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Interaction between the Human Hippocampus and the Caudate Nucleus during Route Recognition

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Summary

Navigation through familiar environments can rely upon distinct neural representations that are related to different memory systems with either the hippocampus or the caudate nucleus at their core. However, it is a fundamental question whether and how these systems interact during route recognition. To address this issue, we combined a functional neuroimaging approach with a naturally occurring, well-controlled human model of caudate nucleus dysfunction (i.e., preclinical and early-stage Huntington's disease). Our results reveal a noncompetitive interaction so that the hippocampus compensates for gradual caudate nucleus dysfunction with a gradual activity increase, maintaining normal behavior. Furthermore, we revealed an interaction between medial temporal and caudate activity in healthy subjects, which was adaptively modified in Huntington patients to allow compensatory hippocampal processing. Thus, the two memory systems contribute in a noncompetitive, cooperative manner to route recognition, which enables the hippocampus to compensate seamlessly for the functional degradation of the caudate nucleus.

Introduction

Learning and memory relies on distinct memory systems, which are anatomically defined neural networks that support specific mnemonic operations (Gabrieli, 1998). Two examples of well-defined memory systems are the declarative memory system, which has the hippocampus as its central structure (Squire and Zola-Morgan, 1991; Squire et al., 2004), and the habit learning system, which has the basal ganglia at its core (Knowlton et al., 1996; Packard and Knowlton, 2002). In the past five decades (Scoville and Milner, 1957), memory research has focused on the dissociation between memory systems and the specification of their roles in information storage and behavioral adaptation. However, because the cognitive systems of the brain work in an integrated fashion, presumably the different memory systems do not work in isolation (White and McDonald, 2002). There is a growing body of evidence indicating that different memory systems interact intimately in some circumstances. Therefore, research has recently focused on investigating these interactions (Poldrack et al., 2001).

For example, the interaction between the hippocampus and the basal ganglia (in particular the caudate nucleus) in navigational memory has been investigated in rodents (Potegal, 1972; Packard et al., 1989; Packard and McGaugh, 1992, 1996). This research suggested that the caudate nucleus supports incremental learning of stimulus-response associations, or more specifically, the acquisition of place-appropriate responses leading to habitual behavior (White and McDonald, 2002). In contrast, the hippocampus is central to the rapid acquisition of declarative knowledge about the environment, generating a so-called cognitive map (O'Keefe and Nadel, 1978). It is thus suggested that both memory systems support navigational memory, albeit based on the processing of different representations (Packard and Knowlton, 2002; White and McDonald, 2002). It has been hypothesized that both systems work in parallel, receiving similar input information, but processing this information according to principles that emphasize different relationships among the elements of a given event or situation (White and McDonald, 2002; Packard and McGaugh, 1996). Consequently, functional neuroimaging studies in humans have indicated that both systems are involved in navigational memory and that their relative engagement depends on the strategy used by the subject. It has also been shown that these systems may be engaged sequentially in the course of training or familiarization with a virtual environment (Hartley et al., 2003; Iaria et al., 2003).

So far, human neuroimaging data have provided evidence for a competitive or interfering interaction between the caudate nucleus and the hippocampus (Poldrack et al., 2001), a successive involvement of the two systems at different stages of proficiency or a strategy-dependent participation of each system (Poldrack et al., 2001; Hartley et al., 2003; Iaria et al., 2003). In addition, animal studies have provided evidence for a noncompetitive interaction: the hippocampal system can, under suitable circumstances, compensate for caudate dysfunction, and the hippocampus thus provides means to sustain task performance at, or close to, normal levels (McDonald and White, 1995). One way to investigate whether such noncompetitive, compensatory mecha-

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nisms are present also in humans is to investigate a naturally occurring human lesion model in which one of the two systems is selectively dysfunctional. Preferably, dysfunction occurs in a graded fashion, so that the dysfunction of one system is behaviorally compensated (i.e., normal task performance is sustained) by a gradual increase in engagement of the other system. Furthermore, one may assume that the interaction between the caudate and hippocampal memory system is stronger in healthy subjects compared to patients with damage to one of the two systems.

To address this issue, we combined a lesion approach with functional neuroimaging, similar to a recent study of Parkinson patients that investigated the neural correlates of movement planning and motor selection (Dagher et al., 2001). A well-controlled human model of caudate dysfunction is provided by preclinical or early-stage Huntington's disease (HD). HD is a useful model for caudate dysfunction, because it is a genetically well-defined neurodegenerative disorder, which, in its early stages, is characterized by a selective, gradual dysfunction of the caudate nucleus with no or only mild atrophy (Harper, 1996; Vonsattel and Di Figlia, 1998). In line with the reasoning outlined above, we investigated whether caudate dysfunction, present to a varying degree in our sample of HD patients, would lead to a varying degree of compensatory activity in the hippocampus with normal or close to normal task performance in a navigational memory task.

In the present functional magnetic resonance imaging (fMRI) experiment, subjects had to memorize and recognize well-defined routes through virtual homes in a navigational memory task. The experiment included four conditions: route encoding, route recognition, visuomotor control, and a rest condition. To minimize possible confounds introduced by potential motor symptoms of the HD patients, we reduced the motor demands by using a simple two-alternative button-press response. Moreover, we compared only conditions with identical motor responses.

In accordance with previous imaging studies revealing caudate activation in navigational memory tasks (Hartley et al., 2003; Iaria et al., 2003; Maguire et al., 1998), we focused on the recognition part of the experiment and predicted that less impaired HD patients would show more recognition-related activity in the caudate nucleus and the relatively more impaired HD patients would show more recognition-related activity in the hippocampus, while at the same time their performance levels would be comparable. Such correlation between brain activity and disease severity will be corroborated if the healthy control subjects, with similar performance levels, show a stronger caudate and weaker hippocampal activity than the HD patients. Furthermore, with the caudate nucleus as the seed region, we predicted a greater psychophysiological interaction in the hippocampus of the healthy control subjects compared to the HD patients. This set of findings would indicate that the hippocampus interacts with the caudate nucleus during route recognition in healthy subjects in a noncompetitive manner and it would suggest that this interaction is adaptively modified in HD patients in a way that allows the hippocampus to compensate for basal ganglia dysfunction.

Table 1. Neuropsychological Test Results of HD Patients

	Mean (SD)	Classification
Memory		
Immediate Memory Index	85.5 (17.7)	low average
Auditory Immediate Index	88 (15.3)	low average
Visual Immediate Index	88.3 (15.5)	low average
General Memory Index	82.8 (13.7)	low average
Auditory Delayed Index	88.7 (16.1)	low average
Visual Delayed Index	84.8 (11.5)	low average
Auditory Recognition Delayed Index	82.9 (16.8)	low average
Working Memory Index	97.5 (8.1)	average
Intelligence		
Total Intelligence Index	95.3 (16.4)	average
Verbal Intelligence Index	91.3 (21)	average
Performance Intelligence Index	105 (19.7)	average
Left-Right Orientation		
Total score	27.8 (3.2)	normal

HD patients were tested on memory, intelligence, and left-right orientation using Dutch versions of the Wechsler Memory Scale (WMS-III, Wechsler, 1997a), Wechsler Adults Intelligence Scale (WAIS-III, Wechsler, 1997b; Wechsler et al., 2000), California Verbal Learning Test (CVLT, Delis et al., 1987; Buytenhuijs et al., 1994), and the Standardized Road Map Test of Directional Sense (Money, 1976).

Results

Task Performance

The neuropsychological characterization of the HD group is provided in Table 1. Route recognition performance was well above chance level (50%) in both groups (patients: mean correct = 65.2% [SD: 15.8], $t_{11} = 3.33$, $p < 0.01$; control subjects: mean correct = 72.2% [SD: 12.4], $t_{17} = 7.56$, $p < 0.01$) and did not differ significantly between groups ($t_{28} = -1.34$, n.s.). Moreover, the cognitive subscore of the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996; Table 2) estimating disease severity did not correlate significantly with route recognition performance in the HD group ($r = 0.47$, n.s.).

Structural Imaging Data

The HD patients investigated in the present study showed no or only subtle caudate atrophy. The comparison of the bicaudate ratio (BCR) of HD patients (mean BCR: 0.48 [SD: 0.1]) and normal control subjects (mean BCR: 0.40 [SD: 0.08]) just failed to reveal a statistically significant difference (Mann-Whitney $U = 64.0$, $p = 0.06$). The BCR was not reliably correlated with the cognitive subscore of the UHDRS ($r = -0.41$, n.s.). Furthermore, in line with previous reports (Vonsattel and Di Figlia,

Table 2. UHDRS Scores

	Mean	Range
Motor assessment	10.7 ± 9.7	0–29
Cognitive assessment	284 ± 50.7	184–350
Behavioral assessment	11.1 ± 12.5	0–41
Functional assessment	23.4 ± 2.3	19–25

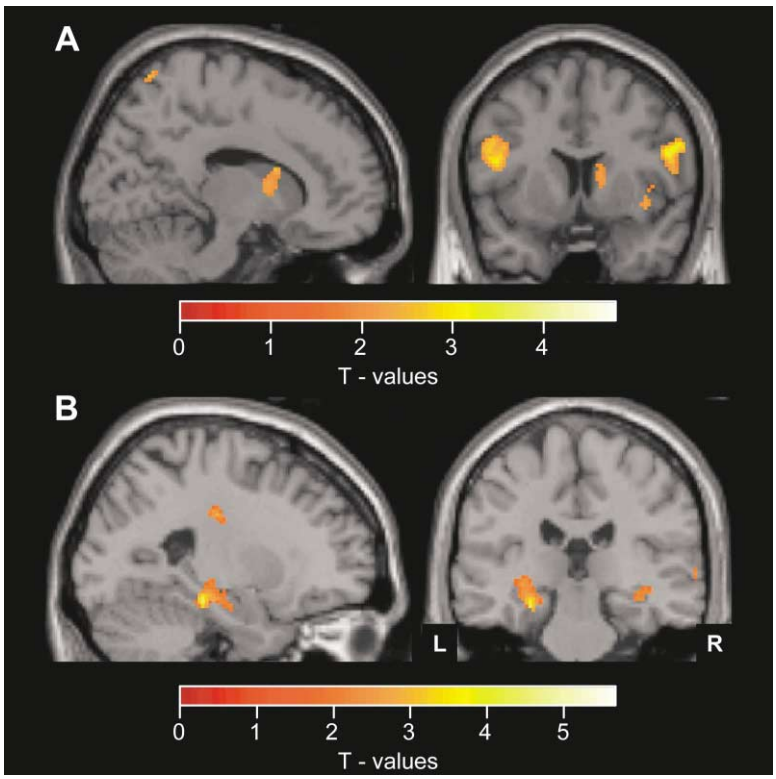

Figure 1. SPM[t] Showing the Significant Correlation between the Cognitive Score of the UHDRS and the Recognition versus Control Condition Activity

(A) A significant positive correlation, i.e., more activity with less severe impairment, was observed in the right caudate nucleus.

(B) In contrast, significant negative correlations, i.e., more activity with more severe impairment, was observed in the hippocampus bilaterally.

1998), the caudate atrophy in our sample of HD patients was highly symmetric (mean right-BCR: 0.48 [SD: 0.1], mean left-BCR: 0.47 [SD: 0.1]; $r = 0.88$, $p < 0.001$). Hence, a correlation between caudate activity and disease severity as well as differences in caudate activity between HD patients and healthy control subjects is unlikely to be related to asymmetric caudate atrophy or structural brain damage associated with HD but is likely related to caudate dysfunction per se.

Functional Imaging Data

We first investigated the correlation between the cognitive subscore of the UHDRS with the route recognition versus visuo-motor control activity. Thus, we used the UHDRS subscores as a regressor to explain the observed route recognition-visuo-motor control activity. The results showed a positive correlation in the right caudate nucleus (local maximum at [x y z] = [14 10 18]; $p = 0.017$, SVC FWE-corrected) between the recognition-related activity and the cognitive subscore. In contrast, disease severity was positively correlated with activity in the medial temporal lobe (MTL) bilaterally (right hippocampus/parahippocampal local maximum at [24 −6 −26], $p = 0.044$; left hippocampal local maximum at [−24 −28 −14], $p = 0.024$, SVC FWE-corrected). Thus, recognition-related activity of the hippocampus was positively correlated and of the right caudate nucleus negatively correlated with disease severity (see Figure 1).

Although performance did not correlate significantly with the cognitive subscore of the UHDRS, it cannot be entirely excluded that performance might explain part of the systematic variability related to the cognitive subscore. In order to investigate this and to estimate the relationship between the cognitive subscore and the recognition-related activity of the caudate as well as the MTL more conservatively, we included the performance scores as a confounding covariate in the above analysis, yielding similar results (right caudate [24, 4, 24], $p = 0.049$; right hippocampus/parahippocampal cortex [24 −6 −26], $p = 0.017$; left hippocampus [−22 −28 −12], $p = 0.018$, SVC FWE-corrected).

In order to confirm these observations, we predicted analogous results with respect to the caudate nucleus and the hippocampus in the comparison between the HD patients and the control group. This was indeed the case: in route recognition versus visuo-motor control, healthy control subjects showed significantly greater activity in the right caudate nucleus ([6 −2 10], $p = 0.011$, SVC FWE-corrected), and a similar effect was observed in route recognition versus route encoding ([6 14 2], $p = 0.028$, SVC FWE-corrected). Thus, in both comparisons, greater recognition-related activity was observed in the right caudate nucleus of the control subjects in comparison with HD patients, suggesting that this effect is related to route recognition rather than route encoding (see Figure 2). With respect to the MTL, the HD patients showed greater recognition-related activity compared to the control group in the right hippocampus ([40 −28 −16], $p = 0.017$, SVC FWE-corrected), in route recognition versus visuo-motor control, as well as in route recognition versus route encoding (right parahippocampal cortex [32 −32 −18], $p = 0.013$; [32 −30 −22], $p = 0.024$, SVC FWE-corrected). Thus, the HD patients showed greater right MTL activity compared to the healthy control subjects; again, specifically

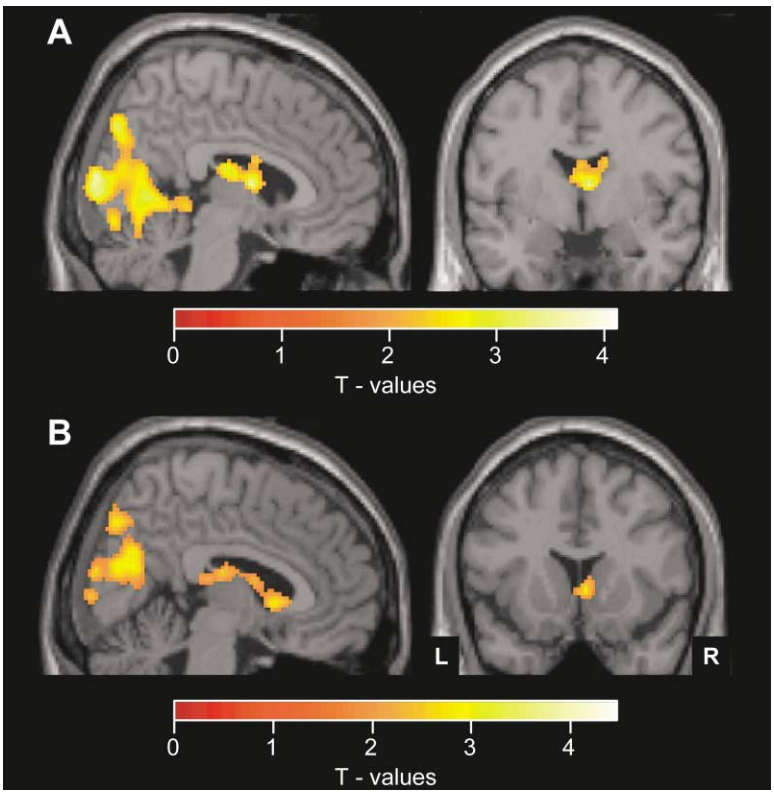

Figure 2. SPM[t] Showing Greater Activation in the Healthy Control Group Compared to the HD Patient Group

(A) Recognition versus visuo-motor control contrast: healthy controls showed significantly greater activity in the right caudate nucleus.

(B) Route recognition versus route encoding: a similar effect was also observed in route recognition versus route encoding.

for route recognition. When we included performance as a confounding covariate, similar results were observed (the control subjects showed greater activity in the right caudate nucleus [8 0 12], $p = 0.017$, SVC FWE-corrected, while the HD patients showed greater activity in the right MTL [40 −16 −22], $p = 0.027$, SVC FWE-corrected, in route recognition versus visuo-motor control; and in route recognition versus route encoding, healthy control subjects showed greater activity in the right caudate nucleus [8 12 2], $p = 0.009$, SVC FWE-corrected, while the HD patients showed greater activity in the right MTL [32 −32 −18], $p = 0.003$ and [32 −30 −22], $p = 0.003$, SVC FWE-corrected).

To characterize the relation between the caudate nucleus and the MTL more directly, we investigated the psychophysiological interaction (Friston et al., 1997) between these structures with respect to route recognition and visuo-motor control, using the caudate nucleus as the seed region. Group comparison showed a greater effect in the control subjects compared to the HD patients in the right anterior MTL (Figure 3). This effect reflects a stronger correlation of activity in the control group between the right caudate nucleus and the anterior hippocampus in route recognition compared to visuo-motor control ([26 −4 −26], $p = 0.010$, [16 −14 −20], $p = 0.018$, SVC FWE-corrected).

Although the main focus of the present study was on the interaction between the caudate nucleus and the hippocampus, additional results were obtained in the group comparison (see Table 3). Briefly, in route encoding versus visuo-motor control, control subjects showed greater activation in the right medial occipital-temporal region (cluster $p = 0.065$, corrected), and similar right medial occipital-temporal effects (cluster $p = 0.021$, corrected) were observed in route recognition versus visuo-motor control. Moreover, the control group showed greater left medial occipital-temporal activity (cluster $p = 0.014$, corrected) compared to the HD patients in route recognition versus route encoding. In contrast, the patient group showed greater activation of the frontal eye fields bilaterally (cluster $p = 0.069$, corrected) compared to the control group in the recognition versus encoding contrast. Finally, the control group showed a significantly greater psychophysiological interaction in the left middle/superior frontal region (cluster $p = 0.011$, corrected) and in the right anterior cingulate region (cluster $p = 0.007$, corrected) compared to the HD group (for further details concerning local maxima, see Table 3).

Discussion

The main finding of the present study was that the hippocampus in HD patients compensates for caudate dysfunction during route recognition, maintaining close to normal route recognition performance. This finding received further support from the results of the psychophysiological interaction, which suggested an increased interaction between the caudate nucleus and the MTL during route recognition in healthy subjects compared to the HD patients. This interaction appears to be adaptively modified in the HD patients to allow for more independent and presumably compensatory MTL processing. Hence, it appears that the two memory systems contribute in a parallel, noncompetitive way to route recognition as tested here. This suggests that the MTL is able to compensate seamlessly for the gradual functional deg-

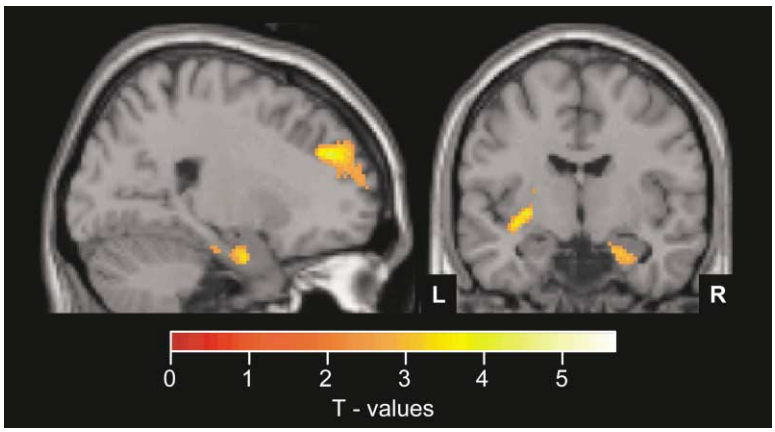

Figure 3. Psychophysiological Interaction between the Anterior Caudate Nucleus and the MTL Related to the Route Recognition versus Visuo-Motor Control Condition

The SPM[t] shows significantly greater psychophysiological interaction for control subjects than HD patients in the anterior hippocampus.

radation of the caudate nucleus. Hence, our findings provide an explanation for the common clinical observation that HD patients preserve route-recognition skills well into the course of the disease.

Although the two memory systems appear to be redundant in the route-recognition task, animal data have indicated that navigational information is stored in different representations by these two systems (Packard and Knowlton, 2002; White and McDonald, 2002). Routes can be stored as stimulus-response associations relying on the caudate nucleus. However, it has been suggested that these representations are not available for flexible use. Instead, they are tied to the re-occurrence of a specific stimulus context; hence, they can be readily used during repeated traveling of a given route. In contrast, a cognitive map of the environment, including the specific route, is represented in the hippocampus, and this representation is available for flexible use (Eichen-

Table 3. Significant Activation Clusters

Greater [Encoding-Baseline] Activation in the Control Group Compared to the HD Group		
Cluster $p = 0.065$ with local maxima ($p \leq 0.001$) at		[x y z]
Cuneus BA 17/18	$Z = 3.37$	[2 −88 10]
Right parahippocampal BA 30	$Z = 3.25$	[12 −48 −2]
Right lingual/fusiform BA 18/19	$Z = 3.06$	[12 −66 −6]
Lingual BA 18	$Z = 3.02$	[2 −70 −18]
Greater [Recognition-Baseline] Activation in the Control Group Compared to the HD Group		
Cluster $p = 0.021$ with local maxima ($p \leq 0.001$) at		
Cuneus BA 17/18	$Z = 3.57$	[2 −88 12]
Precuneus/cuneus BA 7/19	$Z = 3.42$	[0 −80 40]
Right lingual/fusiform BA 18/19	$Z = 3.10$	[12 −64 −4]
Right lingual BA 19	$Z = 3.06$	[10 −58 0]
Left superior parietal BA 7	$Z = 3.06$	[−14 −80 44]
Greater [Recognition-Encoding] Activation in the Control Group Compared to the HD Group		
Cluster $p = 0.014$ with local maxima ($p \leq 0.001$) at		
Precuneus BA 7	$Z = 3.95$	[−4 −76 42]
Cuneus BA 18	$Z = 3.18$	[−4 −88 18]
Greater [Recognition-Encoding] Activation in the HD Group Compared to the Control Group		
Cluster $p = 0.069$ with local maxima ($p \leq 0.001$) at		
Right middle frontal BA 6	$Z = 3.48$	[40 6 34]
Middle frontal BA 6	$Z = 3.39$	[38 2 36]
Middle frontal/precentral BA 6	$Z = 3.14$	[40 0 28]
Middle frontal BA 8	$Z = 3.10$	[34 12 34]
Greater Psychophysiological Interaction in the Control Group Compared to the HD Group		
Left middle/superior frontal cluster $p = 0.011$ with local maxima ($p \leq 0.001$) at		
Left middle/superior frontal gyrus BA 9/10	$Z = 4.55$	[−36 50 24]
Left middle frontal gyrus BA 10	$Z = 4.06$	[−30 56 20]
Left middle frontal gyrus BA 10	$Z = 4.06$	[−30 54 6]
Anterior cingulate cluster $p = 0.007$ with local maxima ($p \leq 0.001$) at		
ACC BA 24/32	$Z = 4.51$	[0 18 28]
Right ACC BA 24/32	$Z = 4.37$	[2 26 28]
Right ACC BA 24	$Z = 3.38$	[4 30 18]

Note: [x y z] coordinates according to the Montreal Neurological Institute (MNI) template (Evans et al., 1993).

baum et al., 1996). Hence, the learned route, and even alternative routes, can be recalled without actually traveling them and thus independently of any particular stimulus context. In the route-recognition task used here, the two navigational memory modes seem to be activated simultaneously and can support performance in parallel.

Previous studies, specifically addressing the ability to shift the cognitive strategy in response to different task conditions, have found caudate activation in navigational memory tasks after repeated training or exposure to the stimuli or when a certain strategy is imposed by the subject (Hartley et al., 2003; Iaria et al., 2003). These findings were interpreted as an involvement of the caudate nucleus in slowly evolving habit learning, which guides navigation in highly familiar environments. Our results indicate, however, that the caudate nucleus is not only involved after repeated training, but also after single-trial learning and thus in parallel with the hippocampus.

The interpretation that the caudate nucleus and the hippocampus support task performance based on distinct representations (either stimulus-response associations or cognitive-spatial information) might be challenged by a functional dissociation within the caudate nucleus found in rats (Devan and White, 1999). The results of that lesion study suggest that the medial and lateral part of the caudate nucleus and the putamen are functionally heterogeneous; the lateral subregion interacts competitively with the hippocampus based on distinct representations while the medial subregion interacts cooperatively with the hippocampus based on the same cognitive-spatial representation. Functional MRI is at present limited with respect to its localization precision at the group level, but our data suggest a medial focus in the caudate nucleus. Hence, our results are also consistent with the interpretation that the medial subregion of the caudate nucleus and the hippocampus are parts of a system that promotes navigational memory based on the same or a similar kind of representation, learned cognitive-spatial representation.

The observed differential caudate activation is unlikely to be a simple consequence of structural degeneration, as indicated by our structural investigation. In line with previous findings, we observed differential activity in the right caudate nucleus only (Hartley et al., 2003; Iaria et al., 2003; Maguire et al., 1998), while the subtle caudate atrophy observed was highly symmetric. This finding is in accordance with the previous literature as well as clinical experience, implying that caudate atrophy in HD generally lags behind clinical manifestation (Vonsattel and Di Figlia, 1998). Furthermore, the asymmetry of the caudate activations excludes a simple, systemic pharmacological effect introduced by the two patients taking neuroleptics that can affect basal ganglia activity. Finally, it is generally highly unlikely that the data of two subjects affect significantly a random effects analysis including either 12 or 30 subjects.

Our findings have clarified some aspects of the interaction between the caudate and medial temporal lobe memory systems but have also raised new questions. Demonstrating that compensation can occur between the hippocampus and the caudate nucleus leaves unanswered the question of how this compensation is precisely implemented and which neural pathways are involved. In principal, the significant psychophysiological interaction between the caudate nucleus and the MTL can be based on two mechanisms. There might be either a direct interaction between the two structures or alternatively there might be a third region driving the two: a direct interaction might be mediated by a direct anatomical link between the two systems, the cortico-striatal loop (Alexander et al., 1986). In contrast, the two systems might have a common outflow or interact via a third structure with a role in route recognition (e.g., the prefrontal cortex [cf. Packard and Knowlton, 2002; White and McDonald, 2002; Poldrack and Packard, 2003]).

In addition, our results do not clarify whether the interaction between the hippocampus and the caudate nucleus is symmetric bidirectional or not. To confirm a symmetric interaction with a balanced bidirectional cooperation between the hippocampus and the caudate nucleus, one has to test whether compensatory activation of the caudate nucleus occurs in case of hippocampal dysfunction. However, data from human lesion studies do not indicate that such compensation takes place, since patients with hippocampal or MTL lesions exhibit severe navigational memory deficits (Bohbot et al., 1998, 2000; but see Ramos, 2000). Nevertheless, the navigational memory deficit might be more severe following combined lesions of the caudate nucleus and the hippocampus than after an isolated lesion of the hippocampus, arguing for a partial compensation by the caudate nucleus. Following the idea of complementary but different types of representations supported by the two memory systems, one cannot expect that route-like representation can compensate for a map-like representation in all circumstances. However, a map-like representation should be able to compensate for a route-like representation. Thus, it is likely that the caudate-hippocampal interaction is asymmetric if it is based on two distinct memory systems. In other words, the hippocampal system can compensate fully for caudate dysfunction, but not vice versa.

Regardless of the mechanism or pathway(s) involved and whether this interaction is bidirectional or not, our results indicate that the two memory systems can interact noncompetitively during route recognition after single-trial learning and that this interaction seamlessly enables normal or close to normal route recognition in patients with caudate nucleus dysfunction by a gradual increase of compensatory hippocampal activity.

Experimental Procedures

Participants

Fourteen participants with genetically confirmed Huntington's disease (HD) were initially enrolled, but two were excluded from further investigations due to claustrophobic symptoms in the scanner. Thus, we completed the investigation of 12 HD patients (3 female, 9 male; mean age = 49 years [SD = 10]; mean CAG trinucleotide repeats: 44 [range: 40–47]; mean disease duration: 1.3 years [range: 0–4]; mean number of years of formal education = 12.6 [SD = 3]). To avoid patients with more general, unspecific brain damage and wide-ranging cognitive and motor impairments, which would affect performance in the task used for fMRI, we only included preclinical and moderately impaired HD patients without severe memory or intelligence deficits and with normal left-right orientation (Table 1). Nevertheless, we were able to include HD patients with a moderate spectrum of disease severity as confirmed by the wide range of

disease severity scores (Table 2) obtained by using the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996). This spectrum of disease severity enabled us to investigate the compensation account by a correlative approach as outlined above.

In addition, 18 healthy control subjects participated in the study (4 female, 14 male; mean age = 49 years [SD = 11]; mean number of years of formal education = 12.6 [SD = 3]). The patient and the control group were matched for age (t_{28} = 0.09, n.s.), duration of formal education (t_{28} = 0.28, n.s.), gender (proportion of women: 0.33 versus 0.29), and handedness. All but one HD patient and two control subjects were strongly right-handed as indexed by an Edinburgh handedness index $\geq$ 90 (Oldfield, 1971).

Eight patients and two control subjects used regular medication (patients: prednisone, zuclopenthixol, olanzapin, paroxetine, oxazepam, simvastatin; controls: captopril, nifedipine, hydorchlorthiazide). Two of the twelve patients took drugs that interfere with cerebral dopamine action and basal ganglia function: zuclopenthixol (strong basal ganglia effect) and olanzapin (weak basal ganglia effect). One patient took 2 mg zuclopenthixol daily (recommended dosage: 10–50 mg/day) and another patient took 10 mg olanzapin (recommended dosage: 5–15 mg/day). None had a history of drug abuse, head trauma, or psychiatric disorder other than related to HD. All subjects had normal or corrected-to-normal vision. Written informed consent was obtained according to the Declaration of Helsinki, and the local medical ethics committee approved the study.

Stimulus Material

We constructed 16 video sequences of ground-level first-person indoor routes through virtual environments, each showing different furnished home and lasting 31 s using Traumhaus Designer 4.0 software (http://www.databecker.de). The homes were approximately of the same size and similar topology. Moreover, they contained the same number of furniture and common everyday objects. Each video sequence depicted a fixed route through the different rooms of the homes and included five decision points (intersections). Two arrowheads, indicating left, right, or straight ahead, appeared at every decision point for 2.5 s accompanied by a freeze of the video sequence for 2 s. In the route-encoding condition, one arrowhead was yellow (predicting the direction where the "travel" will go) and the other red. During the route-recognition condition, both arrowheads were red. The interval between each decision point was 3.5 s. For the visuo-motor control task, one additional virtual environment was constructed, which depicted an empty, straight hallway. Here, the video sequence showed the same straight "walk" and two arrowheads at the end of the hallway (one in yellow and one in red) for five times. The timing of this control video sequence was identical to the other sequences described.

Procedures

The experiment included four conditions: route encoding, visuo-motor control, rest, and route recognition. Each condition cycle started with a route-encoding condition and ended with a route-recognition condition, with the order of the control and rest condition randomly changing over cycles. Before entering the MR scanner, subjects practiced the task in two cycles with virtual homes not used during the experiment. In the scanner, video sequences were presented by a computer using ERTS software (http://www.erts.de) for stimulus presentation and response recording. Stimuli were back-projected via an LCD projector onto a translucent screen, which subjects viewed through a mirror mounted at the head coil. Subjects responded with an optical button device held in their dominant hand. Altogether, the experiment consisted of 14 cycles, separated into two runs of seven cycles each. Across subjects, two versions of the experiment were used, differing in the order of cycles only. The subject's head was immobilized using a vacuum cushion to reduce head motion.

Route Encoding

While the subjects viewed a video sequence of a virtual home, they were instructed to remember the directions taken at each of the five decision points (left, right, straight ahead) and to press the respective button on the button-box to confirm the direction indicated by the yellow arrowhead and subsequently taken by the video sequence. Each cycle started by indicating to the subject that a new house had to be learned.

Visuo-Motor Control

Subjects "traveled" repeatedly along the same empty hallway. When they saw the yellow and the red arrowhead at the end of the hallway, they were instructed to press the button assigned to the direction indicated by the yellow arrowhead.

Rest

During the rest period, the display showed a white, central fixation cross on a black background and no response was required. Subjects were instructed to fixate and concentrate on scanner noise.

Route Recognition

Subjects saw the same video sequence as shown previously during the route-encoding condition of the same cycle. They were instructed to specify by appropriate button-press as fast and accurately as possible the correct of the two alternative directions indicated by two red arrowheads at each decision point. If the subject made an incorrect response, the video continued with the predetermined sequence.

MRI Data Acquisition

During MRI scanning, whole-head T2*-weighted EPI-BOLD fMRI data were acquired with a Siemens Sonata 1.5 T MR-scanner using an interleaved slice acquisition EPI sequence (volume TR = 1.93 s, TE = 30 ms, 90° flip angle, 28 axial slices aligned with the AC-PC plane, slice-matrix size = 64 $\times$ 64, slice thickness = 3.5 mm, slice gap = 0.5 mm, field of view = 224 mm, voxel size = 3.5 $\times$ 3.5 $\times$ 3.5 mm) in a blocked design. For structural high-resolution MRI, we acquired a T1-weighted MP-RAGE sequence (volume TR = 2250 ms, TE = 3.93 ms, 15° flip angle, 176 axial slices aligned with the AC-PC plane, slice matrix size = 256 $\times$ 256, slice thickness = 1 mm, slice gap = 0 mm, field of view: 256 mm, voxel size = 1 $\times$ 1 $\times$ 1 mm).

Structural MRI Analysis

To estimate caudate nucleus atrophy, we measured the bicaudate ratio (BCR) on axial slices of the structural high-resolution MRI as described elsewhere (Aylward et al., 1991). In short, the BCR is the ratio of the bicaudate distance (minimum distance between the frontal horns of the lateral ventricles) and the bifrontal distance (maximum distance between the frontal horns of the lateral ventricles). In addition, to estimate the symmetry of caudate nucleus atrophy, we calculated the BCR index separately for the right and left hemisphere, resulting in a right BCR and a left BCR.

Functional MRI Data Analysis

Image preprocessing and statistical analysis was performed using the SPM99 software (http://www.fil.ion.ucl.ac.uk). The functional EPI-BOLD images were realigned and the subject mean were coregistered with the corresponding structural MR images using mutual information optimization. These were subsequently spatially normalized (i.e., the normalization transformations were generated from the structural images and applied to the functional images) and transformed into a common space, as defined by the SPM99 MNI T1 template (Evans et al., 1993), and finally spatially filtered by convolving the functional images with an isotropic 3D Gaussian kernel (8 mm FWHM). The fMRI data were proportionally scaled to account for global effects and analyzed statistically using the general linear model and statistical parametric mapping (Friston et al., 1995). The linear model included convolved explanatory variables (regressors), modeling the encoding, the retrieval, and visuo-motor control conditions using boxcar regressors. The explanatory variables were temporally convolved with the canonical hemodynamic response function. In addition, the linear model included the session/subject effects and a temporal high-pass filter to account for various low-frequency effects. In order to account for temporal autocorrelation, the fMRI data were convolved with a Gaussian (FWHM = 4 s) temporal kernel, and effective degrees of freedom estimated (Worsley and Friston, 1995).

For the statistical analysis, relevant contrasts parameter images were generated for each subject and these were subsequently subjected to a second-level random effects analysis. The performance scores were included as a confounding covariate when relevant and

it turned out that the reported results did not depend strongly on whether performance was taken into account or not (see Results). In the whole brain search, the results from the random effects analyses were thresholded at $t_{28} = 2.72$ and the cluster size was used as the test statistic. Only clusters significant at $p < 0.1$ (corrected for multiple nonindependent comparisons; Worsley et al., 1996) are described. The significant clusters were resolved into peak-height of local maxima, and only local maxima significant at the level $p < 0.001$ (uncorrected) are reported. In the regional-specific search (i.e., with respect to the MTL and the caudate nucleus), the results from the random effects analyses were thresholded at $t_{28} = 2.46$ and nearest significant cluster to [x y z] = [30 −20 −14] and [14 8 14] in the MTL and caudate nucleus, respectively, and they were investigated in combination with small volume correction (SVC) based family-wise error (FWE) correction. The same procedure was used in the psychophysiological interaction investigations. In the analysis of psychophysiological interactions, we followed standard procedures (Friston et al., 1997). Basically, in the psychophysiological interactions approach, we investigated how the functional connectivity between regions changes with experimental condition. In other words, a seed voxel was chosen in the right caudate nucleus [14 8 14] and the observed BOLD fMRI time series was extracted. The condition × caudate activity interaction (= the psychophysiological interaction) was then generated from the extracted time series and the two condition regressors and subsequently orthogonalized with respect to the condition and the caudate-activity regressors in order to conservatively estimate any effect. A design matrix of regressors is then created, including the two condition regressors, the caudate-activity regressor and the psychophysiological interaction regressor, and the effects related to the psychophysiological interaction estimated. The estimated psychophysiological interactions from all subjects are then subjected to a second-level random effects analysis in order to evaluate group differences as outlined above.

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References

Alexander, G.E., DeLong, M.R., and Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. *9*, 357–381.

Aylward, E.H., Schwartz, J., Machlin, S., and Pearlson, G. (1991). Bicaudate ratio as a measure of caudate volume on MR images. AJNR Am. J. Neuroradiol. *12*, 1217–1222.

Bohbot, V.D., Kalina, M., Stepankova, K., Spackova, N., Petrides, M., and Nadel, L. (1998). Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia *36*, 1217–1238.

Bohbot, V.D., Allen, J.J., and Nadel, L. (2000). Memory deficits characterized by patterns of lesions to the hippocampus and parahippocampal cortex. Ann. N Y Acad. Sci. *911*, 355–368.

Buytenhuijs, E.L., Berger, H.J., Van Spaendonck, K.P., Horstink, M.W., Borm, G.F., and Cools, A.R. (1994). Memory and learning strategies in patients with Parkinson's disease. Neuropsychologia *32*, 335–342.

Dagher, A., Owen, A.M., Boecker, H., and Brooks, D.J. (2001). The role of the striatum and hippocampus in planning: a PET activation study in Parkinson's disease. Brain *124*, 1020–1032.

Delis, D.C., Kramer, J.H., Kaplan, E., and Ober, B.A. (1987). The California Verbal Learning Test—Research Edition (San Antonio, TX: The Psychological Corporation).

Devan, B.D., and White, N.M. (1999). Parallel information processing in the dorsal striatum: relation to hippocampal function. J. Neurosci. *19*, 2789–2798.

Evans, A.C., Collins, D.L., Mills, S.R., Brown, R.D., Kelly, R.L., and Peters, T.M. (1993). 3D statistical neuroanatomical models from 305 MRI volumes. Proc. IEEE Nucleic Sci. Symp. Med. Imag. Conf., 1813–1817.

Eichenbaum, H., Schoenbaum, G., Young, B., and Bunsey, M. (1996). Functional organization of the hippocampal memory system. Proc. Natl. Acad. Sci. USA *93*, 13500–13507.

Friston, K.J., Frith, C.D., Frackowiak, R.S., and Turner, R. (1995). Characterizing dynamic brain responses with fMRI: a multivariate approach. Neuroimage *2*, 166–172.

Friston, K.J., Büchel, C., Fink, G.R., Morris, J., Rolls, E., and Dolan, R.J. (1997). Psycho-physiological and modulatory interactions in neuroimaging. Neuroimage *6*, 218–229.

Gabrieli, J.D. (1998). Cognitive neuroscience of human memory. Annu. Rev. Psychol. *49*, 87–115.

Harper, P.S. (1996). Huntington's Disease, Second Edition (London: Saunders Company Ltd).

Hartley, T., Maguire, E.A., Spiers, H.J., and Burgess, N. (2003). The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans. Neuron *37*, 877–888.

Huntington Study Group (1996). Unified Huntington's Disease Rating Scale: reliability and consistency. Mov. Disord. *11*, 136–142.

Iaria, G., Petrides, M., Dagher, A., Pike, B., and Bohbot, V.D. (2003). Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. J. Neurosci. *13*, 5945–5952.

Knowlton, B.J., Mangels, J.A., and Squire, L.R. (1996). A neostriatal habit learning system in humans. Science *273*, 1399–1402.

Maguire, E.A., Burgess, N., Donnett, J.G., Frackowiak, R.S., Frith, C.D., and O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. Science *280*, 921–924.

McDonald, R.J., and White, N.M. (1995). Hippocampal and non-hippocampal contributions to place learning. Behav. Neurosci. *109*, 579–593.

Money, J.A. (1976). A Standardized Road Map Test of Directional Sense (San Rafael, CA: Academic Therapy Publications).

O'Keefe, J., and Nadel, L. (1978). The Hippocampus as a cognitive map (Oxford, UK: Oxford University Press).

Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia *9*, 97–113.

Packard, M.G., and Knowlton, B.J. (2002). Learning and memory functions of the basal ganglia. Annu. Rev. Neurosci. *25*, 563–593.

Packard, M.G., and McGaugh, J.L. (1992). Double dissociation of fornix and caudate nucleus lesions on acquisition of two water maze tasks: further evidence for multiple memory systems. Behav. Neurosci. *106*, 439–446.

Packard, M.G., and McGaugh, J.L. (1996). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. Neurobiol. Learn. Mem. *65*, 65–72.

Packard, M.G., Hirsh, R., and White, N.M. (1989). Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. J. Neurosci. *9*, 1465–1472.

Poldrack, R.A., and Packard, M.G. (2003). Competition among multiple memory systems: converging evidence from animal and human brain studies. Neuropsychologia *41*, 245–251.

Poldrack, R.A., Clark, J., Pare-Blagoev, E.J., Shohamy, D., Creso Moyano, J., Myers, C., and Gluck, M.A. (2001). Interactive memory systems in the human brain. Nature *414*, 546–550.

Potegal, M. (1972). The caudate nucleus egocentric localization system. Acta Neurobiol. Exp. *32*, 479–494.

Ramos, J.M. (2000). Long-term spatial memory in rats with hippocampal lesions. Eur. J. Neurosci. *12*, 3375–3384.

Scoville, W.B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatry *20*, 11–21.

Squire, L.R., and Zola-Morgan, S. (1991). The medial temporal lobe memory system. Science *253*, 1380–1386.

Squire, L.R., Stark, C.E.L., and Clark, R.E. (2004). The medial temporal lobe. Annu. Rev. Neurosci. *27*, 279–306.

Vonsattel, J.P., and DiFiglia, M. (1998). Huntington disease. J. Neuropathol. Exp. Neurol. *57*, 369–384.

Wechsler, D. (1997a). The Wechsler Memory Scale, Third Edition (San Antonio, TX: The Psychological Corporation).

Wechsler, D. (1997b). The Wechsler Adult Intelligence Scale, Third Edition (San Antonio, TX: The Psychological Corporation).

Wechsler, D., Van der Steene, G., Vertommen, H., Bleichrodt, N., and Uiterwijk, J.M. (2000). WAIS-III. Nederlandstalige bewerking (Amsterdam: Lisse, Swets & Zeitlinger).

White, N.M., and McDonald, R.J. (2002). Multiple parallel memory systems in the brain of the rat. Neurobiol. Learn. Mem. *77*, 125–184.

Worsley, K.J., and Friston, K.J. (1995). Analysis of fMRI time-series revisited—again. Neuroimage *2*, 173–181.

Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., and Evans, A.C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. Hum. Brain Mapp. *4*, 58–73.