be greater during spatial memory periods followed immediately by a motor response (consistent with the motor planning hypothesis). Because segregation of striatal efferents focuses the majority of caudate nucleus output (via subsequent stations of the basal ganglia and the thalamus) on prefrontal and limbic cortical regions associated with higher cognitive function, and the majority of putaminal output on motor areas of frontal cortex [4], we limited our analyses to the caudate nucleus.

2.2. Methods

2.2.1. Subjects

We studied 6 right handed subjects (5 males; mean age = 23 years). All subjects were recruited from the undergraduate and medical campuses of the University of Pennsylvania, and all gave informed consent.

2.2.2. Behavioral procedure

Each trial began with an instructional cue (500 ms), followed by an initial target stimulus presentation (1 s) followed by a delay period ('delay 1'; 6.5 s) followed by the presentation of the initial target stimulus ('match') and a foil stimulus ('intermediate stimulus presentation'; 1.5 s), followed by a second delay period ('delay 2'; 6.5 s), followed by a probe stimulus ('final probe'; 1 s; Fig. 1a). A fixation cross appeared with the onset of the initial target, and remained on the screen until the offset of the final probe. An intertrial interval (ITI) of 15 s separated each trial; the time from trial onset to trial onset was 32 s. The instructional cue read 'shape first' or 'location first' in a pseudorandomly determined order. In 'shape first,' or what-then-where, trials, subjects encoded the featural details of the initial target, ignoring its location on the screen, and retained this featural information during delay 1. The two intermediate stimuli both appeared in a location different from that occupied by the initial target, and their onset prompted a discrimination as to which of the two was an identical featural match with the initial target. Immediately upon making this discrimination, subjects encoded the location of the match stimulus and retained this location information during delay 2. (In this way, the match probe for the 'what' portion of the trial became the target for the 'where' portion of the trial.) Finally, subjects indicated whether or not the final probe occupied the same location as the location target stimulus (i.e., as the match stimulus from the intermediate stimulus presentation), and indicated their decision with a 'yes' or 'no' button press. In 'location first,' or where-then-what, trials, subjects were trained to perform spatial delayed response during the first half of the trial, and to encode featural information about the location match stimulus from the intermediate stimulus presentation in order to perform object delayed response during the second half of the trial. Each block of trials, corresponding to one fMRI scan, contained six what-then-where and six where-then-what trials presented in a pseudorandomized order, each featuring an equal number of 'yes' and 'no' final probes. Five of the six experiments consisted of eight scanned blocks of testing, or 96 trials

Fig. 1. (a) Schematic diagram and timeline of a what-then-where trial of the delayed-response task featured in Experiment 1. Each box represents a stimulus display event, and the dotted lines connecting each box to the timeline represent the sequence and duration of each of these events. The numbers along the timeline represent seconds, and the two arrows indicate the positioning of the two delay-sensitive independent variables in our statistical model. A where-then-what trial would be formally identical, but with the instructions reading 'location first,' one of the two intermediate stimuli occupying the same location on the screen as the initial target, and neither of the two intermediate stimuli matching the featural identity of the initial target. See text for a description of the task. (b) Results of single subject analyses in the four subjects exhibiting significantly greater caudate nucleus activity during spatial delay 2 than during spatial delay 1. Analogous behavior was not observed in the object condition for subjects AK, MA, and EW. Subject EP also exhibited greater delay 2 than delay 1 activity in the object condition; note that these suprathreshold object delay voxels were located on a more inferior slice than the voxels exhibiting suprathreshold spatial delay activity for this subject. (c) Superimposed trial averaged BOLD fMRI data from what-then-where and where-then-what trials for the suprathreshold voxels identified in the [spatial delay 2 − spatial delay 1] contrast for subject EP. The gray bars represent the two delay periods of each trial; the time on the horizontal axis corresponds to the diagram of trial events presented in panel a. Changes in BOLD data lag behind putatively causal behavioral events by 4 to 6 s. Note that spatial delay-period activity is higher in what-then-where than in where-then-what trials, whereas object delay activity is at a comparable level during the two conditions.

Fig. 2. (a) Schematic diagram and timeline for the motor-set task featured in Experiment 2; the conditional visuo-motor task is illustrated above the delayed-matching task. All graphical conventions are the same as Fig. 1. Note that the two delay-specific independent variables are positioned within the same delay period. (b) Results of single subject analyses in the four subjects exhibiting significantly greater caudate nucleus activity during conditional visuo-motor delay 1 than during conditional visuo-motor delay 2. Analogous behavior was not observed in the delayed-matching task for subjects JHo and JL. Subjects JHa and WK also exhibited greater delay 1 than delay 2 activity in the delayed-matching task; note that suprathreshold conditional visuo-motor and delayed-matching voxels are overlapping for these two subjects. (c) Superimposed trial averaged BOLD fMRI data from conditional visuo-motor and delayed-matching trials from the suprathreshold voxels identified in the [conditional visuo-motor delay 1 − conditional visuo-motor delay 2] contrast for subject JHo. The gray bar represents the delay period of each trial; the time on the horizontal axis corresponds to the diagram of trial events presented in panel a. Note that conditional visuo-motor delay-period activity is higher in the first portion of the delay period, whereas delayed-matching delay-period activity is relatively stable throughout the delay period.

(and, therefore, 96 spatial delay periods and 96 object delay periods); one subject was scanned for five blocks.

2.2.3. fMRI procedure

Imaging was carried out on a 1.5 T SIGNA scanner (GE Medical Systems) equipped with a prototype fast gradient system for echo-planar imaging. A standard radiofrequency (RF) head coil was used with foam padding to restrict comfortably head motion. High resolution axial T1-weighted images (21 axial slices) were obtained in every subject. A gradient echo, echoplanar sequence (TR = 2000 ms, TE = 50 ms) was used to acquire data sensitive to the blood oxygen level dependent (BOLD) signal. Scans of the behavioral task were preceded by a scan in which we derived the impulse response function (IRF) for each subject. The IRF, which characterizes the fMRI response resulting from a brief pulse of neural activity [9], was used to smooth independent variables in the general linear model (GLM) that we used to analyze the results of the scans of our behavioral task (see *fMRI data processing*, below). The derive-IRF scan lasted 5 min 20 s (160 images/slice). Our method for deriving the IRF is described in detail elsewhere [16]. Each fMRI scan of our behavioral task lasted 6 min 24 s (180 images/slice). FMRI data collection during all scans was preceded by 20 s of dummy gradient and RF pulses to achieve a steady state of tissue magnetization.

2.2.4. fMRI data processing

The principle of the fMRI time series analysis was to model the fMRI signal changes occurring during particular periods of the behavioral trials with covariates comprised of shifted, BOLD IRFs [49]. The fMRI time series were tested with covariates that modeled the expected BOLD signal response in the event of an increase in neural activity (relative to the ITI) occurring during each behaviorally significant portion of each trial (i.e., stimulus presentation, delay, and response periods). Importantly, we used this method to obtain measures of delay-period activity in voxels in the caudate nucleus that were not contaminated by variance in the fMRI time series attributable to stimulus presentation or response activity. We could accomplish this because smoothness of the fMRI response to neural activity allows fMRI responses to be resolved on the order of 4 s [49]. False positive rates were controlled at $\alpha = 0.05$ by Bonferroni correction for the number of voxels per region of interest (ROI) [48].

All our analyses were performed with ROIs. Caudate nucleus ROIs were drawn for each subject on that subject's T1 anatomical images, and incorporated the head of the caudate nucleus, beginning rostrally and ventrally at approximately the level of the anterior commissure, and the body of the caudate nucleus, extending caudally along the lateral wall of the lateral ventricle and ending at the ventral-most level at which the body of the lateral ventricle appeared intact in one slice (i.e., one slice dorsal to the slice in which the atrium became visible). We also performed analyses on three cortical areas that are linked anatomically and functionally with the basal ganglia: areas 9 and 46 of dorsolateral prefrontal cortex (DLPFC), primary motor cortex (M1), and area 7 of posterior parietal cortex (PPC). DLPFC and PPC both exhibit delay-related activity during working memory tasks, both are important sources of afferent input to the caudate nucleus, and DLPFC is an important recipient (via subsequent stations of the basal ganglia and the thalamus) of caudate nucleus output. We created ROIs for these two cortical regions by drawing them onto the 'canonical' representation of a brain in Talairach space that is provided in SPM96b, using the atlas of Talairach and Tournoux [40] to confirm our identification of anatomical landmarks. Next, we transformed these ROIs from Talairach space into the native space in which each subject's data had been acquired by applying the 12 parameter affine transformation [20] with nonlinear deformations [5], routine in SPM96b (effectively, a 'reverse normalization'). Movement-related activity in M1 is closely correlated temporally with movement-related activity in the striatum [2,3,13]. M1 thereby represents an effective control region for dissociating motoric from mnemonic activity in the caudate nucleus. We defined the M1 ROI in each subject as the cortex immediately anterior to the central sulcus.

2.2.5. Single subject analyses

Our analyses were performed in two steps: single subject analyses and group analyses. Single subject analyses permitted us to maintain the high spatial resolution afforded by fMRI, and to detect intersubject variability. Such information is lost in analysis approaches that combine data from all subjects at an early stage of analysis, and are thus restricted to testing for activation patterns that are consistent enough across subjects in a standard space to be detected after group-averaging. Our single subject analyses, in contrast, treat each subject as a case study, and permit us to assess replication of (as well as variation in) effects across individual cases. In essence, data from 6 subjects performing the same task represent a single result with 5 replications. Single subject analyses with methods comparable to those used in the present study (and, importantly, with a large number of observations per subject, as in the present study) have been demonstrated to feature ample sensitivity to detect signal intensity changes of interest [16,50]. Contrasts performed with single subject data in the present study had in excess of 1200 effective degrees of freedom.

We effected tests of our first hypothesis, a main effect of stimulus material, by generating a two-tailed *t*-map of the contrast [(spatial delay 1 + spatial delay 2) − (object delay 1 + object delay 2)] and detecting suprathreshold voxels. We tested our second hypothesis, interactions of stimulus material and position in delay-period activity, by generating two-tailed *t*-maps of the contrast [spatial delay

1 − spatial delay 2] and of the contrast [object delay 1 − object delay 2]. The identification of suprathreshold *t*-values in this analysis would indicate that delay-period activity within a particular working memory condition (spatial or object) was sensitive to position within the trial. In the event of significant interactions, tests for main effects of delay position [(spatial delay 1 + object delay 1) − (spatial delay 2 + object delay 2)] would be performed to discount simple order effects. Analysis of activity during the response phase of the task ([spatial final probe − object final probe]), which would reflect motor activity, served as a control for the memory-related analyses described above.

2.2.6. Group analyses

Our group analyses were performed as random effects models, an approach that permits generalization of results obtained from a sample to the population represented by that sample. This inferential step cannot be made with the fixed effects group analyses that have been employed by the majority of fMRI experimentalists to date [24,47]. Importantly, random effects analyses are invulnerable to spurious results that can arise if a disproportionately large effect size in a single subject 'drives' the mean effect size for the group, as can happen with fixed effects analyses. All our group analyses used *t*-values as dependent measures, because they represent an index of the signal-to-noise ratio for a given contrast. *T*-values are proportional to the magnitude of the hypothesized effect, and they are normalized measures because they are scaled by the error in each subject. Group tests for a main effect of stimulus material were performed by first identifying for each subject the voxels within the caudate nucleus ROI showing a main effect of delay period activity [spatial delay 1 + spatial delay 2 + object delay 1 + object delay 2] and, from these voxels, extracting a spatially averaged time course and calculating the orthogonal contrast of [(spatial delay 1 + spatial delay 2) − (object delay 1 + object delay 2]). The resultant *t*-value represented, for each subject, the extent to which the sensitivity of delay-period activity was greater for spatial or for object stimuli. (A positive *t*-value would indicate that spatial delay-period activity was greater than object delay-period activity, a negative *t*-value the converse.) A paired *t*-test on these *t*-values, one from each subject, assessed the significance of any trends in the data across subjects.

To conduct group analyses of our second hypothesized effect, a greater influence of trial position on delay-period activity with one stimulus type than with another, we generated an index of the sensitivity of caudate nucleus activity to trial position by identifying critical voxels showing a main effect of delay period activity within the caudate nucleus ROI, extracting a spatially averaged time course from these critical voxels, and calculating the orthogonal contrast of [(spatial delay 1 − spatial delay 2) − (object delay 1 − object delay 2)]. The two-tailed *t*-value arising from this contrast represented, for each subject, a normalized measure of the interaction of stimulus material and delay period position. A paired *t*-test on these *t*-values, one from each subject, assessed the significance at the group level of this interaction. Comparable analyses were performed within the DLPFC, M1, and PPC ROIs.

2.3. Results

2.3.1. Single subject analyses

The test of our first hypothesis yielded a null result: direct contrast of spatial vs. object delay-period activity (collapsed across trial position) revealed no suprathreshold voxels in the caudate nucleus in any subject. We did, however, observe an interaction of stimulus material with delay position in several subjects: Trial-position differences (delay 2 > delay 1) achieved significance in the caudate nucleus for four subjects in the spatial condition as contrasted with only one subject in the nonspatial condition (Fig. 1b). (The contrast of delay 1 vs. delay 2 [collapsed across stimulus material] yielded no significant differences in any subject.) Spatial delay 2 > delay 1 suprathreshold voxels were located in the right head of the caudate nucleus in two subjects, in the left head of the caudate nucleus in one subject, and bilaterally in the head of the caudate nucleus in one subject (subject EP); object delay 2 > delay 1 voxels were also found in the head of the caudate nucleus, bilaterally, in subject EP, although in a different, nonoverlapping set of voxels. Probe differences (spatial final probe > object final probe) were significant in only one subject. No significant trial-position effects were observed in DLPFC, M1, or PPC.

2.3.2. Group analyses

All group analyses failed to achieve significance in each of the four ROIs (caudate nucleus, DLPFC, M1, PPC).

2.4. Discussion

Experiment 1 revealed the absence of main effects of stimulus material or of delay position, but an effect of delay position on spatial delay-period activity in four of six subjects, indicating that spatial delay-period activity in the caudate nucleus was more sensitive to trial position than was object delay-period activity in the majority of our subjects. Thus, the caudate nucleus may make functionally different contributions to working memory for 'where' than to working memory for 'what.' Voxels with delay-period activity that exhibited significant sensitivity to trial position were all located in the head of the caudate nucleus, with no clear trend in lateralization. These results suggest that the caudate nucleus, unlike its important sources of cortical afferents or the cortical targets of its efferents, may be preferentially activated in the delay period of working memory tasks by the coincidence of spatial memory and the need to formulate a response based

on that information. This pattern of activation could be characterized as spatially mediated motor preparation. It is dissociable from final probe-related activity in the caudate nucleus, which was greater in the spatial condition in only one subject. Although this effect was significant in four of six subjects, the nonsignificant result of our group analysis prompted us to test the hypothesis that arose from Experiment 1 with a second experiment.

3. Expt 2: 'Motor set'

3.1. Introduction

An important feature of the hypothesis generated in Experiment 1 is that caudate nucleus delay period activity is more sensitive to motor contingencies when memoranda are coded spatially than when they are coded nonspatially. We tested this hypothesis with a 'motor set' experiment (Fig. 2a), based on Ref. [21], that featured a spatial conditional visuo-motor task and a nonspatial delayed-matching task. In this experiment the delay period was lengthened to 12 s to permit assessment of caudate nucleus activity during two discrete portions of the same delay period (see Section 3.2.2). Our design permitted us to test hypotheses analogous to those tested in Experiment 1:1) a main effect of task type; and 2) an interaction of task type and delay position. A finding of a greater interaction in the conditional visuo-motor task would be consistent with a preferential role for the caudate nucleus during working memory task performance in spatially mediated motor preparation.

3.2. Methods

3.2.1. Subjects

The six subjects participating in our study (3 males, mean age = 22.7) were recruited from the undergraduate and medical campuses of the University of Pennsylvania, and all gave informed consent.

3.2.2. Behavioral procedure

The conditional visuo-motor task and the delayed-matching task both featured color-behavior associations that subjects learned prior to scanning. In the conditional visuo-motor task, the initial presentation of either of two colored stimuli ('cue'; 600 ms) in the top position of a three-circle array indicated whether the position to choose at the end of the trial was on the left (blue cue) or the right (yellow cue). After the 11.4 s delay the three circle array was re-presented, but with all three circles colored white ('probe'; 1 s). Subjects chose the circle on the left or the right with a button press (Fig. 2a). Cue presentation in this task informed subjects explicitly about the correct response for that trial, and thus subjects could guide performance by retaining a representation of either the spatial location associated with the cue or the motor response associated with the cue during the delay period (a prospective memory code [34,46]).

The initial cue in the delayed-matching task was red or green. Subjects remembered this color until the probe presented the two colors, in pseudorandomly determined order, in the two bottom positions, whereupon they chose the color that matched the cue. Timing, sequence, and layout of this task were identical to the conditional visuo-motor task (Fig. 2a). In contrast to the conditional visuo-motor task, however, the delayed-matching task required memory for the color of the initial cue, and task-relevant spatial and motor information was unavailable until a response was prompted by the re-presentation of the cued color at the end of the trial (Fig. 2a). Previous behavioral testing with this task has indicated that subjects respond more quickly on conditional visuo-motor than on delayed-matching trials, consistent with the assumption that conditional visuo-motor trials permit motor preparation during the delay period [15].

3.2.3. fMRI scanning and data processing procedures

These were the same as those used in Experiment 1, with the exception that the two delay-period independent variables of interest were not separated by intervening task events. The 'delay 1' independent variable was positioned 4 s into the trial in order to model variance in the fMRI time series that was attributable to the first portion of the delay period, and the 'delay 2' independent variable was positioned 8 s into the trial in order to model activity that was attributable to the second portion of the delay period. The 4 s spacing between delay 1 and delay 2 covariates ensured that they would not model a significant amount a shared variance [49], and, therefore, that the loading on each would index delay-period activity uncontaminated by delay-period activity occurring later or earlier in the trial, respectively.

3.2.4. Single subject analyses

We tested our first hypothesis, a main effect of task, by generating a two-tailed *t*-map of the contrast [(Conditional visuo-motor delay 1 + Conditional visuo-motor delay 2) − (Delayed-matching delay 1 + Delayed-matching delay 2)] and detecting suprathreshold voxels. We tested our second hypothesis, interactions of task type and position in delay-period activity, by generating two-tailed *t*-maps of the contrast [Conditional visuo-motor delay 1 − Conditional visuo-motor delay 2] and of the contrast [Delayed-matching delay 1 − Delayed-matching delay 2]. The identification of suprathreshold *t*-values in this analysis would indicate that delay-period activity within a particular task varied systematically over time. In the event of significant interactions, tests for main effects of delay position [(Conditional visuo-motor delay 1 + Delayed-matching delay 1) − (Conditional visuo-motor delay 2 + Delayed-matching delay 2)] would be performed to discount simple position

effects. We also tested for differential motor activity with a contrast of probe-related activity in the two tasks.

3.2.5. Group analyses

Random effects group analyses were performed on our first hypothesis by generating a one-tailed *t*-map of the main effect of delay-period activity for each subject [Conditional visuo-motor delay 1 + Conditional visuo-motor delay + Delayed-matching delay 1 + Delayed-matching delay 2], identifying suprathreshold voxels and extracting from them a spatially averaged time series, applying to this time series the orthogonal contrast of [(Conditional visuo-motor delay 1 + Conditional visuo-motor delay 2) − (Delayed-matching delay 1 + Delayed-matching delay 2)], and performing a paired *t*-test on the resultant *t*-values contributed by each subject. We tested our second hypothesis by extracting a spatially averaged time course from the voxels in the caudate nucleus ROI showing a main effect of delay-period activity, calculating the orthogonal contrasts of [(Conditional visuo-motor delay 1 − Conditional visuo-motor delay 2) − (Delayed-matching delay 1 − Delayed-matching delay 2)], and performing a paired *t*-test on the resultant *t*-values contributed by each subject. As in Experiment 1, this analysis would be repeated in M1 to confirm the mnemonic nature of this interaction.

3.3. Results

3.3.1. Single subject analyses

Analysis of delay-period activity in caudate nucleus ROIs revealed no overall effects of task (conditional visuo-motor, delayed matching) or of position in the delay (delay 1, delay 2)—a failure to reject the null hypotheses that there was no main effects of task. There was, however, a significant position effect (delay 1 > delay 2) in the conditional visuo-motor task in four of the six subjects, as contrasted with a significant position effect in two of the six subjects in the delayed-matching task (Fig. 2b). Suprathreshold voxels identified in the conditional visuo-motor task were located in the right head of the caudate nucleus in two subjects (JHa and JL), in the left head and left body of the caudate nucleus in one subject (WK), and bilaterally in the head of the caudate nucleus in one subject (JHo). There were no differences in probe-related activity in any subjects. Suprathreshold voxels identified in the delayed-matching task were overlapping with, or adjacent to, the voxels identified in the conditional visuo-motor task: right head and left body in one subject (JHa), and left head and left body in one subject (WK).

3.3.2. Group analyses

These revealed no significant effects of task or of position in the delay. The analysis of the task by delay-position interaction in caudate nucleus, however, revealed greater sensitivity to delay position in the conditional visuo-motor task than in the delayed-matching task in each of the five subjects for whom we performed this analysis ($t(4) = 6.9$; $p < .005$). (Data from one subject were excluded from the analyses because a significant difference between tasks in fMRI signal associated with cue presentation rendered analysis of delay-period activity equivocal [49].) This effect was not observed in frontal areas 9 and 46 or M1, or in posterior parietal area 7. Finally, there was no significant difference, at the group level, in probe-related activity.

3.4. Discussion

Delay-period activity of the caudate nucleus in the Experiment 2 showed greater time dependence in a task that featured spatial and motoric memory demands than in a comparable task requiring nonspatial memory. The motor effector function of the caudate nucleus, in contrast, did not differ in the two tasks. These results are consistent with the model, generated by the results of Experiment 1, of caudate nucleus working memory activity reflecting spatially mediated motor preparation. The spatial information needed for preparation of a motor plan was available to subjects with the presentation of the cue only on conditional visuo-motor trials. The reliable pattern of *delay 1* activity exceeding *delay 2* activity (significant in the group analysis as well as in the majority of the single subject analyses) suggests that this motor preparation takes place in the initial portion of the delay period.

The fact that caudate nucleus activity was greater during the first portion of the delay period of motor-set conditional visuo-motor trials suggests that the caudate nucleus modulation that we observed in the spatial condition of the what-then-where task in Experiment 1 did not reflect a 'ramping up' of caudate nucleus activity as the response drew nearer. Indeed, the delay-period behavior of caudate nucleus voxels in the conditional visuo-motor task of the motor-set experiment stands in contrast with such 'ramping up' behavior that Fuster observed in many prefrontal cortical neurons in monkeys performing this task, behavior that he characterized as 'motor set' activity [21]. Such motor-set activity has been observed in individual PFC voxels of the subjects who participated in this experiment, and is described elsewhere [15].

4. General discussion

The present study confirms that the caudate nucleus is an important neural locus of the dissociation between spatial and nonspatial visual working memory, as has been suggested by previous studies of PD patients [29,32,33]. Although the 'what'/'where' dissociation in human working memory has been demonstrated in behavioral [23,32,38,42] and electrophysiological [27] studies, and candidate cortical substrates have been identified in neuroimaging studies [12,14,31,38], the present report offers

the first evidence in humans that this dissociation may reflect more than simply an extension of the parallel, segregated spatial and nonspatial visual information processing pathways [43,45]. Our results suggest that spatial delay-period activity task performance may feature greater interaction with the motor system than does nonspatial delay-period activity. Spatial working memory must play an important role in planning and executing motor action in the service of behavioral objectives, and the data presented here suggest that the caudate nucleus is an important mediator of this function. One implication of the results of these two experiments is that the deficits observed in PD patients on tests of spatial memory [19,29,32,33,41] may reflect disrupted formulation of a motor response based on a spatially coded mnemonic representation, rather than a purely sensory deficit, as may have been predicted from previous models [8,25]. The present results are also not easily reconciled with a proposed role for the neostriatum in the governance of amodal strategic and general attentional processes [30], because they did not demonstrate reliable evidence for differential position- or time-dependent activity during delay periods of *nonspatial* working memory tasks.

Our results are consistent with the view that the caudate nucleus, with its central position in the motor system, is preferentially involved in spatial mnemonic processing because of the integral role of spatial information in the formulation motor behaviors [1,11]. An alternative model positing a role for the caudate nucleus in nonspatial working memory task performance, however, derives support from an autoradiographic study in monkeys that revealed topographical differences in caudate nucleus activity associated with performance of spatial and object delayed alternation tasks, with the former associated with activation of more anterior regions, and the latter with more posterior regions [26]. Our single subject analyses did not find reliable evidence for nonspatial delay-period activity in the caudate nucleus that was dependent on impending motor contingencies, nor did they reveal evidence of topographically dissociable patterns of spatial and nonspatial mnemonic activity. Our group analysis technique for contrasting spatial and object delay-related activity, however, did not permit an investigation of the possibility of topographically differential representation of spatial and nonspatial working memory. Rather, by collapsing across all voxels demonstrating delay-period activity, it represented a 'winner-take-all' approach. We opted for this approach to maximize our sensitivity to experimentally induced changes in activation. Methods affording greater sensitivity and higher spatial resolution than those employed in this study (e.g., fMRI at higher field strength) will be necessary to determine conclusively whether the human caudate nucleus participates preferentially in spatial working memory function, or whether topographical differences may also characterize differential representation of spatial and nonspatial working memory in the human caudate nucleus.

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