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RESEARCH ARTICLE

Eye–head coordination in moderately affected Huntington's Disease patients: do head movements facilitate gaze shifts?

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Abstract In addition to many other symptoms, Huntington's Disease (HD) also causes an impairment of oculomotor functions. In particular, saccadic eye movements become progressively slower and more difficult to initiate; ultimately, patients are forced to recur to large head thrusts as means to initiate gaze shifts. We wondered whether, as a precursor of this condition, head movements would facilitate gaze shifts already in early stages of the disease. We studied horizontal head movements and eye–head coordination in 29 early stage HD patients (Ps) and 24 age matched controls (Cs). Subjects tracked random horizontal steps of visual or auditory targets while their heads were either stabilised (saccade amplitudes $\leq$40°) or free to move (amplitudes $\leq$160°). Subjects were to react either immediately (reactive mode), or wait until a go signal was sounded (delayed mode), or by antisaccades. Ps' head velocity was found to depend on the age of disease onset in a similar way as their saccadic eye velocity does, being clearly reduced in early affected Ps, but increasing to normal levels in lately affected Ps. Yet, saccade and head velocity were only loosely correlated although both exhibited a negative correlation with the severity of Ps' genetic condition (number of Ps' CAG repeats). Eye–head coordination turned out to be identical in Ps and Cs except for quantitative differences caused by the lower saccade and head velocities of Ps. Specifically, the timing between head and eyes and the head contribution to gaze shifts were similar in both groups. Moreover, preventing head movements did not affect the saccade latency or accuracy of Ps. Although Ps made more small involuntary head movements in this condition than Cs, these movements were not instrumental in generating saccades since they occurred only late after saccade onset. Thus, the head manoeuvres of severely affected patients must be considered a late adaptive behaviour. Finally, the ability of both Ps and Cs to suppress immediate reactions in the delayed and antisaccade conditions diminished as target distance decreased, with failure rates in Ps being much larger than in Cs. Unlike eye and head velocity, these failure rates were not correlated with age and, by the same token, neither with the variations in head and eye velocity nor with the number of CAG repeats. Hence, the pattern of brain areas prominently affected by HD is likely to vary significantly among individuals.

Keywords Eye–head coordination · Huntington's Disease · Head velocity · Gaze saccades · Delayed saccades · Antisaccades

Abbreviations

ANOVA	Analysis of variance
Cs	Control subjects
ΔL	Increase in latency with respect to reactive saccades
E	Eye position
EOG	Electrooculography
G	Gaze position
H	Head position
HD	Huntington's disease
LED	Light emitting diode
nCAG	Number of CAG repeats of IT15 gene of chromosome 4
NRG	Nucleus reticularis gigantocellularis
PPRF	Paramedian pontine reticular formation

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Ps	Patients
riMLF	Rostral interstitial nucleus of medial longitudinal fasciculus
rip	Nucleus raphe interpositus
RL	Relative latency of head with respect to saccade onset
SC	Superior colliculus
SNpr	Substantia nigra pars reticulata
Ss	Subjects
T	Target position

Other abbreviations as listed in Table 1.

Introduction

Huntington's Disease (HD) is an autosomal dominant, slowly progressing neurodegenerative disorder which is caused by a trinucleide (CAG) expansion of the IT15 gene of chromosome 4 producing a mutant of the protein huntingtin (Huntington's Disease Collaborative Research group 1993). HD not only causes choreatic movements, cognitive decline and psychiatric symptoms, but also various oculomotor disorders affecting fixation, saccades and smooth pursuit eye movements (Lasker and Zee 1997). Many HD patients make significantly slower saccades than normal control subjects (Avanzini et al. 1979; Oepen et al. 1981; Beenen et al. 1986; Bollen et al. 1986; Lasker and Zee 1997; Collewijn et al. 1988; Garcia-Ruiz et al. 2001). Saccadic slowing progresses during the course of the disease (Beenen et al. 1986; Leigh et al. 1983; Rubin et al. 1993) and is more prominent in patients with early clinical onset of HD (Lasker et al. 1988; Rubin et al. 1993; Garcia-Ruiz et al. 2001). The patients' age at onset, in turn, is largely determined by the number of their CAG repeats (nCAG; Andrew et al. 1993); ultimately, therefore, the degree of saccade slowing can largely be traced back to this genetic condition. Moreover, HD patients often display an increase in reaction time (Leigh et al. 1983; Bollen et al. 1986), the amount of which depends on the mode of saccade release. It is least prominent in reactions to newly appearing targets, becomes more conspicuous with 'volitional' saccades (e.g. saccades directed upon command at already visible targets; Lasker et al. 1987) and is most marked when patients are asked to look into a verbally specified direction in the absence of a visual target object (Leigh et al. 1983). Impaired initiation of volitional saccades therefore is considered a cardinal symptom of HD. To overcome this impairment, patients have been reported to use auxiliary, 'catalysing' manoeuvres such as blinking or head movements (Starr 1967; Avanzini et al. 1979; Leigh et al. 1983).

As HD progresses, saccade slowing and difficulties of saccade initiation may worsen to such a degree that patients find it impossible to shift gaze without resorting to large head movements (see example in Koeppen 1989). Reportedly, as a precursor of this state, already moderately affected patients exhibit an altered pattern of eye–head coordination such that the head movement starts simultaneously with, or even prior to, the eye movement (Zangemeister and Mueller-Jensen 1985). In healthy subjects, such a pattern occurs only when very large (e.g. >60°) or predictable target steps are being tracked (Barnes 1979; Goldring et al. 1996), otherwise the head lags the eye by 30 ms or more.

In the present study, we examined eye–head coordination in a group of mildly to moderately affected HD patients in more detail. In particular, we addressed the following questions: to what degree are head movements compulsory during the patients' attempts to shift gaze? Does the effort to voluntarily suppress head movements in any way impair their gaze shifts? How does patients' eye–head coordination depend on the age at clinical HD onset and, related to this question, how does it correlate with nCAG? Finally, how do patients' head movements compare with those of normal subjects?

In order to characterise patients as fully as possible, we also considered the executive control of eye and head movements. Since HD patients have difficulties to suppress their visual grasp reflex when a new target object appears in their visual field (e.g. in a delayed saccade or antisaccade task, Lasker et al. 1987; Leigh et al. 1983), we asked whether they have also more difficulties to suppress unsolicited head movements during such tasks. Therefore, we extended the delayed saccade and antisaccade paradigms to head free gaze saccades.

Methods

Equipment

Subjects (Ss) were seated at the centre of a hemicylindrical screen with a radius of 1.60 m carrying a horizontal array of light emitting diodes (LED) at eye level that served as visual targets. Target positions were spaced at intervals of 5° and extended from 80° left to 80° right. At each position, a red and green LED were paired (vertical separation <1°; LEDs invisible when not lit). The array was under computer control allowing for an independent switching of each LED. In addition, two auditory targets (loudspeakers) were placed at eccentricities of 90° left and right, respectively.

Recording of eye and head movements

Horizontal eye movements were recorded by DC-electrooculography (EOG) using a pair of bitemporal electrodes. To detect blink artefacts, vertical EOG was recorded from

the right eye. To record horizontal head movement, Ss wore a lightweight helmet coupled to a precision potentiometer 'floating' above their head and tolerating inclinations of the axis of head rotation. EOG and head position signals were filtered (50 Hz, second order filter), sampled at 500 Hz, and stored in computer files. For a preliminary calibration of EOG, the subject's head was manually rotated back and forth (±20°, 0.1 Hz) while the subject was fixating his gaze at a stationary central target. A factor c then was determined that would minimise $c{\cdot}\mathrm{EOG} - \mathrm{H}$ (H, head position). Eventually however, calibration was fine-tuned during data analysis (cf. below).

Procedures

The test battery developed for the present study was a compromise dictated by two constraints: We wished to examine as many aspects of oculomotor and cephalomotor behaviour as possible but wanted patients to spend no more than 90 min in the laboratory in view of their limited capacity to concentrate on the various tasks of the battery.

The test battery comprised ten saccade conditions, which differed regarding (1) whether the head was stationary (HS) or free to move (HF), (2) whether saccades were reactive (rS) or delayed (dS), and (3) the way the head was either stabilised or moved. A systematic summary of these conditions is listed in Table 1.

For reactive saccades, the target stepped in pseudorandom manner within a range of ±20° (HS) or ±40° (HF) calling for saccades of 5° to 40° and 5° to 80°, respectively. Subjects were instructed to "immediately refixate the target after each step, as accurately as possible".

To obtain delayed saccades, a new target was lit while the current one remained on for the time being. Subjects were to continue fixation and to shift gaze to the new target only when an auditory "go" signal was sounded after a random delay of 2 ± 0.5 s. After a further 2 ± 0.5 s, the first target disappeared and the new target assumed the role of starting position for the next trial; target positions varied similarly as for reactive saccades.

For antisaccades (aS), the initially red central fixation spot turned green and stepped, after 0.5 s, to 20° (HS) or 40° (HF) left or right whereupon subjects were to immediately make a saccade into the opposite direction and fixate at the spot's mirror position in the empty visual half field.

During HS conditions, the head was either blocked (although not rigidly) by a chin rest or held stationary by voluntary control without chin support. During HF conditions, subjects were either told that they were free to move their head in a natural way ("as if you watched a scene"; Hn) or asked to deliberately rotate it by "pointing the nose as *rapidly* and as *accurately* as possible toward the target" (Hp). To obtain very large HF saccades, the two loudspeakers at +90° and −90° alternately sounded a brief white noise; upon hearing it, subjects were to immediately shift gaze and to fixate on the activated speaker (saccades to sound sources, sS).

The ten saccade conditions were always run in the same order (Table 1, column OoP). Delayed saccade and antisaccade conditions were preceded by familiarising trials upon their first occurrence during an experiment. A break was usually given after the first four conditions or when requested by the subject.

Subjects

Twenty-eight patients were recruited from the HD outpatients of the Department of Neurology. Their demographic data are summarised in Table 2 (left); their age ranged from 25 to 63 (mean 42.4), the duration of illness since clinical onset from 2 to 10 years (mean 4.8), the number of CAG repeats from 35 to 59 (mean 46.1), and the clinical stage

Table 1 Summary of saccade paradigms

Head condition	Saccade mode	Head mode	*N*	OoP	Acronym
HS, head stationary, range ±20°	rS, reactive saccades	Head blocked by chin rest	14	5	rSHs
		Head held stationary by subject	14	6	rSHs
	dS, delayed saccades	Head blocked by chin rest	14	1	dSHs
		Head held stationary by subject	14	2	dSHs
	aS, antisaccades	Head blocked by chin rest	8	8	aSHs
HF, head free, range ±40°	rS, reactive saccades	Hn, natural eye-head coordination	28	7	rSHn
	dS, delayed saccades	Hn, natural eye-head coordination	28	3	dSHn
		Hp, head pointing	28	10	dSHp
	aS, antisaccades	Hn, natural eye-head coordination	8	9	aSHn
HF, head free, range ±80°	sS, reactive saccades to sound sources	Hn, natural eye-head coordination	8	4	sSHn

Acronyms do not distinguish between "head blocked" and "head held" modes of head stabilisation because results were identical

N Number of trials, *OoP* order of presentation during experiment

Table 2 Demographic data

HD patients (Ps)							Controls (Cs)		
Subj #	Gender	Age	Duration of illness	nCAG large allele	HD stage	Medication	Subj #	Gender	Age
P03	M	25	4	46	1	Memantine	N02	M	24
P25	M	27	4	54	1	Memantine, Citolopram	N12	F	24
P09	M	27	7	56	2	None	N13	M	24
P12	F	29	9	59	1	Sertraline	N03	F	25
P28	M	29	10	57	1	None	N10	M	25
P24	M	29	10	51	3	Levodopa	N01	F	27
P13	M	31	4	50	1	None	N05	M	31
P17	M	32	4	50	1	None	N11	M	31
P19	F	34	2	53	3	Unknown	N04	F	34
P10	F	38	4	45	1	None	N19	M	34
P14	F	40	2	43	1	Doxepine	N24	M	39
P06	F	41	4	43	1	Seratraline	N15	M	41
P29	F	41	6	43	2	Citalopram, Tiapride, Tetrabenazine	N20	M	42
P21	F	42	4	44.5	1	Sertraline	N17	F	43
P04	M	42	2	45	1	None	N16	F	44
P20	F	42	6	47	2	None	N09	F	49
P07	F	44	6	45	1	Seratraline	N14	F	49
P26	M	45	3	44	1	None	N23	M	54
P02	F	46	4	45	1	Memantine	N06	M	58
P23	M	47	8	47	2	None	N22	F	59
P27	F	48	2	44	1	Amitriptyline	N18	F	60
P18	F	52	6	44	1	Sertraline	N21	M	60
P01	M	53	5	44	1	None	N07	F	66
P08	M	55	5	43	1	None	N08	F	70
P15	M	56	6	42	1	Gabapentine			
P22	M	57	8	40	1	Sertraline			
P16	M	57	3	40	1	Mirtazapine, Sertraline, Venlafaxine			
P11	M	63	2	40	1	None			
Mean		41.8	5.0	46.6	1.3				42.2
SD		10.8	2.4	5.1	0.6				14.7
Median		42.0	4.0	45.0	1				41.5

Subjects ordered according to age at time of examination

(scoring impairment of various daily life capacities on a scale from 1 to 5, cf. Shoulson and Fahn 1979) ranged from 1 to 3 (median 1) indicating that, functionally, patients were in an early stage of the disease. Twenty-four paid subjects without neurological affections served as controls; they were selected for their age such as to obtain an age distribution (range 24–70, mean 42.2; Table 2 right), roughly similar to that of patients.

Patients and controls gave their written informed consent. The study was approved by the ethics committee of the University of Ulm.

Definitions

'*Gaze*' (*G*) refers to the direction of the line of sight in space; it is the sum of the angular eye-in-head (*E*) and head-in-space (*H*) positions ($G = E + H$; cf insets in Fig. 1). The term '*saccade*', or more explicitly '*gaze saccade*', refers to all saccadic gaze movements whether there is head movement or not. It is the sum of an eye-in head saccade (*'eye saccade'* for short) and the concurrent head movement; when there is no head movement, it is identical to the eye saccade. '*Gaze shift*' refers to the total sequence

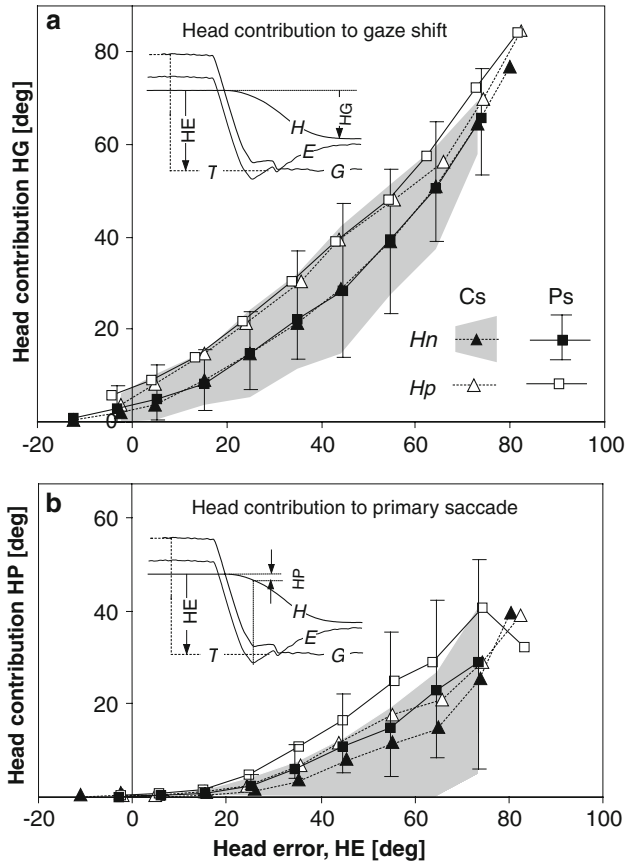

Fig. 1 Contributions of head to gaze shift (*HG*) and primary saccade (*HP*) as functions of head error (*HE*). *Insets* Standard pattern of eye–head coordination with definition of *HG*, *HP* and *HE*; *T, E, H, G* position traces of target, eye-in-head, head and gaze, respectively; sample recording from patient #1 reacting to a target step from 30° right to 30° left. **a** Head contribution to gaze shift (=total head amplitude), grand averages of patients (*Ps*, *continuous curves* with *squares*) and controls (*Cs*, *dashed* with *triangles*) during natural eye-head coordination (*Hn*, *filled symbols*) and rapid head pointing (*Hp*, *open symbols*). Reactions without head movement included as movements with zero amplitude. *Vertical bars* 90% range of *Ps* during *Hn*; *grey shading* 90% range of *Cs*. Negative head errors arise when initial head position is already beyond target position; as reflected by the positive sign of *HG*, subjects nonetheless tend to make a small movement *in the direction* of the target *step* in such a case (thereby actually increasing negative head error). **b** Head contribution to primary saccade, same format as in **a**

of events accompanying the alignment of gaze with a new target position, up to when both eye-in-head and head-in-space have reached their final positions. Generally, gaze shifts consist of a large '*primary*' saccade followed by one or more corrective secondary saccades, while there is mostly only a single head movement, if any. The angular eye-to-target distance at the beginning of a gaze shift is called '*gaze error*', the head-to-target distance '*head error*' (HE in Fig. 1), and the delay of the head movement upon saccade onset '*relative head latency*' (RL in Fig. 2).

Data analysis

An in-house software package (written in MATLAB®) was used for data analysis. Data were filtered using a digital low pass filter with 25 Hz cut-off, zero delay, and fourth order Bessel characteristics. Horizontal gaze position was calculated from horizontal eye and head position ($G = E + H$). Eye, head and gaze velocities were obtained by digital differentiation. The position and velocity signals were displayed together with the results of an automatic search algorithm identifying saccades and head movements. The operator could accept, reject, or correct these results. For each accepted movement, the program noted the positions and velocities of G and H corresponding to the following five instants: (1) 50 ms before the beginning of the movement, (2) begin, (3) instant of peak velocity, (4) end, and (5) 50 ms after the end. Based on these data, the EOG calibration of each experimental condition was fine-tuned to compensate for changes in the course of the session. To this end, a recalibration factor r was determined that would minimise $r{\cdot}c{\cdot}\Delta\mathrm{EOG} + \Delta\mathrm{H} - \Delta\mathrm{T}$ across all trials of a given condition (least squares method), with Δ representing the total changes in EOG, head position (H) and target position (T) during a trial.

After recalibration with r, the above data and all relevant context information (target position, occurrence of auditory signals, etc.) were transferred to a spread sheet programme for further analysis. Most parameters were considered as functions of either the target displacement (e.g. reaction time, accuracy, etc.) or some other relevant parameter such as saccade amplitude or angular target-to-head distance. To obtain these functions, the recorded values of the independent (x-) parameter of each subject were sorted into bins of either 5° or 10° width, and their averages within each bin were calculated together with the mean or median values of the corresponding dependent (y-) parameter. From the resulting individual functions, population averages or medians were then obtained for patients and controls. To test for statistical significance, we variously used parametric or non-parametric tests, depending on the distribution of the results; $P < 0.05$ was considered significant.

Results

Head contribution to gaze shifts during head free conditions

During most trials, the head was not exactly aligned with the current target. Therefore, when the next target was presented, head error differed from gaze error. Head error determines how much head contribution is needed in order to avoid large or impossible orbital eccentricities of the eyes during target acquisition. Therefore, Fig. 1 plots the head contributions to the gaze shift (panel a) and primary

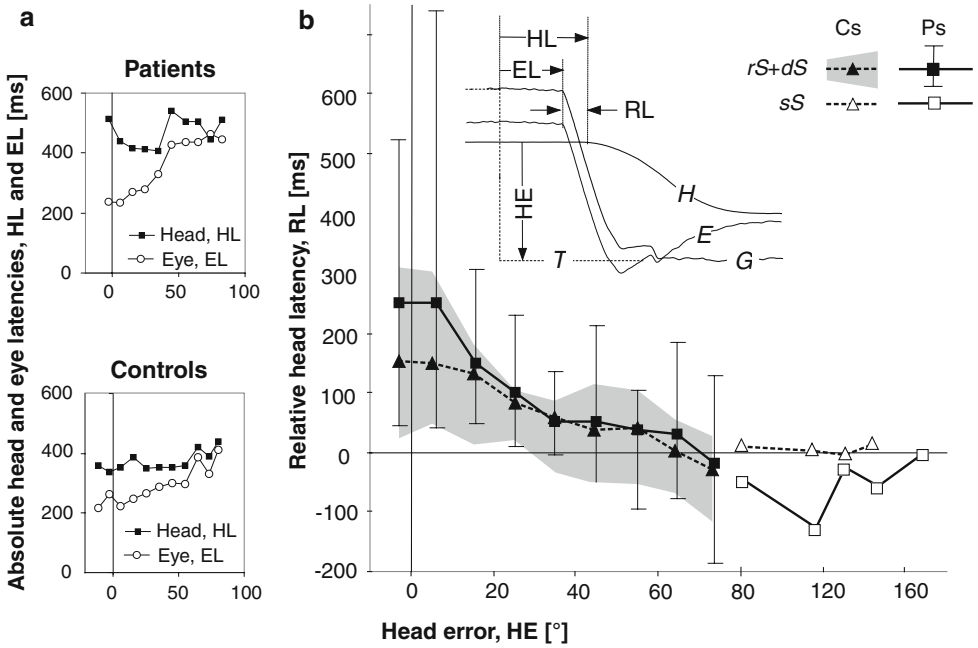

Fig. 2 Absolute and relative head latencies, population averages of individual median values. **a** Comparison of absolute head (*HL*, see *inset* for definition) and eye latencies (*EL*) of reactive saccades as functions of head error (*HE*) in patients and controls. **b** Relative head latency (*RL*) as a function of HE. *rS* + *dS* Pooled data from reactive and delayed saccades; *sS* saccades to sound sources; other s*ymbols* as in Fig. 1. Note compressed scale for *abscissa* values exceeding 80°

saccade (b) as functions of head error. During natural coordination (filled symbols, representing pooled data from reactive and delayed saccades), the head contribution to gaze shift (=total head amplitude) was virtually identical in Ps (panel a, squares) and Cs (triangles). With the instruction to deliberately move the head so as to point at the target (open symbols), head amplitude increased significantly in both groups over most of the head error range and by identical amounts (up to 30%), yielding again two indistinguishable curves. In summary, there was no difference, whatsoever, in total head amplitude between Ps and Cs.

A difference between Ps and Cs emerged, though, when the head contribution to the primary saccade was considered (panel b). This contribution was larger in Ps than in Cs (ANOVA of data pooled across head errors ranging from 10° to 40°, $P = 0.022$).

Head latency during head free conditions

In both Ps and Cs, head latency was independent of head error, whereas eye latency, hence also gaze latency, increased with head error (Fig. 2a). As a result, the relative latency of the head with respect to saccade onset was a decreasing function of head error (Fig. 2b). This function was similar under the two conditions with natural coordination (rSHn, dSHn), so that the data could be pooled (filled symbols). With small head errors, the saccade led head movement by 150–250 ms (population average of individual medians) so that the head often started only after the saccade was finished. As head error increased, saccade and head movement began to overlap in time. Ultimately, head onset became synchronised with saccade onset or could even slightly lead in some individuals, in particular when very large saccades were elicited by the sound sources at ±90° (sSHn, open symbols). Patients did not differ from Cs except for a larger inter-individual scatter; the differences at the low and high ends of the head error range suggested by Fig. 2 were not significant (Mann–Whitney *U* test). When subjects were primed to deliberately move their heads (dSHp), latencies had the same general relation with head error, but were about 25 ms shorter ($P < 0.001$, ANOVA of latencies pooled across head errors of 20° to 60°) except for large head errors where the difference gradually disappeared.

Involuntary head synkinesis during head fixed conditions

With very few exceptions, Cs made no head movements during HS conditions (average frequency about 1%), whereas in Ps the average frequency of involuntary movements rose from 6% with saccades of 5° to 20% with 40° saccades (overall mean, 10%), and individual values ranged from 0 to 30–50%. There were no consistent differences related to whether the head was on a chin rest (which did not rigidly block the head) or was held stationary by voluntary control. These movements were goal directed in the sense that they started in the direction of the target. However, their amplitudes averaged less than about 3° and did not exceed 6°, except for a single subject who reached 12°. For head errors of similar magnitude, involuntary head synkinesis generally occurred later than, or at best as late as, the head movements in HF conditions. Pooled across all values of head error, its relative latency upon saccade onset had a median value close to 200 ms indicating that it started either late during the saccade or after its end.

Head velocity

In both Ps and Cs, the average peak velocity of the head movements occurring during head free gaze shifts was a linear function of movement amplitude (Fig. 3a). With naturally coordinated reactive saccades (rSHn), its slope averaged 3.1°/s per deg of head amplitude in Cs, and 2.6°/s per deg in Ps. Slightly smaller values resulted during deliberate head pointing (dSHp: Cs, 2.8°/s per deg; Ps, 2.4°s per deg), in spite of the instruction to move the head "as rapidly as possible". However, a 2-way repeated measures ANOVA of the velocity of 30°-head movements indicated that this difference was not significant, whereas the effect of group (Ps, Cs) almost was ($P = 0.051$) indicating that head movements of ≤50° were marginally slower in Ps than in Cs. An appreciable difference between the two groups emerged only with larger head movements (Fig. 3a).

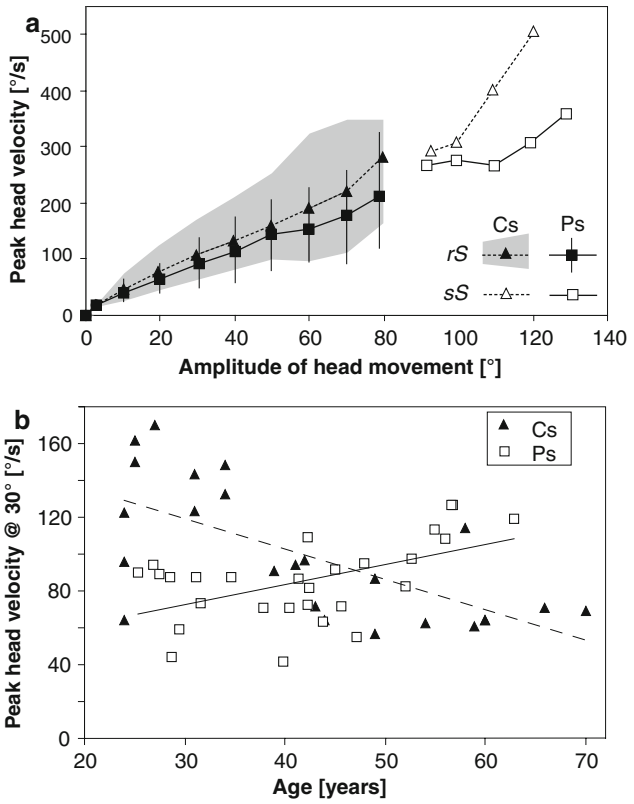

Fig. 3 Peak head velocity. **a** Grand average as a function of head amplitude. *Square symbols* show patients (*Ps*), *triangles* controls (*Cs*). *Filled symbols* correspond to naturally coordinated reactive gaze saccades (*rS*), with 90% ranges of Ps and Cs indicated by *bars* and *grey* shading, respectively; *open symbols* reactive gaze saccades to sound sources (*sS*). **b** Scatter plot of peak head velocity versus age at time of examination. Each *symbol* corresponds to one subject and represents his mean peak head velocity during head movements of 30°. *Open squares* Patients. *Filled triangles* Controls. *Straight lines* show linear trends (*continuous* patients; *dashed* controls)

A much clearer difference between Ps and Cs emerged when the relation between head velocity and subjects' age was considered. To examine this relation, data from all head free conditions were pooled and the velocities for head movements of 30° were calculated from linear regressions. Figure 3b shows a scatter plot of these velocities as a function of subjects' age. In healthy subjects, peak head velocity decreased with age ($r = -0.67$), whereas it increased in patients ($r = 0.52$). Because the trends of the two groups cross over at an age between 45 and 50 years, young Ps were slower than similarly aged Cs, whereas elderly Ps, surprisingly, tended to be faster than the corresponding Cs. Therefore, when averaged across all ages, as in Fig. 3a, the velocities of Ps and Cs appear to be not very different.

Saccades

Saccades made with the head stationary were similar irrespective of whether the head was blocked by a chin-rest or held stationary by voluntary control. This held for both patients (Ps) and controls (Cs). Results from these two HS conditions were pooled, therefore. Moreover, most properties of head free saccades and of head stationary saccades were very similar or even indistinguishable in both Ps and Cs. Therefore, unless specifically mentioned, the descriptions below refer to both head conditions. The results from HS and HF conditions are nonetheless graphed separately in the following figures so that their similarity (which is an important result with regard to the patient group) can be appreciated.

Saccade latency

The latency of reactive saccades amounted to 256 ms (HS conditions) and 258 ms (HF) in Cs and to 280 and 281 ms, respectively, in Ps (population medians reflecting responses to target steps of 10°, 20°, and 40°). Thus, in both goups, preventing head movements had no effect on latency. The difference between Ps and Cs was not significant (Mann–Whitney *U* test).

To compare the ability of Cs and Ps to initiate voluntary saccades (tested in the delayed saccade condition), we calculated the *difference* in latency (ΔL) between delayed and reactive saccades for each subject. In Cs, ΔL reached 31 ms (HS) and 17 ms (HF), whereas the corresponding values of Ps were 146 ms and 102 ms, respectively. These population medians were all significant (Wilcoxon test for matched pairs) indicating that, on average, the delayed saccades of both Ps and Cs had longer latencies (with respect to the acoustic "go"-signal) than the corresponding reactive saccades (note, however, that a few individuals from both groups exhibited the opposite

behaviour). There was no correlation of ΔL with age, neither in Ps nor in Cs. The difference in ΔL between Ps and Cs was significant only in the HS conditions (Mann–Whitney *U* test). Finally and most importantly, neither in Ps nor in Cs were the differences between HS and HF significant; thus, preventing head movements (condition HS) did not cause a differential delay of voluntary saccades in patients.

Saccade peak velocity

Peak velocity was significantly lower in Ps than in Cs, but exhibited otherwise similar characteristics in both groups (Fig. 4a). In particular, the group averages of the velocities recorded in HS conditions (open symbols) and HF conditions (filled symbols) were identical within their range of overlap, and the individual velocity values correlated tightly across the two conditions (Table 3, row 7). These observations demonstrate that preventing head movements did in no way impede the dynamics of patients' saccades. Moreover, in both groups, the curves of peak velocity from head free conditions, after having reached a saturation level for amplitudes of about 30°, exhibited a tendency to further increase at amplitudes beyond 50°. This tendency clearly continued in the curves obtained from saccades to auditory targets (right part of Fig. 4a).

As with head velocity, opposite trends emerged for Cs and Ps when peak saccade velocity was analysed as a function of age (Fig. 4b; Table 3, row 2). In Cs, it decreased slightly with age, whereas it increased in Ps, reaching similar values as Cs in the eldest subjects.

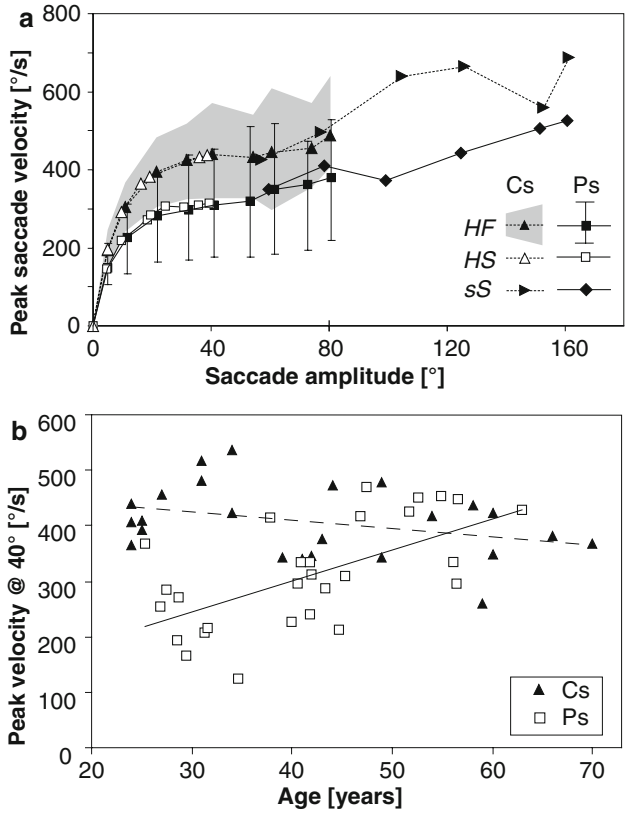

Fig. 4 Peak velocity of gaze saccades. **a** Grand average as a function of saccade amplitude. *Square symbols* show patients (*Ps*), *triangles* controls (*Cs*). *Filled symbols* Head free saccades (*HF*) with 90% ranges of *Ps* and *Cs* indicated by *vertical bars* and *grey* shading, respectively; data from patients represent pooled results of all head free conditions, whereas data from controls represent only reactive saccades (saccades were slower in conditions *dSHn* and *dSHp*). *Open symbols* Head stationary (*HS*) saccades. *Diamonds* and *arrow heads* Head free saccades to sound sources (*sS*). Note compressed scale for *abscissa* values exceeding 80°. **b**, Scatter plot of peak velocity of head free saccades versus age at time of examination. Each *symbol* corresponds to one subject and represents the velocity of saccades of 40° (bin 37.5°–42.5°, pooled data from all head free conditions). Same format as Fig. 3

Accuracy of primary saccade

In both Ps and Cs, the accuracy of primary saccades in terms of gain (=amplitude / target distance) was similar during reactive and delayed conditions. A 3-way repeated measures ANOVA with between-factor *group* and within-factors *head condition* (HS, HF) and *target distance*, revealed no significant difference between Ps and Cs, whereas *head condition* and *target distance* mattered; gain was larger with HF saccades than with HS saccades and decreased with target distance. However, there was no indication that holding the head stationary would have a stronger effect on saccade accuracy in Ps than in Cs.

Errors during delayed saccades

In the delayed saccade conditions, saccades initiated before the auditory go-signal was sounded were scored as errors. In both the HS and HF conditions, the frequency of such errors was largest with small target distances (5°) and decreased with larger ones (Fig. 5a). This behaviour was similar in Ps and Cs. However, Ps exhibited significantly larger error rates than Cs ($P < 0.001$, Kolmogorov–Smirnov two sample test), although there was considerable overlap between the two groups (note 90% ranges in Fig. 5a). In Ps, but not in Cs, the error rate exhibited a significant positive correlation with the increase in latency (ΔL; Table 3, row 5).

Interestingly, in HF conditions most errors consisted of pure eye saccades. Only in 16% (Ps) and 13% (Cs) was there also a head movement, whereas for correct responses the corresponding figures were 90% (Ps) and 97% (Cs).

Finally, there were no consistent trends with age except that in the group of Cs the three eldest subjects made by far the most errors (Fig. 5b).

Table 3 Coefficients of correlation

Group		Cs			Ps		
Head condition		Stationary	Free		Stationary	Free	
R#	Parameter	pVGaze	pVGaze	pVHead	pVGaze	pVGaze	pVHead
1	Age at onset				0.66***	0.58***	0.55**
2	Age at examination	−0.18	−0.34	−0.67***	0.68***	0.62***	0.52**
3	nCAG				−0.65***	−0.56**	−0.39*

Group		Cs		Ps	
Head condition		Stationary	Free	Stationary	Free
R#	Parameter pairs				
4	pVGaze ∞ pVHead		0.51*		0.32
5	ΔL ∞ Err (delayed Sacc)	−0.26	0.00	0.57**	0.43*
6	nCAG ∞ Age at onset			−0.85***	

Group		Cs	Ps
R#	Parameter		
7	pVGaze	0.88***	0.93***
8	L (reactive saccades)	0.79***	0.73***
9	Errors (delayed saccades)	0.49*	0.89***
10	Δ*L* (delayed saccades	0.63**	0.73***

Ps, HD patients; Cs, controls; pVGaze, peak gaze velocity; pVHead, peak head velocity; *R#*, row number; nCAG, number of CAG repeats on large allele; Δ*L*, increase in latency of correctly executed delayed saccades with respect to reactive saccades; Err, error rate in delayed saccade conditions; *L*, latency of reactive saccades

Top part of table (rows 1–3) to be read as a matrix showing correlation between row and column parameters

In middle part (rows 4–6), symbol ∞ denotes correlation between terms to left and right of symbol

Lower part (rows 7–10), correlation between head stationary and head free conditions of given parameters

Coefficients in rows 1–4 and 6–7 are Pearson's product moments; other coefficients are Spearman's rank correlations

Asterisks indicate levels of significance; * $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$

Antisaccades

Performance in the antisaccade condition is summarised in Table 4. Ps made significantly more errors than Cs in terms of both the percentage of subjects erring on at least one trial and the percentage of wrong responses in erring subjects (Table 4, rows 1–3). The error rates of Ps were positively correlated with those in the delayed saccade task (Table 4, row 5). No dependence on age could be discerned.

There was no difference between Ps and Cs with regard to saccade and head amplitude of both correct and wrong responses. Saccade amplitude of correct responses was fairly close to the instructed value (20° or 40° mirror image of visible target) with gains of the order of 0.8–0.9. Head amplitude of correct head free responses averaged 22° to 23°, a value similar to the 25° expected from reactive head free saccades (cf. Fig. 1), given a head error of 40° in the HF antisaccade condition. In Ps and probably also in Cs (cave small number of subjects with errors), the saccade amplitudes of erroneous responses were smaller in comparison to correct responses, and head movements occurred less frequently (Table 4, rows 13–15 vs. 8–10).

The latency of correct antisaccades was significantly larger in Ps than in Cs, whereas that of erroneous saccades was similar in both groups (Table 4, rows 6 and 12). However, when the *increase* in latency of correct antisaccades with respect to reactive saccades (Δ*L*; Table 4, row 7) was examined, a significant difference between Ps and Cs emerged only with small target displacements (20°, HS), but not with large ones (40°, HF). Note also that some individuals among both Ps and Cs made antisaccades with shorter latencies than their reactive saccades. Finally, relative head latency exhibited no significant differences either between Ps and Cs or between correct and erroneous responses. Its range (≈40–70 ms; Table 4, row 11) was of the same order of magnitude as observed for similar head errors (40°) in reactive head free saccades (≈55 ms).

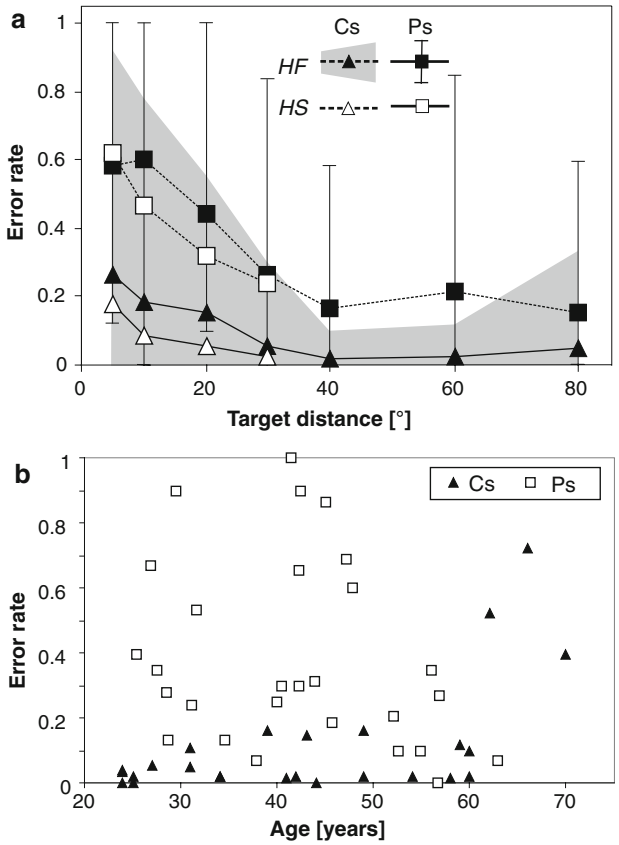

Fig. 5 Rate of errors (premature reactions) in delayed saccade conditions. **a** Error rate as a function of angular target distance. **b** Scatter plot of individual error rates versus age at time of examination. Symbols as in Fig. 4

Discussion

We will discuss three main topics. First, we consider the metrics of our patients' saccades and head movements separately and compare our results to previous reports. In doing so, we will emphasise the importance of patients' age and genetic status. Second, we examine the similarity of eye–head coordination in patients and controls and suggest that the mechanism of coordination is unchanged in patients. Third, we ask which pathophysiological changes of the neural substrates of eye and head movements could be responsible for the slowness of these movements in HD patients.

Metrics of eye and head movements

Peak velocity: effect of age and number of CAG-repeats

The saccade peak velocity of our control subjects decreased with age (Fig. 4b), in accordance with previous studies (Spooner et al. 1980; Sharpe and Zackon 1987; Wilson et al. 1993). The velocity of patients differed from that of Cs in two respects: (1) It was significantly lower, on average, as originally reported by Starr (1967) and confirmed in most later studies (e.g. Avanzini et al. 1979; Oepen et al. 1981; Lasker et al. 1988; Beenen et al. 1986; Garcia-Ruiz et al. 2001). (2) It correlated positively with Ps' age at the time of examination, with young patients being considerably slower than young controls, but most aged Ps about as fast as elderly Cs. This age-related variation is responsible for the large 90% ranges shown in the population averages of Fig. 4a and probably explains why some authors failed to observe slower saccades in patients; for example, the patients studied by Blekher et al. (2006) and Winograd-Gurvich et al. (2003) had mean ages of 50 and 51, respectively, which is not far from where the age-related trends of Ps and Cs intersect in the present study.

As a new finding, we observed that peak head velocity seems to exhibit similar age related differences between Ps and Cs as saccade velocity does. Whereas the head velocity of Cs decreased with age, that of patients increased and, somewhat surprisingly, reached higher values in aged Ps than in aged Cs. As a result, the trends of Ps and Cs crossed at an age of about 47 years, which explains why the population averages of Ps and Cs were not much different. It is unclear why the two trends did not meet at the high end of the age range as in the case of saccade velocity. It was our impression, though, that many elderly Ps were eager to prove their fitness and may have endeavoured to make particularly brisk head movements.

Because disease duration spanned a limited range in our sample (median 4 years), peak saccade and head velocities also correlated with Ps' age at disease onset (Table 3, row 1). The dependence of saccadic slowing on age at onset in mildly affected patients has already been noted by Lasker et al. (1988), and correlations qualitatively similar to ours have been observed by Garcia-Ruiz (2001). Age at disease onset, in turn, is known to correlate negatively with the number of CAG expansions (Andrew et al. 1993; Duyao et al. 1993; Snell et al. 1993; Persichetti et al. 1994; Brinkman et al. 1997; in our sample $r = -0.85$). Thus, it is tempting to view nCAG as the primary determinant of saccade slowing and expect a tighter correlation of saccade velocity with nCAG than with age at the time of examination. This was not the case, though; there was a slight trend in the opposite sense that applied to both gaze and head velocity (compare row 3 to rows 1–2 in Table 3). After eliminating the mean linear effect of nCAG upon the age of onset, a positive relation between velocity and the residual age of onset variation emerged, which reached significance in the case of head velocity; the positive sign suggests that Ps who were affected later than predicted by the linear effect of nCAG made faster movements than those affected earlier. These observations are reminiscent of the finding by

Table 4 Antisaccade results

			Head stationary		Head free	
	R#	Parameter	Cs	Ps	Cs	Ps
	1	Ss without errors	20 (83%)	7 (33%)	14 (58%)	10 (36%)
	2	Ss with errors	4 (17%)	14 (67%)	10 (42%)	18(64%)
	3	Number of errors	1.7 (22%)	4.0 (55%)	1.5 (20%)	3.8 (51%)
	4	$\Delta L \infty$ errors		0.25		0.40
	5	Err (delayed) ∞ Err (anti)		0.60***		0.56**
Correct responses	6	Reaction time (ms)	365	461***	355	469**
	7	ΔL (ms)	83	134*	60	120
	8	Gaze amplitude (°)	18 (0.9)	18 (0.9)	35 (0.88)	32 (0.80)
	9	Head amplitude (°)			23	22
	10	Frequ. of head movem.			96%	91%
	11	Relat. head latency (ms)			42	65
Wrong responses	12	Reaction time (ms)	[313]	309	338	361
	13	Gaze amplitude (°)	[19 (0.95)]	18 (0.90)	22 (0.55)	27 (0.68)
	14	Head amplitude (°)			13	14
	15	Frequ. of head movem.			78%	57%
	16	Relat. head latency (ms)			65	72

Ps, patients; Cs, controls; *R#*, row number; ∞ denotes correlation (Spearman's *R*) between terms on left and right of symbol; ΔL, increase in latency of correct antisaccades relative to reactive saccades

Percent values in rows 1 and 2 are referenced to total number of subjects in population. Percent values in row 3 represent population averages of individual percentages referenced to number of valid trials obtained from each subject. Row 5 gives correlation between error rates in the delayed and antisaccade conditions, respectively. Amplitude values in rows 9 and 14 are grand averages. Reaction times (rows 6 and 12), ΔL (row 7), and relative head latencies (rows 11 and 16) represent averages of individual median values. In row 8 and 13, figures in round brackets show gain of responses with respect to mirror position of the visible target (row 8) and target position (row 13), respectively. Square brackets in rows 12 and 13 indicate scarce data because of low number of incorrect responses

Asterisks indicate level of significance of correlation (rows 4 and 5, same coding as in Table 3) and of difference between Ps and Cs (Mann–Whitney test). Note that not always the same subjects remained error free in both conditions

Rosenblatt et al. (2003) that the age at disease onset is a better predictor of neuropathological severity (in terms of the Vonsattel grade, Vonsattel et al. 1985) than nCAG. Apparently, the age of onset reflects additional genetic and environmental factors not accounted for by nCAG. Indeed, recent work suggests that nCAG explains only about 70% of the variance of the age of onset (in our sample 72%) and that modifier genes account for part of the remaining variance (Wexler et al. 2004; Rosenblatt et al. 2001).

Since both head velocity and gaze saccade velocity covaried in a similar way with age at onset, one could expect them to be interdependent. However, their mutual correlation ($r = 0.32$) was not significant in Ps, in contrast to Cs ($r = 0.51$). Thus, at the individual level, a strong affection of the neural substrate of saccade generation does necessarily entail a corresponding dysfunction of the head movement substrate and vice versa.

Latency

Many of our HD patients had normal saccade latencies, whereas others had extremely long ones without there being any obvious relation to demographic or clinical parameters. This observation probably explains why Ps' latency has been variously reported to be either similar to that of controls as in the present study (Lasker et al. 1988; Tsai et al. 1995; Winograd-Gurvich et al. 2003; Blekher et al. 2006) or significantly longer (Lasker et al. 1987; Avanzini et al. 1979; Blekher et al. 2004; Garcia-Ruiz et al. 2001; Golding et al. 2006; Leigh et al. 1983; Tian et al. 1991; Ali et al. 2006).

Lasker et al. (1987, 1988), comparing the latencies of delayed saccades to those of reactive ones observed a significantly larger increase in Ps, which they interpreted as a specific impairment of volitional saccade initiation. An analogous differential latency increase in HD patients has been reported for correctly executed antisaccades (Blekher et al. 2004), consistent with the view that also antisaccades call for a volitional initiation, and this probably even more so than delayed saccades as there is no visual target. However, the present data concur only partially with these reports as we found a significant differential increase only for small target steps (delayed saccades, 5° and 10°; antisaccades, 20°). With larger steps, the behaviour of Ps and

Cs became highly idiosyncratic, with some individuals exhibiting even shortened latencies Therefore, at the individual level the increase in latency (ΔL) of delayed saccades and antisaccades does not seem to be a very reliable feature of HD. Also the lack of significant correlation of ΔL between the two tasks leads to such a conclusion. Thus, it appears questionable whether ΔL reflects in any consistent way the volitional effort required in these paradigms.

Suppression of reflexive saccades

The delayed saccade and antisaccade paradigms both probe the ability to suppress immediate reactions to newly appearing targets. Like previous authors (delayed saccades: Lasker et al. 1987; antisaccades: Blekher et al. 2006), we found Ps to make significantly more errors on these tasks than Cs and observed a positive correlation between their error rates and increments in latency of their delayed saccades (Table 3, row 5).

A new finding is the dependence of the error rate of delayed saccades on angular target distance in both Ps and Cs. An analogous decrease of distractibility from high values with near targets to low ones with distant targets has been observed in an antisaccade task (Smyrnis et al. 2002). As an explanation, one could invoke the mutual inhibition between collicular fixation neurones and saccade neurones (Munoz and Istvan 1998). The weight of these interactions might vary with the distance of the saccade neurones from the collicular fixation zone. As a result, nearby saccade neurones, which code for small saccades might become more easily disinhibited than the more distant caudal ones which code for large saccades.

The tight correlation between the delayed and antisaccade conditions with regard to distractibility (Table 4, row 5) is not surprising since there is no reason to assume that the suppression of the visual grasp reflex invokes different processes in these two conditions. The tightness of the correlation supports the view that distractibility is a reliable trait of individuals. However, the elevated level of distractibility found in many HD patients of every age (cf. Fig. 5b) is not a specific sign of HD. Similarly increased error rates are observed in a number of other degenerative diseases (e.g. Idiopathic Parkinson's Disease, Chan et al. 2005; Progressive Supranuclear Palsy, Pierrot-Deseilligny et al. 1989; Alzheimer's Disease, Currie et al. 1991) as well as in psychiatric conditions (e.g. psychotic affective disorders, Curtis et al. 2001; schizophrenia, Fukushima et al. 1994).

Similarity of eye–head coordination in Patients and Controls

In both Ps and Cs, the amplitude and the relative latency of the head movements accompanying head free gaze shifts were 'smooth' functions of head error with no hints at fundamental differences between head movements starting before saccade termination and those starting thereafter. Therefore, rather than excluding the latter from analysis (Stahl 1999), we here treat both cases as parts of a natural continuum.

Our data show that the mechanisms of eye–head coordination in control subjects and in mildly or moderately affected HD patients are indistinguishable. Within each group, the saccade characteristics were either similar in the head free and head stationary conditions (peak velocity, latency) or exhibited similar differences between these conditions (accuracy). There were no signs of any qualitative differences in patients that would suggest that head movements are needed as a primer for gaze shifts or have to become particularly large in order to enable gaze shifts. Indeed, the amount of head contribution to gaze shifts was similar in Ps and Cs and exhibited the same dependence on head error. Moreover, in both Ps and Cs the relative timing between head and eyes followed a qualitatively similar course as a function of head error, with relative head latency of Ps being slightly longer, at best, instead of being shorter as would be expected for a priming function. This was true not only for reactive saccades but, remarkably, also for delayed saccades and antisaccades although these are considered more difficult to initiate for Ps than for Cs. The similarity of the relative head latencies in Ps and Cs (Fig. 2) is clearly at odds with the report of Zangemeister and Mueller-Jensen (1985), according to which relative head latency is shortened in Ps so that head and eyes start in near synchrony. This discrepancy cannot be explained by methodological differences, since these authors also used a combination of EOG and potentiometer recording. It is unclear whether their patients were in considerably worse condition than ours (stage of HD not reported) or whether the dependence of relative head latency on head error (cf. Fig. 2) was not taken into account.

The qualitative similarity of the velocity–amplitude characteristics of Ps and Cs suggests also an identical mechanism of eye and head velocity interaction in both groups. With saccades of up to 40°, a VOR appears to compensate for the kinematic summation of eye-in-head and head-in-space, hence the identical HS and HF velocities in this range (this result is trivial, though, for saccades of <20° where most head movements start only late during the saccade or after it). On the other hand, the conspicuous increase of the peak velocity of very large saccades (>120°; condition sS) by roughly 200°/s beyond the familiar saturation level of saccade velocity in both Ps and Cs, strongly suggests that no VOR was operating in these cases; a low gain or a complete shut-off of the VOR during large saccades (e.g. ≥40°) has been repeatedly postulated (Laurutis and Robinson 1986; Pélisson et al. 1988).

Also the head movements occurring when subjects failed to suppress their immediate reaction in the delayed and antisaccade conditions support the notion that eye–head coordination is similar in Ps and Cs. In neither of these two conditions were there any significant differences between Ps and Cs with regard to the relative timing, frequency and amplitude of head movements. In particular, there was no hint of a more frequent occurrence of head movements in HD patients as compared to controls, neither during erroneous nor during correct responses.

Finally, we found no evidence that a suppression of head movements would hinder in any way the generation of saccadic gaze shifts. In patients, as in controls, reactive saccades had similar latencies whether the head was stabilised or free to move, and the same was true for the latency of delayed saccades. Likewise, the gain of primary saccades was not differentially affected irrespective of whether the head was free or stabilised.

It is true, though, that in accordance with clinical experience, a number of Ps had more difficulties to suppress head movements in head stationary conditions. However, their involuntary head movements, like those of Cs, always occurred *after* the initiation of the eye saccade (often only after this saccade was completed) and later than during natural coordination, thus precluding any role as a catalyst for saccades. Head synkinesis during gaze shifts appears to be a phylogenetically old pattern that even healthy subjects cannot not completely suppress as testified by the saccade and eye position-related modulation of neck motor unit activity in head fixed subjects (André-Deshays et al. 1988; André-Deshays et al. 1991). Thus, these movements are primed by the effort to make saccades rather than priming these saccades.

In summary, we suggest that the few quantitative differences that exist between Ps and Cs with regard to eye–head coordination result from the slower saccades of Ps rather than from a different mode of eye–head coordination. For example, the larger contribution of the head to the primary saccade in Ps (cf. Fig. 1b) arose because Ps' head velocity was not as much reduced as their saccadic eye-in-head velocity. A differential reduction of, respectively, eye and head velocity can even alter the pattern of eye–head coordination without there being a change in the underlying mechanism. This was illustrated by one of our HD patients whose eye saccades had become slower than her head movements so that these could overwhelm the eyes by way of a vestibulo-ocular reflex (VOR). As a result, almost immediately after the onset of a gaze saccade, eye-in-head motion reversed its direction and opposed the head movement. Only when the head started to slow down did the eyes resume a movement in the direction of the target.

Pathophysiology

Among the differences between our moderately affected HD patients and controls, the most robust ones were the reduced velocities of (1) the saccades and (2) the head movements in subjects with an early onset of the disease and the gradual *increase* of these velocities with age of onset as opposed to the age-related *reduction* in controls, and (3) the increased rate of failures to suppress reactive saccades ("distractibility") in the delayed and antisaccade conditions. Less consistent were the differential increments of the reaction times (ΔL) of delayed saccades and antisaccades.

It is striking that most of the parameters that deviate from normal in HD were mutually not well correlated. In particular, neither the error rates nor the increments in latency of delayed or antisaccades were in any way related to the variations in saccade or head velocity. Moreover, for some characteristics (latency, ΔL, error rate), no demographic or clinical parameter could be identified that would reliably predict their idiosyncratic variations. These facts suggest a variable pattern of affected brain structures. In the following, we shall focus on three candidate structures in turn, the basal ganglia, the pontine and mesencephalic reticular formations, and the nucleus gigantocellularis of the pons.

Basal ganglia

Neurodegeneration in HD is most prominent in the caudate nucleus whose atrophy is considered the pathological hallmark of the disease (Vonsattel and DiFiglia 1998). The oculomotor division of the caudate (Alexander et al. 1990) is a part of two the pathways relaying frontal cortical signals via substantia nigra pars reticulata (SNpr) to superior colliculus (SC) (Hikosaka et al. 2000). An indirect pathway, relayed by the external pallidal segment and the subthalamic nucleus, exerts a tonic inhibitory control of SC which is thought to prevent the occurrence of undesired saccades that otherwise could be triggered by excitatory inputs to this structure. In contrast, the direct pathway from the caudate to SNpr is thought to facilitate the initiation of purposeful saccades by providing a phasic, spatially selective disinhibition of the collicular motor map (Hikosaka et al. 2000). Therefore, lesions of the caudate would seem to have the potential of affecting both the stability of fixation and the reaction time of purposeful saccades. Since pharmacological inactivation of SNpr or its projection to SC causes a release of uncontrolled spontaneous saccades (Hikosaka and Wurtz 1985a; Hikosaka and Wurtz 1985b), the impairment most likely attributable to basal ganglia pathology would seem to be the distractibility of HD patients. However, selective striatal lesions apparently do

not increase distractibility (Pierrot-Deseilligny et al. 2005). Moreover, an inability to suppress reactive and other involuntary saccades is also observed in many conditions unrelated to basal ganglia dysfunction (Alzheimer: Currie et al. 1991; schizophrenia: Fukushima et al. 1994; psychotic affective disorders: Curtis et al. 2001) and often can be traced back to a malfunction of dorsolateral prefrontal cortex which may also be affected in HD patients (Wolf et al. 2007; Mühlau et al. 2007).

Because SNpr activity modulates SC excitability, it not only affects the release of saccades but could also influence their velocity. Muscimol injection into SC mimicking increased SNpr activity strongly reduces saccadic velocity (Hikosaka and Wurtz 1985a). Thus, a contribution of basal ganglia malfunction to saccade slowing in HD cannot be precluded a priori. However, it is difficult to see how the conditions for distractibility (SC disinhibition) and saccade slowing (SC inhibition) could coexist. The lack of a correlation between distractibility and saccade slowing also argues against a modified SC excitability from basal ganglia pathology as a single common cause.

Reticular formation

At the prenuclear level, saccade velocity depends critically not only on the firing rate of excitatory and inhibitory burst neurones in the paramedian pontine reticular formation (PPRF; horizontal saccades, Henn and Büttner 1982) and in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF; vertical saccades, Büttner-Ennever et al. 1982), but also on the intactness of the omnipauser neurons in the raphe interpositus nucleus of the caudal pons (rip, Kaneko 1996). Little is known regarding the neuropathology of these structures in HD. In a post-mortem analysis of nine patients, Koeppen (1989) observed a shrinkage of the nucleus pontis centralis caudalis (which encompasses PPRF and rip) and a loss of large cells in eight of them. Leigh et al. (1985), examining the riMLF of four deceased patients found signs of brain shrinkage and loss of large cells, although to a significant degree only in the most severely affected patient. Leigh et al. concluded that these changes may not be the only cause of the slowing of vertical saccades in patients and invoked the possibility of an impaired input. This input could originate from the area examined by Koeppen since bilateral lesions of PPRF are known to abolish not only horizontal but also vertical saccades (Henn et al. 1984). Taken together, available evidence is compatible with the notion that pontine degeneration could be partially or fully responsible for the saccade slowing in early affected HD patients without proving it in any way.

In the caudal vicinity of n. pontis centralis caudalis, the rostral part of n. reticularis gigantocellularis (NRG) harbours prenuclear cells of the head motor system (Robinson et al. 1994) which receive monosynaptic input from SC (Cowie and Robinson 1994; Cowie et al. 1994). Its electrical stimulation evokes head movements (Cowie and Robinson 1994; Cowie et al. 1994; Quessy and Freedman 2004) and modifies eye–head coordination (Freedman and Quessy 2004). These findings suggest that NRG is a vital stage on the pathway leading to the execution of the head component of gaze shifts. Regarding a possible degeneration of the NRG area in HD, even less is known than for n. pontis centralis caudalis; in view of its vicinity to this area, an analogous loss of large neurones is an acceptable hypothesis, though. Then, the weakness of the correlation between peak gaze and peak head velocity could indicate that the degenerative process is not reliably centred in a circumscribed area but affects the pontine reticular formation in a manner that varies from patient to patient.

Task sharing between eyes and head

A still unresolved issue is where and how the task sharing between eyes and head is decided. Proposed substrates reach from the frontal eye fields (e.g. Knight and Fuchs 2007) to unidentified stages downstream of the superior colliculus (e.g. Freedman and Quessy 2004). Current consensus acknowledges that the amplitude of the head movement and the timing between the head and the eyes depend on the head error (or a related parameter such as orbital eye eccentricity). This dependence arises because head error indicates how much head movement is required in order to avoid uncomfortable or impossible orbital eye positions during or after the gaze shift (in human: Becker and Jürgens 1992; Fuller 1996; Stahl 1999; in monkey: Freedman and Sparks 1997). Within the limits of this constraint, the head contribution can be widely manipulated by cortical input up to the point of suppressing it. Therefore, the head components of individual gaze shifts can be quite variable, although on average a stereotyped signature is obtained in each subject. In contrast, the eye saccade system requires a precise notion of current head behaviour to determine when saccadic burst activity should start (so as to appropriately delay the saccade when head error is large), when it should cease, and when the VOR should be switched on again during large gaze shifts. How and where the required modulation of burst activity by head-related signals takes place, is yet an unsolved issue. At any rate, it is remarkable that this mechanism was by no means impaired in our HD patients. Even in the most severely affected patients, the coordinative mechanism underlying this behaviour was apparently fully operative. Hence, its neural substrate is likely to be localised outside the structures prominently affected by the disease. As we learn more about the typical extent of neural degeneration in Huntington's Disease from pathoanatomical

studies, we might be able, by way of exclusion, to narrow down the most likely candidate structures.

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