PAPER

Differential impairment of spatial location memory in Huntington's disease

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Objective: To determine whether a differential impairment of spatial memory exists in Huntington's disease (HD).
Methods: Patients with HD and age matched neurologically normal subjects, as well as patients with Alzheimer's disease (AD) and Parkinson's disease (PD), learned the locations of nine items on a 3×3 grid over as many as 10 trials. Delayed recall of the items and their spatial locations was tested.
Results: Patient with HD performed worse than normal subjects on all measures, and intermediate between AD and PD patients. However, they were the only subject group in whom delayed recall of spatial locations was poorer than delayed recall of object identity. This effect was independent of the severity of dementia.
Conclusions: HD patients have a differential impairment in memory for object–location information. This finding may relate to the involvement of the caudate nucleus, the primary site of pathology in HD, in corticostriatal circuits linking it with parietal association cortex. It is also consistent with views of the dorsal striatum as responsible for the acquisition over trials of specific place responses.

Impairments in aspects of executive control and memory are the most conspicuous cognitive alterations in early to mid-stage Huntington's disease (HD).[1 2] However, these patients typically have significant deficits in spatial cognition as well.[3–6] The severity of these spatial impairments may be overlooked or underappreciated in the face of patients' motor impairments. Indeed, we recently reported that patients with HD have much more severe spatial deficits than patients with equivalently severe movement disorders due to cerebellar degeneration.[7]

The present study evaluated learning and memory of object identity and spatial location in a large group of patients with HD. Patients with Alzheimer's disease (AD) and those with Parkinson's disease (PD) served as neurological comparison groups, and clinically healthy persons served as a normal control group.

METHODS

Subjects

We studied 110 patients with definite HD during annual research visits to the Baltimore Huntington's Disease Project at the Johns Hopkins Hospital, Baltimore, MD, USA. All patients were diagnosed by a positive family history, presence of choreiform movements or voluntary motor impairment, and cognitive or emotional changes.[8] All had an expanded triplet repeat mutation (*CAG* ⩾36) in the *huntingtin* gene.[9 10]

A total of 143 patients with the clinical diagnosis of possible or probable AD were studied in the context of annual assessments at the Johns Hopkins Alzheimer's Disease Research Center. In each case, the diagnosis of AD was made by an experienced behavioural neurologist or neuropsychiatrist based on NINCDS-ADRDA criteria.[11] In cases for which a consensus diagnosis conference was held (the majority), those diagnoses were used.

We also studied 77 patients with idiopathic PD as part of their baseline evaluations in the Johns Hopkins Parkinson's Disease Research Center. In all cases, movement disorder specialists made the diagnosis of PD using the UK Brain Bank clinical criteria.[12] No patient with PD met the criteria for AD or dementia with Lewy bodies.

Finally, we studied a group of 147 neurologically normal individuals. To compare the control sample with the patient samples, we divided the control group into a younger subgroup (age <65 years, matched in age to the HD group), and an older subgroup (age ⩾65 years).

Procedures

First we showed the subjects nine stimulus cards, one at a time, in haphazard order. Each card had a line drawing of a common object on it, which the subjects were asked to name. The objects were chosen to be as universally recognisable and namable as possible (for example, an ear, a tree).[13] Responses were recorded verbatim, and errors were corrected.

Next, the nine cards were placed in predetermined positions on a 35.56×35.56 cm (14″×14″) board on which a 3×3 grid was drawn. The examiner said, ''Watch me as I place these pictures on this board. Try to remember where they go, because I am going to ask you to put them in the same places.'' After all nine stimulus cards were placed, an additional 20 seconds of study was allowed. The cards were then removed, shuffled, and handed one at a time to the subjects who attempted to place them in their original positions. Incorrect placements were scored as errors and were immediately corrected. This procedure was repeated until two consecutive trials with no errors (that is, correct placement of all nine cards) were achieved, up to a maximum of 10 trials. Both errors to criterion and trials to criterion were tallied.

After 20–30 minutes, the subjects were asked to recall the names of the pictures, providing a measure of delayed item memory. They were then handed the deck of nine cards and asked to place the cards on the board in their original locations. No feedback was provided, but subjects were

Abbreviations: AD, Alzheimer's disease; HD, Huntington's disease; MMSE, Mini-Mental State Examination; PD, Parkinson's disease

allowed to rearrange the cards until they were satisfied. The number correctly placed provided a measure of delayed spatial memory.

Collectively, these test procedures have come to be known as the "Hopkins Board". More detailed administration instructions and scoring rules appear in a preliminary test manual,[14] available on request from the first author.

All subjects gave informed consent to this testing in the context of their participation in research protocols that were fully reviewed and approved by the Johns Hopkins Institutional Review Board.

RESULTS

The characteristics of the five subject groups and their performance on the Hopkins Board appear in table 1. The patients with HD are well matched in age and sex distribution with the young normal subjects, but they had slightly fewer years of education ($t_{165} = 2.72$, $p<0.007$). As a result, statistical comparisons covaried for education.

Learning spatial location

A total of 41 HD patients, 107 AD patients, 14 PD patients, and 11 older normal subjects failed to learn the locations all nine objects in 10 trials and were therefore assigned the default trials to criterion score of 10. Their data are included in the analyses.

Although the patients with HD had no difficulty naming the nine objects, they performed more poorly than their age matched normal peers on initial learning of the Hopkins Board. Whether measured by errors to criterion ($F_{1,164} = 39.55$, $\eta^2 = 0.194$, $p<0.001$) or trials to criterion ($F_{1,164} = 76.10$, $\eta^2 = 0.317$, $p<0.001$), the HD patients were severely impaired. The learning performance of the HD group was intermediate between that of the AD and PD groups.

Delayed recall of items and locations

Among the normal control subjects, delayed recall of the identity of test items was slightly worse than recall of their spatial locations (paired $t_{146} = 4.09$, $d = 0.338$, $p<0.001$). Compared with the young normal group, the HD group was impaired on both delayed recall measures (group $F_{1,164} = 41.67$, $\eta^2 = 0.203$, $p<0.001$). But whereas the young normal subjects had higher location scores than item scores, the reverse pattern was seen in the HD patients (interaction $F_{1,164} = 6.60$, $\eta^2 = 0.038$, $p = 0.01$).

HD compared with other dementias

The mean score for location recall was higher than the mean score for item recall for both the AD and PD groups, as well as the normal groups. Delayed recall scores of the three patient groups were compared with a 3×2 (group by recall type) repeated measures analysis of covariance (ANCOVA), with education as the covariate (fig 1). Eleven AD patients and one PD patient had missing data on one or both of these variables and were excluded from the analysis. A significant interaction was found between group and recall type ($F_{2,314} = 31.59$, $\eta^2 = 0.168$, $p<0.001$). Both AD and PD patients were better at recalling spatial locations than the names of the nine items, whereas the opposite was true for the HD patients. The group effect was also statistically significant ($F_{2,314} = 177.52$, $\eta^2 = 0.531$, $p<0.001$), but the education effect was not ($F_{1,314} = 1.473$, $\eta^2 = 0.005$, $p = 0.226$).

Influence of dementia severity

To determine whether the apparent impairment in spatial memory in HD is a product of severity of dementia, each of the three patient groups was stratified by level of functional impairment. Different functional impairment scales are used in the three research centres from which the patients were drawn. For the HD group, the Huntington's Disease Activities of Daily Living (HD-ADL) Scale[15 16] was used to divide the sample into minimally impaired (score $\leqslant 5$), mildly impaired (score 6–20), and moderately impaired (score $\geqslant 21$) subgroups. For the AD patients, the Clinical Dementia Rating

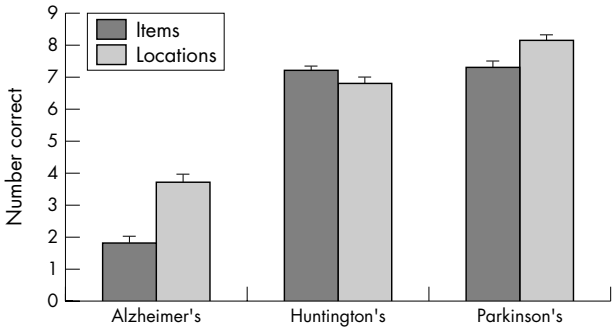

Figure 1 Delayed recall of items and their spatial location in Huntington's disease (n = 110), compared with Alzheimer's disease (n = 132) and Parkinson's disease (n = 76). Analyses covaried for education. Values are mean (SD).

Table 1 Performance on the Hopkins Board of patients with Huntington's disease, Alzheimer's disease, and Parkinson's disease, as well as younger (age <65) and older (age ⩾65) normal control subjects. Values are mean (SD), except where noted

	Huntington's disease	Alzheimer's disease	Parkinson's disease	Normal	
				Young	Old
N	110	143	77	57	90
Age (years)	49.44 (12.35)	73.05 (9.22)	63.83 (9.93)	50.04 (10.61)	72.70 (4.76)
Sex (men:women)	48:62	56:87	53:24	18:39	35:55
Education (years)	14.52 (2.81)	12.89 (3.94)	16.51 (3.12)	15.74 (2.63)	15.20 (2.87)
Duration of illness (years)	7.68 (5.00)	3.91 (2.75)	10.09 (7.36)	N/A	N/A
Mini-Mental State Examination (score)	25.65 (3.15)	19.11 (5.49)	27.57 (2.54)	29.14 (1.00)	28.40 (1.44)
Hopkins Board					
Naming (range 0–9)	8.92 (0.31)	8.30 (1.14)	8.74 (0.66)	9.00 (0.00)	8.89 (0.15)
Errors to criterion (range 0–68)*	16.53 (15.09)	39.62 (20.88)	8.78 (10.77)	2.96 (4.61)	4.67 (6.34)
Trials to criterion (range 2–10)	7.86 (2.79)	9.27 (1.85)	6.10 (3.08)	3.98 (2.30)	4.98 (2.86)
Delayed item recall (range 0–9)	7.21 (1.62)	1.93 (2.50)	7.30 (1.88)	8.42 (0.82)	7.87 (1.21)
Delayed location recall (range 0–9)	6.83 (2.14)	3.82 (2.92)	8.18 (1.55)	8.70 (0.76)	8.42 (1.08)

*Testing was discontinued if the subject made six or more errors on two consecutive trials. Six errors (representing chance performance) are recorded for each non-administered trial.

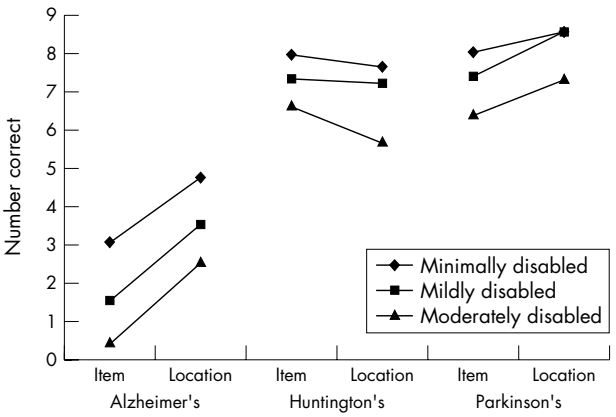

Figure 2 Delayed recall of visual objects and spatial locations in dementia as a function of impairment in everyday activities. Analyses covaried for education.

(CDR) Scale[17] was used to create minimally impaired (CDR = 0.5), mildly impaired (CDR = 1), and moderately impaired (CDR ⩾2) subgroups. For the PD patients, the Instrumental Activities of Daily Living (IADL) Scale[18] was used to create minimally, mildly, and moderately disabled subgroups (scores ⩽8, 9–13, and ⩾14, respectively). Delayed recall of locations was superior to delayed recall of items at every level of functional impairment for both the AD and PD patients (fig 2). This was not the case for any level of functional impairment for the HD patients. In a confirmation of this, a 3×3×2 (group by functional level by recall-type) repeated measures ANCOVA yielded a modest effect size for the group by recall-type interaction ($F_{2,308} = 28.11$, $\eta^2 = 0.154$, $p<0.001$). However, neither of the two way interactions involving functional level nor the three way interaction was significant.

To evaluate further the selectivity of the spatial memory defect in HD, groups of HD and AD patients, matched for overall cognitive performance, were compared. By selecting the AD patients with the highest MMSE scores (⩾18) and the HD patients with the lowest MMSE scores (⩽25), well matched groups were constructed (table 2). Although the AD patients had greater difficulty than the HD patients in learning the spatial locations of the stimuli (as reflected in their higher errors to criterion), their recall of the locations was better than their recall of the item themselves; this was not the case for the HD patients (interaction $F_{1,131} = 26.51$, $\eta^2 = 0.168$, $p<0.001$).

DISCUSSION

The patients with HD were impaired on all components of the Hopkins Board, but they displayed disproportionate impairment in memory for spatial locations. This differential impairment refers both to the cognitive deficit (that is, location memory being worse than item memory) as well as the patient group (that is, the impairment not being seen in equivalently or even more severely demented AD or PD patients). Thus, the findings do not reflect simply a generalised deficit.

Previous studies have typically found that HD patients have substantial impairments in egocentric (body position dependent) spatial orientation but, at most, only mild impairments in allocentric spatial processing (location of objects in extrapersonal space, irrespective of body location).[3 4] In addition, animal studies have generally revealed impairments in egocentric but not allocentric spatial memory after striatal lesions.[19] Although the methods of the present study do not allow us to determine whether performance of the Hopkins Board requires the processing of egocentric or allocentric representations (since there is no manipulation of body position *vis a vis* the to-be-remembered stimuli), several previous studies have purported to find deficits in allocentric as well as egocentric spatial memory in HD. Davis *et al*[20] found relatively greater impairment in memory for spatial locations than objects among 13 patients with HD. However, since the patients in that study were compared with only neurologically normal subjects, it is unclear whether the spatial memory deficit was simply a consequence of brain disease or dementia generally, or was specific to HD. A second study by the same investigators[21] found that patients with HD performed more poorly than normal subjects on both recognition of sequential hand positions (described as a test of egocentric spatial memory) and recognition of spatial locations (an allocentric task). Using self-ordered memory tasks, Lawrence and colleagues[2 5] found spatial working memory to be impaired in HD and "visual object" (actually, design) working memory to be intact. However, this latter observation appears to be in conflict with some of Lawrence's other findings of object/pattern memory deficits in HD, as well as Rich *et al*'s[22] finding of impaired self-ordered memory for abstract designs.

The particular vulnerability of spatial location memory in HD might be understood by considering the relation of the caudate nucleus, the major site of pathology early in HD, to visual association areas. It is well established that there are two major pathways, or streams, of visual information processing in the primate cortex: a ventral stream, projecting from striate cortex to inferior temporal lobe, concerned with the processing of object identity (the "what" of visual cognition) and a dorsal stream, projecting from striate cortex to the superior posterior parietal cortex, coding the location of objects in space (the "where" of visual cognition).[23 24]

Table 2 Performance on the Hopkins Board of Huntington's and Alzheimer's patient groups matched for mean Mini-Mental State Examination score. Values are mean (SD)

	Huntington's disease	Alzheimer's disease	p value
No of patients	48	90	
Age (years)	49.40 (14.18)	73.06 (9.58)	<0.001
Sex (men:women)	17:31	39:51	0.367
Education (years)	13.29 (2.41)	13.42 (3.74)	0.808
Duration of illness (years)	8.63 (5.22)	3.71 (2.98)	<0.001
Mini-Mental State Examination (score)	22.71 (2.13)	22.39 (3.08)	0.477
Hopkins Board			
Naming (range 0–9)	8.92 (0.35)	8.67 (0.65)	0.004
Errors to criterion (range 0–68)	21.17 (15.79)	37.19 (20.53)	<0.001
Trials to criterion (range 2–10)	8.81 (2.03)	9.20 (1.89)	0.276
Delayed item recall (range 0–9)	6.69 (1.94)	2.38 (2.61)	<0.001
Delayed location recall (range 0–9)	6.21 (2.06)	4.15 (2.93)	<0.001

Although the most prominent cortical projections to the striatum are from dorsolateral prefrontal cortex, the caudate nucleus (especially the dorsal aspect of its head and its body) also receives significant input from the superior posterior parietal cortex.[25–28] Thus, primary neuronal loss in the caudate nucleus may result in retrograde degeneration of parietal association areas critical to extrapersonal spatial localisation.[29] Alternatively, degeneration of posterior cortical zones involved in vision may itself be a primary neuropathological event in early HD.[30] Regardless of which region degenerates first, the result is a functional disruption of circuits coding spatial location.

Not surprisingly, the AD patients in this study had very severe learning and memory deficits. However, their memory for locations was relatively better than their memory for items. At first this may appear at odds with conceptualisations of the hippocampus as critically involved in spatial memory.[31] However, our task required that subjects learn fixed, specific positional responses to each stimulus rather than a relational map. Patients with hippocampal damage are most impaired on tasks that require the development of (and capacity to rotate) spatial representations independent of viewpoint and perform better on single vantage point object location tasks.[32] In rodents,[33] as well as humans,[34] the type of stimulus–response association learning required to learn the locations of the Hopkins Board stimuli appears to be mediated more by the dorsal striatum than temporolimbic structures. In addition, our item memory task requires subjects to say the names of the objects. The well described language impairment of AD patients may have contributed to their differential impairment on the item memory task.

Although the present study was not designed expressly to test any specific theory of basal ganglia memory function, our findings are certainly consistent with the view now gaining currency that the caudate nucleus play a major role in the gradual learning over trials of specific stimulus–response associations or habits.[33 35] This memory system is seen as distinct from, but in dynamic interaction with, a system for the rapid acquisition of flexible spatial representations mediated by the hippocampus and associate medial temporal structures.[36–38]

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