

Parameter-based assessment of spatial and non-spatial attentional deficits in Huntington's disease

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A major challenge for neuropsychological research on Huntington's disease is the identification of biomarkers for the disease at the level of cognitive functions. Given that cortical–striatal–thalamic circuits are particularly vulnerable, possible markers loading functionally on these brain regions should be particularly significant. We investigated whether parametric values derived from a 'theory of visual attention' (TVA) can serve that purpose. They are derived as mathematically independent, quantitative measures of attentional components, and the tasks require only non-speeded vocal responses. As such, the methodology seems well suited for testing patients with motor problems and general cognitive decline. Accumulating neuroanatomical evidence suggests that striatal atrophy in Huntington's disease is asymmetrical with a more pronounced left-sided degeneration. We applied a partial-report paradigm to analyse whether this results in a pathological (leftward) bias of the spatial distribution of attention. In partial report, red target letters are presented either alone or accompanied by either a second target or a green distractor letter presented in the same or in the opposite hemi-field. Since basal ganglia lesions have also been shown to cause spatially non-lateralized impairments, that is, reduced perceptual processing speed and visual working memory (WM) storage capacity within both hemi-fields, we tested possible reductions in these parameters with a whole-report paradigm. Here, columns of five red or green letters are briefly presented and the subject has to report as many as possible. Eighteen patients and 18 matched control subjects performed a partial- and a whole-report task with briefly presented letter displays. In partial report, Huntington's disease patients demonstrated a pathological bias, indicating increased attentional weighting to the left hemi-field. The extent of lateralization was strongly related to age at onset and to the number of cytosine–adenine–guanine (CAG) triplet repeats on gene *IT15*. In contrast, the extent of lateralization was not related to disease progression as reflected by the duration of the disease since onset of the first symptoms. In whole report, the non-lateralized attentional parameters processing speed and visual WM storage capacity were reduced bilaterally in both hemi-fields. The extent of the reduction was related to the disease duration since onset, whereas no significant correlation with CAG repeats or age at onset was found. Laterality of attentional weighting may, therefore, represent a possible trait marker reflecting the intensity of the pathogenic mechanisms, while the reduction of visual processing speed and storage capacity may be state markers for the stage of disease progression.

Keywords: Huntington's disease; cognition; visual attention; spatial extinction; neuropsychological markers

Abbreviations: CAG = cytosine–adenine–guanine; WM = working memory; TVA = theory of visual attention

Received September 27, 2005. Revised January 17, 2006. Accepted January 25, 2006. Advance Access publication February 27, 2006

Introduction

Huntington's disease is an autosomal dominant inherited disorder related to an expansion of the trinucleotide repeat cytosine–adenine–guanine (CAG) in the *IT15* gene on chromosome 4p16.3 (Huntington's Disease Collaborative

Research Group, 1993). The underlying neuropathology is characterized by a degeneration of neurons in the caudate nucleus and the putamen, giving rise to a progressive disruption of functionally segregated fronto-striato-thalamic loops (Andrews and Brooks, 1998; Chow and Cummings, 1999). As a result, clinical manifestations, typically emerging in middle adulthood, involve a triad of motor, psychiatric and cognitive symptoms (Brandt and Butters, 1986; Brown and Marsden, 1988). While motor abnormalities may be the most prominent changes in the clinical state of the disease, they can be preceded by cognitive impairments and by psychiatric symptoms even for years (Lawrence *et al.*, 1998; Watkins *et al.*, 2000; Paulsen *et al.*, 2001; Ho *et al.*, 2003b; Tost *et al.*, 2004). A major challenge for neuropsychological research is the identification of biomarkers for Huntington's disease at the level of cognitive functions. Although, at present, no effective treatment is available, several compounds are currently explored with respect to their therapeutic potential (Bender *et al.*, 2005). As any potential treatment should target at-risk subjects as early as possible, cognitive deterioration mainly affecting perception, attention and executive functions has to be detected from the beginning.

Given that cortical-striatal-thalamic circuits are probably particularly vulnerable in early Huntington's disease (Gomez-Tortosa *et al.*, 2001), and caudate and putamen neuropathology is observed many years before estimated neurological disease onset (Aylward *et al.*, 2004; Paulsen *et al.*, 2005), possible markers loading functionally on these brain regions should be of particular significance.

In our study, we investigate whether parametric values derived from a formal 'theory of visual attention' (TVA; Bundesen, 1990), combined with simple psychophysical tasks (partial and whole report of brief letter arrays), can serve that purpose. The parameter values are derived from the theory are mathematically independent, quantitative measures of attentional components, and the tasks used require only non-speeded vocal responses. As such, the methodology seems well suited to be applied in patients with severe motor problems and general cognitive decline. Importantly, however, the domain of visual attention offers a fruitful field for investigation owing to the fact that basal ganglia structures are closely involved in the control of visuomotor behaviour and attention (see Hikosaka *et al.*, 2000, for a review).

The anterior portion of the caudate nucleus, which is among the first striatal areas affected by Huntington's disease (Vonsattel *et al.*, 1985), receives input from the posterior parietal cortex (Alexander *et al.*, 1986; Hikosaka *et al.*, 2000), a core region for controlling selective visual attention (Kanwisher and Wojciulik, 2000; Behrmann *et al.*, 2004). Congruent with the view that striatal components within cortico-subcortical brain circuits serve the same function as the cortical regions with which they communicate (Middleton and Strick, 2000), there is evidence suggesting that the caudate nucleus has an important role for spatial

attention shifts and orienting. For instance, in monkeys, unilateral pharmacological lesions of the caudate nucleus have been shown to induce deficits in oculomotor and attentional orienting to the contralateral hemi-field (Apicella *et al.*, 1991; Kato *et al.*, 1995; Miyashita *et al.*, 1995). In humans, clinical studies have confirmed the occurrence of similar deficits of spatial attention after unilateral striatal lesions (Damasio *et al.*, 1980; Sakashita, 1991; Fimm *et al.*, 2001; Karnath *et al.*, 2002; Habekost and Bundesen, 2003) or in Parkinson's disease (Villardita *et al.*, 1983).

In Huntington's disease, although the presence of attention deficits has been demonstrated in a variety of tasks (Jahanshahi *et al.*, 1993; Georgiou *et al.*, 1995, 1997; Sprengelmeyer *et al.*, 1995; Roman *et al.*, 1998; Müller *et al.*, 2002; Fielding *et al.*, 2005), the existence of impaired spatial attention functions has remained controversial (Filoteo *et al.*, 1995; Tsai *et al.*, 1995; Georgiou *et al.*, 1996). This is surprising in light of the accumulating neuroanatomical evidence that striatal atrophy in Huntington's disease is asymmetrical. While there is a bilateral volume reduction of the striatum that seems to be related to the number of CAG repeats, it seems to be more pronounced on the left side both in pre-symptomatic and in symptomatic patients (Rosas *et al.*, 2001; Thieben *et al.*, 2002; Paulsen *et al.*, 2004; Kipps *et al.*, 2005). In fact, the asymmetry found in healthy subjects, with larger striatal volumes on the left side, seems to be reversed in patients with Huntington's disease (Rosas *et al.*, 2001).

In line with such results suggesting a more pronounced left-hemispheric pathology, Ho *et al.* (2004) reported a consistent leftward spatial bias in Huntington's disease patients at a mild clinical stage. This became manifest as a significant deviation to the left from the objective mid-point in a visuo-motor line-bisection task compared with normal subjects. This pathologically enhanced 'pseudo-neglect,' which is, to a lesser extent, also demonstrated by normal subjects (Luh, 1995; Jewell and McCourt, 2000), was again present as a tendency for a more pronounced leftward bias in the purely perceptual greyscales task (Mattingley *et al.*, 2004). For this task, but not for line bisection, Ho *et al.* (2004) found a significant association between the degree of deviation and the number of CAG triplets. On the other hand, line-bisection performance, but not the greyscales task, was related to a bilateral cortical degeneration in the area of the temporoparietal junction, especially within the region of the angular gyrus. Since the authors focused their analysis on cortical structures and did not use the basal ganglia as a region of interest, a possible correlation with unilateral (left-sided) striatal volume loss cannot be excluded, however.

Taken together, the available anatomical and behavioural data suggest a more pronounced degeneration of the left striatum that may be detected by tests of spatial attentional deviation. Both striatal volume loss and a leftward deviation in a purely perceptual task seem to be related to the severity of the genetic defect in Huntington's disease. As a result, a purely perceptual task, more sensitive than the greyscales task, could be a useful cognitive biomarker for Huntington's

disease patients, given that asymmetries in striatal atrophy seem to exist from the beginning.

To test this assumption, we used partial report of brief letter arrays. In this task, either a single-target stimulus appears within one hemi-field or two stimuli appear bilaterally, one in each hemi-field. Miyashita *et al.* (1995) used a similar paradigm in monkeys with unilateral caudate lesions and found that a contralateral stimulus, which alone was processed normally, was suppressed in the presence of an ipsilateral stimulus. Therefore, such a task might represent a sensitive test for striatal function. In fact, the partial-report task, combined with the analytical power of the 'theory of visual attention' (TVA) of Bundesen (1990), has already proven its capability in revealing spatial attentional deficits in patients with brain damage (Duncan *et al.*, 1999, 2003; Habekost and Rostrup, 2005; Peers *et al.*, 2005; Bublak *et al.*, 2006). Specifically, using this approach, Habekost and Bundesen (2003) found a rightward spatial bias of attention, which was undetected by conventional testing, in a patient with a right-sided brain lesion involving the head of the caudate nucleus, the putamen and the immediately overlying white matter and frontal gyri.

We now applied the same method for further analysis of spatial lateralization in Huntington's disease patients, that is, for assessing the reliability of the leftward lateralization in patients in a clinical state, for measuring its severity and for elucidating possible associations with other clinical markers such as the amount of the genetic defect and illness duration. In order to draw more precise conclusions about the nature and the severity of the attentional bias in Huntington's disease patients, we also wanted to (i) systematically analyse those conditions in which the pathological bias does or does not influence visual performance and (ii) obtain a quantitative estimation of the degree of prioritization of the left over the right visual field. This was the first aim of our study.

The second aim was derived from a further important finding reported by Habekost and Bundesen (2003) in their patient with a right-sided basal ganglia lesion. This patient not only had a pathological ipsilesional bias of spatial attention but also showed spatially non-lateralized impairments, that is, reduced perceptual processing speed and visual working memory (WM) storage capacity within both hemi-fields. In a further study (Habekost and Rostrup, 2005), involving a larger group of subjects with right-hemispheric damage, reduced processing speed (especially prevalent in the contralesional, left hemi-field) was associated with lesions encompassing the putamen and adjacent white matter. Therefore, we also analysed non-lateralized attentional parameters, that is, processing speed and WM storage capacity, in Huntington's disease. Speed reductions and impaired WM have already been reported earlier for such patients (e.g. Jahanshahi *et al.*, 1993; Sprengelmeyer *et al.*, 1995; Lawrence *et al.*, 2000; Müller *et al.*, 2002) and, again, we were interested in relating the attentional parameters derived from the TVA-based method to clinical markers.

To test the clinical relevance of these three attentional parameters assessed in Huntington's disease (spatial bias, speed and WM storage), they were correlated with several medical indices. First, as an index reflecting the intensity of the underlying pathogenetic mechanisms, we used the age of onset (appearance of first clinical symptoms) and, in those subjects who underwent genetic testing, the number of CAG-triplet repeats. High CAG-triplet numbers and early age at onset are coupled with symptom severity (Gusella and McDonald, 1995) and neuropathological damage (Furtado *et al.*, 1996; Penney *et al.*, 1997). Second, as an index reflecting progression stage, the duration of the disease since age of onset (as documented in the medical records) was used. The parameters were also correlated with medication, to control for possible confounding effects.

Before presenting our methods and results, however, we give a brief introduction into the 'theory of visual attention' and into the partial- and whole-report procedures.

The theoretical and methodological framework

Our experiments included partial and whole report of briefly presented letter displays designed by Duncan *et al.* (1999) on the basis of a 'theory of visual attention' (TVA; Bundesen, 1990, 1998, 2002; Bundesen *et al.*, 2005). A detailed formal description and the equations of TVA can be found in Kyllingsbæk (2006).

TVA as a mathematical model instantiates the 'biased competition' framework, the currently dominating view of visual attention in cognitive neuroscience (Desimone and Duncan, 1995, 1996; Schneider, 1995; Duncan *et al.*, 1997; Kastner and Ungerleider, 2000; Reynolds and Desimone, 2003). Objects in the visual field are processed in parallel and compete for selection, that is, for 'conscious' representation within the information processing system. The resulting race among objects can be biased in such a way that some objects are favoured for selection, based either on stimulus-driven, 'bottom-up' or on intentional, 'top-down' factors.

In TVA, selection of an object is synonymous with its encoding into a visual WM store with limited capacity. The probability of selection is determined (i) by an object's processing rate ν , which depends on the attentional weight (w) it receives, and (ii) by the capacity of the WM store (if the store is filled, the selection process terminates). Hence, TVA provides parameters for characterizing the general processing efficiency of the information processing system (processing rate and storage capacity), and for characterizing specific aspects of attentional weighting, such as, for example, spatial distribution of attention. Detailed descriptions of the model fitting procedure, which is based on the maximum likelihood method (e.g. Ross, 2000) and on the software used, can also be found in Kyllingsbæk (2006). A detailed neural interpretation of mathematically specified TVA concepts

for the primate visual brain is described in Bundesen *et al.* (2005).

The spatial distribution of attention can be estimated from a partial-report task, where subjects have to report target objects, only, which are pre-specified (e.g. with respect to colour), whilst ignoring distractors. From the probability of target identification, separate attentional weights are derived for the left hemi-field (w_L) and for the right hemi-field (w_R), respectively. Parameter w_λ , reflecting the spatial distribution of attention, is defined as the ratio $w_L : (w_L + w_R)$. Hence, a value of $w_\lambda = 0.5$ indicates balanced weighting, values of $w_\lambda > 0.5$ indicate a leftward and values of $w_\lambda < 0.5$ a rightward spatial bias. If Huntington's disease patients indeed show a 'pseudo-neglect' preference for the left side of space, this would be indicated by an w_λ value > 0.5 , because weights for objects to the left of fixation would be higher than those for objects to the right.

The general information processing efficiency is assessed within a whole-report task, in which subjects are briefly presented with multiple stimuli and have to identify as many as possible. The probability of identification is modelled by an exponential growth function, in which the growth parameter reflects the rate at which the stimuli (objects) can be processed (processing speed C : number of element/s), and the asymptote of the growth function indicates the maximum number of objects that can be represented within WM (WM storage capacity K).

Method

Subjects

Eighteen patients (5 male, 13 female) with the diagnosis of Huntington's disease in a clinical state were recruited from the Huntington-center South, Taufkirchen, Germany, a special neuropsychiatric ward for Huntington's disease patients. Patients were included when they were able to hold fixation, understand verbal instructions and concentrate on a task for ~30 min. Informed consent according to the Declaration of Helsinki II was obtained from all participants or their legal representatives. According to the Edinburgh Handedness Inventory (Oldfield, 1971) 17 patients were right-handed and 1 was left-handed. All of them had normal or correct-to-normal visual acuity. For a subset of 13 patients, CAG-triplet repeat length had been assessed. All patients were taking medication including antihyperkinetics/neuroleptics, either alone or in combination with antidepressants ($n = 8$), nootropics ($n = 7$), benzodiazepines ($n = 1$), parasympathomimetics ($n = 1$), anti-parkinsonian agents ($n = 2$) and anticonvulsants ($n = 1$). Relevant biographical and clinical data of each patient are listed in Table 1.

An age and education-matched control group of 18 subjects (5 male, 13 female) was tested. None of the control subjects reported any neurological or psychiatric history. All subjects had normal or corrected-to-normal vision. Mean age was 46.8 years (SD = 10.9) and mean education was 9.5 school years (SD = 1.8).

Procedure

The stimuli and the general method were similar to those of Duncan *et al.* (1999) and Finke *et al.* (2005).

Table 1 Patient details

Patient	Sex	Age	Hand	Education (years)	Duration (years)	Onset (years)	CAG (mg/day)	Motor symptoms	Accessory diagnoses	Medication (CPZ)
HM	F	42	R	9	5	37	n.a.	DK, DA, A	—	600
CD	F	64	R	10	12	52	n.a.	DK, DA, SSA	F07.9	3000
MK	F	64	R	8	3	61	42	DK	—	200
EB	F	64	R	9	8	56	n.a.	DK	F02.2	800
GH	F	50	R	8	6	44	45	DA	F07.0	400
JF	M	53	R	8	7	46	46	DK, DA, SSA	F02.2	100
HL	M	38	R	9	7	31	52	DK, DA	F02.2	800
IF	F	48	R	8	8	40	n.a.	DK, DA, SSA	F07.8; F02.2	780
NH	M	35	R	8	1.5	33.5	47	DK, DA, SSA	F06.32	400
PH	M	57	R	8	5	52	43	DK, DA, SSA	F06.32; F07.9	435
CM	F	35	R	9	1	34	46	DK, DA, SSA	—	980
VP	F	39	R	13	3	36	47	DK, DA, SSA	F06.32	270
MSa	F	33	L	10	1	32	50	DK, DA, SSA	F07.9	1100
MSb	F	39	R	9	2	37	n.a.	DK, DA, SSA	—	800
BH	F	51	R	8	4	47	44	DK, DA, SSA	F06.2	375
GW	M	45	R	10	2	43	45	DK, DA, SSA	F06.32	180
DH	F	35	R	9	2	33	46	DK, DA, SSA	F06.32	300
SJ	F	49	R	10	4	45	46	DK, DA, SSA	—	120
Mean		46.7		8.6	4.7	42.7	46.1			646.7
SD		(10.6)		(2.5)	(3.0)	(8.9)	(2.7)			(661.6)

Hand = handedness according to the Edinburgh Handedness Inventory (Oldfield, 1971); Duration = duration of Huntington's disease since first symptoms; Onset = age at onset of the clinical state of the illness; CAG = CAG-triplet repeat length on gene *IT15* on chromosome 4p; Medication (CPZ) = neuroleptic potency of medication converted to chlorpromazine equivalents in mg/day; F = female; M = male; DK = dyskinesia; DA = dysarthria; A = ataxia; SSA = slowed saccadic eye movements; F02.2 = dementia in Huntington's disease; F06.2 = organic delusional disorder; F06.32 = organic depressive disorder; F07.0 = organic personality disorder; F07.8 = organic personality and behavioural disorder; F07.9 = unspecified mental disorder due to brain disease.

Stimuli were presented on a personal computer with a 17" monitor (1024 × 768-pixel screen resolution; 70 Hz refresh rate). Viewing distance was ~50 cm. For the Huntington's disease patients, a well-padded chinrest was used to keep viewing distance and head posture constant. The patients were tested in hospital, and the control subjects in a laboratory at the University of Eichstaett-Ingolstadt. At both locations, experiments were conducted in a dimly lit room.

Each subject completed two test sessions lasting ~0.5 h on different days. In one session, the whole-report, and in the other session, the partial-report experiment was administered. The order of the different sessions was counterbalanced across subjects.

In both experiments, first, subjects were instructed to fixate a central white digit (0.3° visual angle) presented for 300 ms. Then, after a gap of 100 ms, red and/or green letters (0.5° high × 0.4° wide) were presented on a black background for a brief pre-determined exposure duration. Individual exposure durations were determined in a preceding short practice session to agree with a criterion value. The letters for a given trial were randomly chosen from the prefixed set {ABEFHJKLMNPRSTWXYZ}, with the same letter appearing only once. Each subject received the same letter displays in the same order. Stimuli were either unmasked or masked. In unmasked conditions, owing to visual persistence, the effective exposure durations (Sperling, 1960) are prolonged, usually by several hundred milliseconds. Masks should terminate this internal, 'iconic' stimulus representation and consisted of squares of 0.5° filled with a '+' and an 'x' presented for 500 ms at each stimulus location.

The verbal report of individual letters was performed in arbitrary order and without speed stressing. Subjects were instructed to report only those letters they had surely recognized. The experimenter entered the responses on the keyboard and then started the next trial.

The total number of trials was 288 in the partial-report and 192 in the whole-report experiment, separated into blocks of 48 trials each. Within each block, the different trial types of the experiment were presented equally often and in randomized order.

Partial report

On each trial, either a single target (letter), or a target plus a distractor (letter), or two targets (see Fig. 1) were presented at the corners of an imaginary square with an edge length of 5°, centred on the screen. Two stimuli were presented either horizontally (row display) or vertically (column display), but never diagonally. Targets were red and distractors were green. Subjects should only report the targets and ignore the distractors.

An initial test phase consisting of 32 trials was used to determine the individual exposure duration and whether or not masks should be used, aiming for 60–80% accuracy in single-letter trials. Masks were used for all participants who were able to report masked letters. However, unmasked stimuli were used in a number of Huntington's disease patients and one control subject (GR) who had severe difficulties in naming masked single-target letters. In the experiment itself, all stimuli displays were presented for the individually adjusted exposure duration. In Table 2, the exposure duration chosen for each participant is listed.

Sixteen different conditions resulted (4 single-target, 8 target plus distractor, and 4 dual-target conditions) with 42 trials each.

Whole report

On each trial, a column of five equidistant letters was presented 2.5° of visual angle either to the left or to the right of fixation

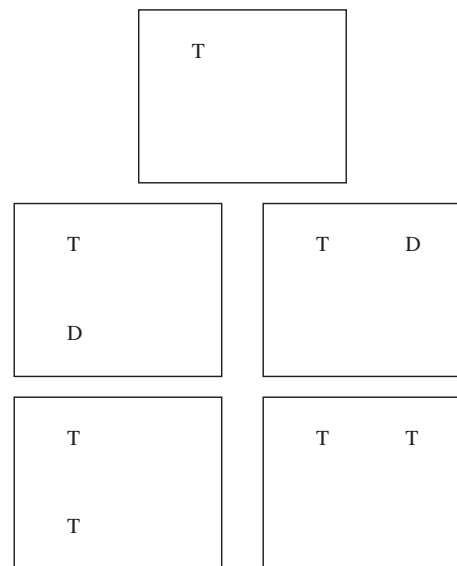


Fig. 1 Different trial types of the partial-report experiment with targets (depicted as 'T') and distractor letters (depicted as 'D'). Targets and distractors differed with regard to colour; targets were red and distractors were green. Presentation of a single target (at the top) of a target accompanied by a distractor in the same or the opposite visual hemi-field (left and right centre) and of two targets in the same or in opposite hemi-fields (bottom left and right).

Table 2 Exposure durations of patients and controls in the partial-report experiment

Patients		Controls	
HM	157 (u)	MB	100
CD	157 (u)	MS	157
MK	157 (u)	GR	157 (u)
EB	157 (u)	WS	157
GH	157 (u)	IG	128
JF	300 (u)	WH	100
HL	600 (u)	WR	128
IF	450 (u)	MJ	100
NH	86 (u)	KK	100
PH	450 (u)	HR	157
CM	300	PB	100
VP	300	CR	100
MSa	157	GK	128
MSb	157	CK	128
BH	300	InG	128
WG	300	PB	157
DH	300	CH	100
SJ	300	KL	86

u = stimuli were unmasked.

(see Fig. 2). All letters were either red or green. Subject's task was to report as many letters as possible.

Again, the experiment comprised two phases: in Phase 1, three exposure durations were determined for Phase 2, in which the data were collected.

In Phase 1 consisting of 24 trials the individual exposure duration was determined at which the subject could report, on average, one letter correctly. This value was then used as the middle exposure

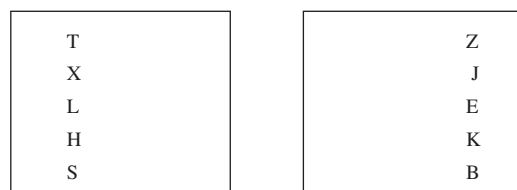


Fig. 2 Different trial types of the whole-report experiment with presentation of five equidistant letters in columns on the left or the right of the fixation point.

Table 3 Exposure durations of patients and controls in the whole-report experiment

Patients		Controls	
HM	157, 300, 600	MB	157, 300, 600
CD	157, 300, 600	MS	157, 300, 600
MK	157, 300, 600	GR	157, 300, 600
EB	157, 300, 600	WS	157, 300, 600
GH	157, 300, 600	IG	157, 300, 600
JF	157, 300, 600	WH	86, 157, 300
HL	157, 300, 600	WR	86, 157, 300
IF	157, 300, 600	MJ	86, 157, 300
NH	300, 600, 1200	KK	86, 157, 300
PH	300, 600, 1200	HR	157, 300, 600
CM	300, 600, 1200	PB	43, 86, 157
VP	86, 157, 300	CR	43, 86, 157
MSa	157, 300, 600	GK	43, 86, 157
MSb	157, 300, 600	CK	43, 86, 157
BH	300, 600, 1200	InG	157, 300, 600
WVG	300, 600, 1200	PB	86, 157, 300
DH	300, 600, 1200	CH	86, 157, 300
Sj	300, 600, 1200	KL	157, 300, 600

duration, together with a shorter (half as long) and a longer (twice as long) exposure duration. In Table 3, the three exposure durations chosen for each participant are listed.

In Phase 2, letter displays were presented either masked or unmasked. The resulting six ‘effective’ exposure durations aimed at a broad performance spectrum that reflects the early as well as the late section of the subject’s whole-report function. Twelve different trial conditions were obtained (2 hemi-fields \times 3 exposure durations \times 2 masking conditions), each with 56 trials.

Results

Demographical data of patients and controls

Patient and control groups did not differ significantly from each other with respect to age, sex or duration of education (all $P > 0.55$). As expected, the 13 genetically tested patients showed a highly significant inverse correlation between CAG repeats and age at onset ($r = -0.83$; $P < 0.01$, two-sided).

Comparison of patients and controls

In the Results section, we first describe the partial- and then the whole-report results. We also report the degree of

correspondence between the observed data and those predicted by the TVA model-based parameter estimates. The model fitting procedure applied in the present study was largely identical with that used by Duncan *et al.* (1999). Then, we present the analyses as they relate to each of the three main questions that were specified within the Introduction section.

We initially present the qualitative pattern of performance obtained by each group. We also report the degree of correspondence between the observed data and those predicted by the TVA model-based parameter estimates. Then, we present the parameter estimates obtained by each participant and compare the results of both groups. To provide information about the clinical relevance of the TVA parameters in the Huntington’s disease group, we document their relationship to illness duration since onset of the first symptoms to age at onset of first clinical symptoms, and to the number of CAG repeats. Finally, we report the inter-parameter correlations between the partial-report parameter laterality of attentional weighting on the one hand and the whole-report parameters processing speed and WM storage capacity on the other.

Partial-report results

The exposure durations used for each participant in the partial-report experiment are listed in Table 2.

The laterality of attentional weighting is a measure of the spatial distribution of attentional weights across the left versus the right visual hemi-field. To illustrate attentional weighting across the two hemi-fields, Fig. 3 shows separately the mean proportion of target letters correctly identified by patients and controls in each hemi-field for five experimental conditions: single-target letter; target accompanied by a distractor or by a target in the ipsilateral field and target accompanied by a distractor or a target in the contralateral field.

In general, the performance levels of both groups in the different experimental conditions resembled those of other partial-report experiments (e.g. Duncan *et al.*, 1999) and were in accordance with the prediction from the TVA model: accuracy was highest in single-target conditions, decreased in conditions with a distractor accompanying the target and was lowest in conditions with a second-target stimulus.

In the single-target baseline condition, due to the individual adjustment of exposure duration, both groups showed a comparable accuracy level ($t = 1.09$, $P > 0.25$) and, on average, reached the 80% accuracy criterion (Huntington’s patients: $M = 81.72$, $SD = 15.91$; controls: $M = 86.17$, $SD = 6.81$).

A visual comparison of performance for left- and right-sided targets indicates visual field differences only in the group of Huntington’s disease patients. Highly similar values for both fields were achieved by the patients in conditions with single targets and with two unilateral stimuli. When two stimuli were presented bilaterally, however, an asymmetric side-effect occurred. Accuracy was much higher for

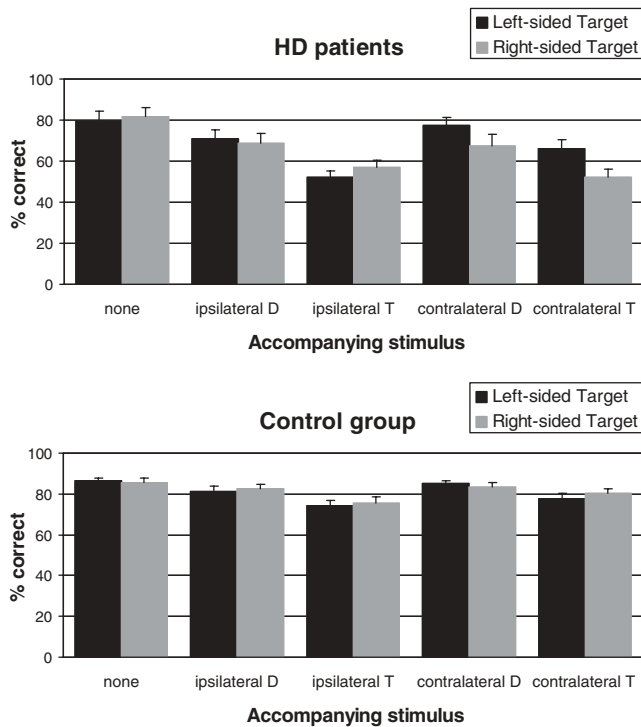


Fig. 3 Mean proportion of correctly reported letters in per cent for left- (black bars) and right-sided targets (grey bars) for Huntington's disease patients (upper graph) and for control subjects (lower graph): single targets, targets accompanied by an ipsilateral target or distractor, and by a contralateral target or distractor. The error bars show the standard deviations. T = target; D = distractor.

left- than for right-sided targets, regardless of whether the opposite stimulus was a distractor or a target stimulus. In contrast, the control subjects performed comparably across both hemi-fields in all conditions.

To analyse these differences statistically, an ANOVA (analysis of variance) with accuracy as the dependent variable was conducted with the between-subject factor Group (Huntington's disease patients, control subjects) and the within-subject factors Side of Visual Field (left, right) and Target Type (alone, with ipsilateral distractor, with contralateral distractor, with ipsilateral target, with contralateral target). Highly significant effects were found for the main effects of Group [$F(1, 34) = 2.40$; $P < .01$] and Target Type [$F(4, 31) = 43.36$; $P < .01$], the two-way interactions Group \times Target Type [$F(4, 31) = 10.34$; $P < 0.01$] and Side \times Target Type [$F(4, 31) = 8.60$; $P < 0.01$] and the three-way interaction Group \times Target Type \times Side [$F(4, 31) = 6.46$; $P < 0.01$]. To further analyse the three-way interaction, separate ANOVAs were carried out for both groups with Side and Target Type as factors. For the Huntington's disease patients, a significant effect of Side [$F(1, 17) = 5.47$; $P < 0.05$], a highly significant effect of Target Type [$F(4, 14) = 39.13$; $P < 0.01$], and also a highly significant interaction of Target Type \times Side [$F(4, 14) = 16.82$; $P < 0.01$], was revealed. For the unilateral presentation conditions Bonferroni-corrected *post hoc* tests showed that accuracy was more or less comparable across both

hemi-fields. Only for targets accompanied by ipsilateral targets a non-significant tendency for higher accuracy in the right hemi-field was found ($t = -1.89$; $P < 0.08$). For both bilateral presentation conditions, however, accuracy was lower in the right compared with the left hemi-field irrespective of whether the opposite stimulus was a distractor ($t = 3.44$, $P < 0.01$) or a target ($t = 4.09$, $P < 0.01$). This means that report of letters appearing in the right hemi-field was much more disturbed by additional letters in the left hemi-field than report of letters in the left hemi-field was by letters in the right hemi-field.

In contrast, for the control subjects, only the factor Target Type was highly significant [$F(4, 14) = 9.36$; $P < 0.01$] (all other $P > 0.30$). Accuracy was highest for single targets and targets accompanied by opposite distractors, decreased slightly for targets accompanied by distractors in the same hemi-field and decreased further for targets accompanied by another target in the same or the opposite hemi-field.

Laterality of attentional weighting

The qualitative pattern of each group's performance was quantitatively described by a TVA-based model that produced individual estimates of attentional weights w_i separately for each of the four display locations.

The mean scores for the different partial-report conditions and those predicted on the basis of the best fits of the TVA model parameters w_λ showed a good correspondence, with a mean correlation of $r = 0.91$ ($SD = 0.06$) for patients and of $r = 0.80$ ($SD = 0.21$) for controls. The predicted values accounted for $r^2 = 84\%$ of the variance of the observed mean score in patients and for $r^2 = 68\%$ in controls.

To differentiate between true attentional and pure sensory effects of stimulus processing, the TVA model additionally provides parameter estimates for basic sensory effectiveness A_i for each of the four possible stimulus locations. A_i parameters, which are independent of attentional weighting, are derived from the accuracy for each (target) location in the single-target condition. Analogous to the computation of the w_λ value for spatial attentional weighting, equal sensory effectiveness of stimuli in both visual hemi-fields is indicated by an A_λ value of 0.5 [$A_L/(A_L + A_R)$]. A_λ values above and below 0.5 indicate better sensory processing on the left and on the right side, respectively.

Parameters (relative sensory effectiveness A_L and A_R , spatial distribution of sensory effectiveness A_λ and spatial distribution of attentional weighting w_λ) from TVA's best fit to each participant's data are shown in Table 4. A_L and A_R were calculated as the mean value of sensory effectiveness for upper and lower positions on the left and on the right and w_L and w_R were similarly calculated as the mean of attentional weights for the upper and lower positions on the left and on the right.

The index for the spatial distribution of sensory effectiveness A_λ within both visual hemi-fields did not differ significantly between patients and controls ($P > 0.25$). Neither the patient nor the control group's index differed

Table 4 TVA partial-report parameters of patients and controls

	A_L	A_R	$A_L/(A_L + A_R)$	$w_L/(w_L + w_R)$
<i>Patients</i>				
HM	1.07	0.59	0.64	0.62
CD	2.16	2.12	0.50	0.59
MK	1.31	1.12	0.54	0.64
EB	0.98	1.25	0.44	0.59
GH	0.88	0.87	0.50	0.69
JF	0.98	1.08	0.47	0.65
HL	1.74	2.81	0.38	0.82
IF	2.37	3.67	0.39	0.68
NH	2.74	2.34	0.54	0.62
PH	3.06	3.37	0.48	0.50
CM	2.54	3.48	0.42	0.70
VP	4.56	4.54	0.50	0.64
Msa ^a	3.37	2.48	0.58	0.58
MSb	1.57	1.59	0.50	0.66
BH	2.63	4.02	0.40	0.59
GW	3.40	3.46	0.50	0.59
DH ^b	1.92	1.63	0.54	0.62
SJ	2.99	4.10	0.42	0.67
Mean	2.24	2.47	0.49	0.63
(SD)	(1.02)	(1.25)	(0.07)	(0.08)
<i>Controls</i>				
MB	2.99	2.91	0.51	0.43
MS	1.66	1.70	0.49	0.44
GR	3.12	6.45	0.33	0.65
WS	2.05	1.75	0.54	0.41
IG	3.32	4.14	0.45	0.51
WH	7.49	4.22	0.64	0.54
WR	1.66	1.90	0.47	0.44
MJ	3.80	2.33	0.62	0.48
KK	3.13	4.20	0.43	0.55
HR	4.16	1.67	0.71	0.56
PB	2.86	4.38	0.39	0.50
CR	6.49	5.22	0.55	0.48
GK	2.80	2.60	0.52	0.50
CK	3.75	3.78	0.50	0.50
InG	3.32	4.13	0.45	0.51
PB	2.94	2.03	0.59	0.59
CH	3.11	3.49	0.47	0.52
KL	2.68	2.65	0.50	0.41
Mean	3.64	3.42	0.51	0.51
(SD)	(1.62)	(1.41)	(0.09)	(0.06)

A_L , A_L = sensory effectiveness for the left and the right hemi-field, respectively; $A_L/(A_L + A_R)$ = laterality index of sensory effectiveness; $w_L/(w_L + w_R)$ = laterality index of attentional weighting.
^aLeft-handed subject. ^bOwing to technical trouble parameter estimations were based on only 188 trials.

significantly from 0.5, the value indicating equal sensory effectiveness on both sides (both $P > 0.35$).

The laterality of attentional weighting w_λ , in contrast, was highly different between groups. The patients showed highly significant increased w_λ -values compared with the controls ($t = 5.20$; $P < 0.01$), indicating a spatial bias to the left visual hemi-field. Whereas the estimates of the control group did not differ significantly from the unbiased value 0.5, indicating equal distribution of weights across both hemi-fields ($P > 0.70$), those of the patients showed a highly significant deviation from 0.5 ($t = 6.80$; $P < 0.01$). In the

Huntington's disease patient group, therefore, attentional weighting was unbalanced with much higher attentional weights assigned to left-sided than to right-sided stimuli.

Because of the known influence of handedness on spatial attention (e.g. Brodie and Dunn, 2005), we excluded the data of the left-handed patient from the further correlations that were carried out to assess the clinical relevance of changes in laterality of attentional weighting w_λ .

With respect to the clinical indices in question, the laterality of attentional weighting showed a highly significant negative correlation to the age at onset ($r = -0.79$, $P < 0.01$), and, in patients with available genetic information, a significant and numerically high correlation to the CAG-repeat length ($r = 0.88$; $P < 0.01$). These correlation coefficients indicate that the stronger the leftward bias in Huntington's disease patients the earlier the onset of symptoms and the more severe the genetic defect (see Fig. 4).

No significant correlation was found between lateral bias and illness duration ($r = 0.13$; $P > 0.60$). The correlation with medication dosage (converted to chlorpromazine equivalents according to Rijcken *et al.* (2003; $r = 0.05$, $P > 0.85$) was not significant.

Whole-report results

The qualitative pattern of the whole-report performance of a representative subject of each group is illustrated in Fig. 5A (patient CD) and B (control subject IG). In the upper graphs of each panel, the mean numbers of letters reported correctly by the subject as a function of effective exposure duration (see below) are presented separately for the left and the right hemi-field. In addition to the observed data points, the solid line represents the best fit to the data based on the TVA parameter estimates. As can be seen, there is a close correspondence between the theoretically predicted and the observed mean scores. The lower graphs of each panel show proportions of trials with 0, 1, 2, 3 and (in the control subject) 4 letters reported correctly, separately for each hemi-field and effective exposure duration.

In both graphs, the function relating number of reported elements to exposure duration initially exhibits the steepest rise and flattens as exposure duration increases to some hundred milliseconds. Visual inspection, however, indicates that the mean scores of patient CD have a much slower increase and approach the asymptote at a lower level than that of the control subject IG. The dashed horizontal line indicating the WM storage capacity K estimated by TVA is, accordingly, lower in the patients' graph. These impairments are evident bilaterally in the left as well as in the right visual hemi-field and performance is very comparable on the left and the right side.

In the lower graphs it can be seen that patient CD as well as the control subject IG show a systematic increase of trials with higher numbers of letters reported with increasing exposure duration. The maximum scores at each exposure (lower graphs), however, are clearly reduced in CD in

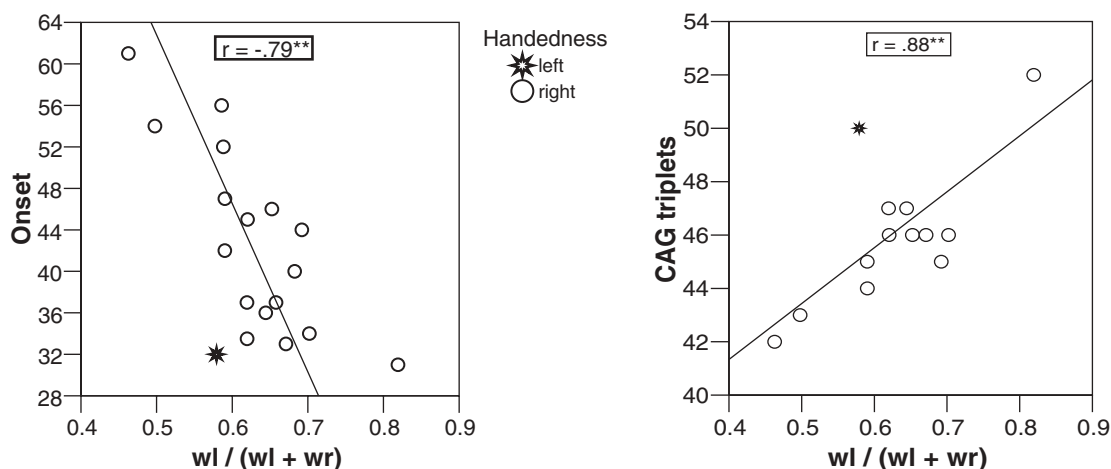


Fig. 4 Scatterplots relating the TVA parameter laterality of attentional weighting w_L to the age at onset (left) of the first Huntington's disease symptoms and to the CAG-triplet repeat length (right) in the Huntington's patient group. Onset = subject's age at the onset of the clinical state of the illness; triplets = cytosine–adenine–guanine (CAG) triplet repeat length on gene *IT15* on chromosome 4p; $w_L/(w_L + w_R)$: laterality of attentional weighting w_L . **Correlation is significant at the $P < 0.01$ level.

comparison to the control subject. The maximum number of letters reported on any given trial is three in patient CD and four in control subject IG.

Again, for each subject, the qualitative pattern of performance was quantitatively described by TVA model fitting, which produced individual estimates for processing speed C and WM storage capacity K . Parameters for TVA's best fits to the data of each participant are shown in Table 5. Processing speed C for the left (C_L) and the right (C_R) visual hemi-field was estimated separately as the summed v values for the objects presented to the left and to the right of fixation, respectively. C reflects the total rate of visual information uptake (number of objects per second), corresponding to the slope of the fitted mean-score curve at t_0 . WM storage capacity K for the left (K_L) and the right (K_R) hemi-field was also estimated separately. It reflects, in effect, the maximum number of letters reported on any single trial.

The observed mean scores for the different exposure durations and theoretically predicted scores show a high correspondence. The average Pearson product–moment correlation coefficient, r , between the observed values and TVA's best fits to the data was 0.92 (SD = 0.06) in the patient and 0.94 (SD = 0.04) in the control group. The predicted values accounted for $r^2 = 85\%$ of the variance of the observed mean score in patients and for $r^2 = 90\%$ in controls.

Separate group analyses were carried out for processing speed C and visual WM storage capacity K to test for differences between the patients' and controls' estimates. For both TVA parameters ANOVAs with the between-subject factor Group (2) and the within-subject factors Side of Visual Field (2) were carried out.

Processing speed

ANOVA revealed a highly significant difference between groups [$F(1, 34) = 73.55$; $P < 0.01$], indicating severely reduced processing speed in the Huntington's disease patients

compared with controls. A non-significant tendency for the effect Side was found [$F(1, 34) = 3.53$; $P < 0.07$]. The Group \times Side interaction was highly significant [$F(1,34) = 9.64$; $P < 0.01$]. In the patient group there was a non-significant tendency for a faster processing speed on the left than on the right side (6.26 versus 5.78; $t = 1.92$, $P < 0.08$). The control subjects, in contrast, were significantly slower on the left than on the right (24.26 versus 26.61; $t = -2.63$, $P < 0.05$). The highly significant reduction of processing speed in the patients compared with controls, however, was found for both hemi-fields (C_L : $t = 7.98$, $P < 0.01$; C_R : $t = 8.81$, $P < 0.01$). In both groups, processing speeds on both sides (C_L and C_R) were highly correlated to each other (Huntington's disease patients: $r = 0.84$; $P < 0.01$; control subjects: $r = 0.93$; $P < 0.01$). Neither in the left nor in the right hemi-field did any of the patients reach the processing speed of the slowest control subject.

Therefore, since we were mainly interested in general speed differences, our analyses for parameter C used the average value across the whole visual field.

WM storage capacity

ANOVA revealed a highly significant difference between groups [$F(34,1) = 17.20$; $P < 0.01$], indicating that the estimates of WM storage capacity for the patients were far below those of the controls. No significant effects were found for Side or for the Group \times Side interaction (both $P > 0.20$). Since, as for processing speed, no significant Side differences were obtained for the WM storage capacity in the Huntington's disease patients, the mean value of the estimates for the left and the right side, parameter K , was used as an estimate of the general WM storage capacity across the whole visual field. Although significantly reduced on average, the WM storage capacity of seven patients (39%) was within the control subjects' range.

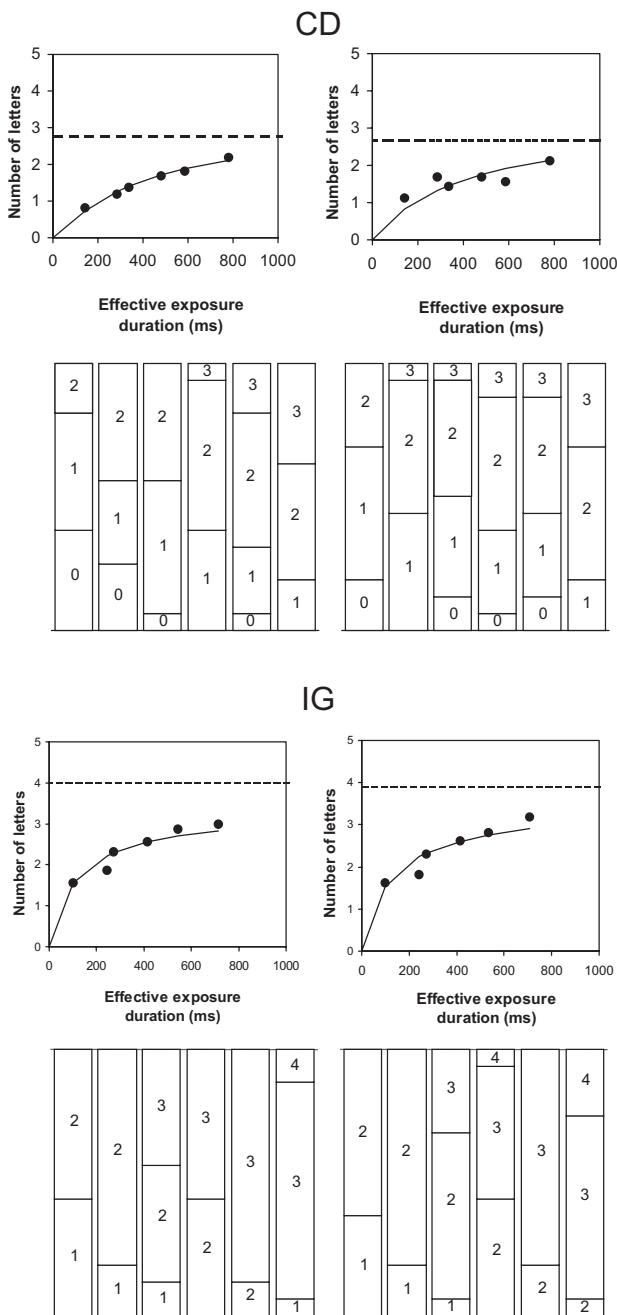


Fig. 5 Whole-report performance in the left and the right hemi-field (A) for a representative patient (CD) and (B) for a representative control subject (IG). In the upper graphs, the mean number of correctly reported letters is shown as a function of effective exposure duration. Solid curves represent the best fits from the TVA to the observations. The estimate of the visual WM storage capacity K is marked by a dashed horizontal line. In the lower graphs, the percentage of trials with 0, 1, 2, 3 or (in the control subject) 4 correct letters reported is plotted on effective exposure duration.

With regard to the clinical relevance of changes in the whole-report parameter processing speed C and WM storage capacity K there was no statistically relevant correlation with age at onset of Huntington’s disease or CAG-triplet repeat

Table 5 TVA whole-report parameters for patients and controls

	C_L	C_R	C	K_L	K_R	K
<i>Patients</i>						
HM	2.26	2.10	2.18	1.42	1.48	1.45
CD	7.01	6.60	6.80	2.77	2.67	2.72
MK	8.16	4.71	6.43	1.57	1.58	1.57
EB	3.67	3.55	3.61	2.00	2.00	2.00
GH	3.53	2.99	3.26	1.51	1.75	1.63
JF	4.34	4.21	4.27	1.96	1.76	1.86
HL	2.61	3.51	3.06	1.00	1.00	1.00
IF	3.64	3.46	3.55	1.00	1.00	1.00
NH	5.87	5.51	5.69	3.87	4.00	3.93
PH	4.17	3.08	3.62	3.00	2.41	2.70
CM	9.38	8.69	9.03	2.88	2.83	2.86
VP	8.53	8.66	8.60	3.00	2.20	2.60
Msa	7.58	5.30	6.44	2.30	2.51	2.40
MSb	3.53	3.77	3.65	3.77	3.55	3.66
BH	8.63	8.01	8.32	3.75	3.96	3.85
GW	7.30	5.59	6.45	4.00	4.00	4.00
DH	6.72	4.48	5.60	1.00	1.00	1.00
SJ	6.93	9.20	8.07	4.00	4.00	4.00
Mean	5.77	5.19	5.48	2.49	2.43	2.46
(SD)	(2.30)	(2.19)	(2.15)	(1.10)	(1.09)	(1.09)
<i>Controls</i>						
MB	29.42	23.51	26.47	4.00	3.85	3.93
MS	15.84	16.26	16.05	2.86	2.94	2.90
GR	15.51	18.99	17.25	5.00	4.88	4.94
WS	13.06	16.80	14.93	2.72	2.61	2.67
IG	29.16	29.39	29.28	3.85	3.96	3.90
WH	19.57	22.78	21.17	3.68	3.53	3.60
WR	17.01	21.24	19.13	2.68	2.72	2.70
MJ	18.82	22.47	20.64	4.00	3.76	3.88
KK	11.79	13.38	12.58	3.08	3.61	3.35
HR	19.77	19.50	19.63	4.00	4.00	4.00
PB	43.86	50.91	47.38	3.84	3.75	3.80
CR	42.89	41.93	42.41	4.76	5.00	4.88
GK	34.87	35.49	34.83	4.66	4.30	4.47
CK	29.40	41.51	35.46	3.69	3.86	3.78
InG	29.16	29.39	29.28	3.85	3.96	3.90
PB	24.06	25.91	24.99	3.46	3.27	3.36
CH	16.21	22.01	19.11	2.91	2.56	2.74
KL	27.28	27.16	27.22	4.00	4.00	4.00
Mean	24.25	26.61	25.43	3.65	3.62	3.63
(SD)	(9.55)	(10.08)	(9.63)	(0.71)	(0.73)	(0.71)

Estimates of processing speed C and WM storage capacity K were made separately for the left and the right hemi-field and mean of both hemi-fields). C_L , C_R , C = processing speed (element/s) in the left and the right hemi-field and across both hemi-fields, respectively; K_L , K_R , K = visual WM capacity (number of elements) in the left and the right hemi-field and across both hemi-fields, respectively.

length (all $P > 0.45$). For both parameters, however, significant inverse correlations were found with illness duration (processing speed: $r = -0.49$, $P < 0.05$, one-sided; WM storage capacity: $r = -0.49$, $P < 0.05$, one-sided). Figure 6 shows that a longer duration of the disease was associated with slower processing speed and lower storage capacity. The time course of the decay was very similar between processing speed and visual WM storage capacity. In both graphs the

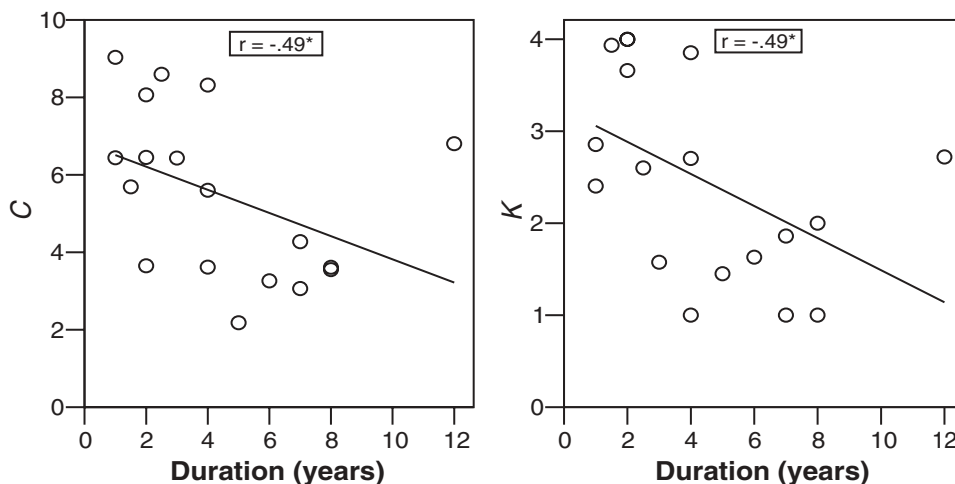


Fig. 6 Scatterplots relating the TVA parameter processing speed C (**A**) and visual WM storage capacity K (**B**) to the duration of the illness in the Huntington's patient group. Duration: duration of the clinical state of the illness; C : processing speed (element/s); K : visual WM storage capacity (number of elements).

data points suggest a linear decline approaching lowest values at a processing speed of two object/s and a WM storage capacity of one object.

As can be seen from Fig. 6A and B there was one outlier value within the patient group. It was related to patient CD, a 64-year-old woman with a rather late onset at the age of 52. She had Huntington's disease symptoms for 12 years at the time of testing and was the only patient who was able to take part in our study despite a disease duration of >10 years revealing a slow progression of cognitive symptoms compared with other patients included in our study. Excluding her value from the correlation between illness duration and processing speed, or WM storage capacity, respectively, resulted in markedly higher negative correlation coefficients (processing speed: $r = -0.67$, $P < 0.01$; WM storage capacity: $r = -0.67$, $P < 0.01$).

The whole-report parameters, also, were not related to medication dosage (C : $r = 0.04$, $P > 0.85$; K : $r = -0.04$, $P > 0.85$) or age (C : $r = -0.21$, $P > 0.35$; K : $r = -0.30$, $P > 0.20$).

Relationship between whole- and partial-report results

No significant correlation was found between the spatial laterality of attentional weighting w_λ on the one hand and either processing speed C ($r = -0.11$, $P > 0.60$ / $r = -0.10$, $P > 0.70$) or WM storage capacity K ($r = -0.35$, $P > 0.15$) on the other.

Discussion

In our study a group of patients with Huntington's disease in an advanced stage of the disease course was assessed with a TVA-based whole- and partial-report paradigm and compared with a healthy control group. The method provided parameter estimates of the spatial lateralization of attention as well as two non-spatial aspects of attentional functions,

that is, processing speed and WM storage capacity. Huntington's disease patients were impaired in all aspects. However, spatial and non-spatial deficits were uncorrelated, indicating that they represent distinct attentional deficiencies with possibly different underlying neuropathological mechanisms.

Spatially lateralized deficit of attentional weighting

The pathological leftward bias of attention we obtained in our sample of patients in an advanced stage of Huntington's disease can extend the findings of Ho *et al.* (2004). These authors found a leftward spatial bias in a perceptuomotor task (line bisection), but no significant deviation from normal subjects in the perceptual 'greyscales task' for patients with only mild symptoms. In addition to this preceding study, a further characterization of the spatial deficit is possible on the basis of our partial-report paradigm.

We found that the patients' performance was absolutely comparable for both sides of space in unilateral stimulus displays. This was reflected in a balanced distribution of basic sensory effectiveness across the left and the right hemi-field excluding any unilateral right-sided sensory loss. This homogeneity of accuracy in unilateral displays also implies that the lateral bias of spatial attention found in Huntington's disease patients is not attributable to an inability to keep central fixation during our task. Any systematic gaze deviation to the left side would have been reflected in higher accuracy and also higher estimates of sensory effectiveness for the left compared with the right hemi-field.

A pronounced accuracy decline for right-hemi-field stimuli occurred in conditions with bilateral presentation, only. Therefore, the patients' lateral attentional bias probably results from an extinction phenomenon—an inability to report a stimulus presented in the right hemi-field when a further stimulus is simultaneously presented in the left hemi-field—not from neglect, that is, complete unawareness

for stimuli in the right hemi-space (Milner, 1997; Driver and Vuilleumier, 2001; Marzi *et al.*, 2001). According to the biased competition view of visual attention proposed by Desimone and Duncan (1995), visual extinction is based on a competitive advantage for the stimulus in the unaffected field over the stimulus in the affected field. That is, owing to a bias, attentional weighting is taken by a stimulus in the unaffected hemi-field at the expense of the weighting assigned to a stimulus in the affected field, the latter one being 'extinguished'. However, the same stimulus in the affected field, presented alone without concurrence from another stimulus, can attain sufficient attentional weighting and be correctly reported. The same pattern has been found by Miyashita *et al.* (1995) in monkeys with unilateral caudate nucleus lesions. Thus, our results are compatible with the predominant caudate involvement in Huntington's disease and a specific sensitivity of tasks like partial report, involving double simultaneous stimulation, in revealing caudate dysfunction. In line with the basal ganglia pathology in Huntington's disease, subcortical regions have also been found in humans to be critically involved in extinction (Vallar *et al.*, 1994). Although extinction, like neglect, affects much more frequently the left than the right hemi-field, right-sided visual extinction is not uncommon (Stone *et al.*, 1993).

Different from such an account, Ho *et al.* (2004) found a bilateral cortical atrophy within the angular gyri to be associated with a left spatial bias of attention. However, the basal ganglia have not been included in a region of interest analysis in this study, which might have produced a significant result, too. Furthermore, the line-bisection task may be less sensitive than our partial-report task in revealing a lateralized deficit. Manual line bisection is a visuomotor task requiring visual scanning of the stimulus and a spatially targeted hand movement. Therefore, it may involve a broader cerebral network than the partial-report task used in our study. In fact, in an imaging study in normal subjects, Fink *et al.* (2001) found bilateral inferior parietal (right dominant) activation already in a perceptual line-bisection task.

Taken together, the leftward spatial bias found both in our study and in that of Ho *et al.* (2004) fits the more pronounced left-hemispheric neuropathology in Huntington's disease that emerges in an increasing number of studies using sophisticated volumetric procedures. This asymmetry is already present in pre-clinical carriers of the gene mutation determining Huntington's disease and, according to our results, seems to prevail also at later disease stages. Interestingly, Hamilton *et al.* (2003) reported symptoms of ideomotor apraxia in Huntington's disease patients in a more advanced stage of disease progression, similar to that of our patients, pointing to a persistent dominance of left-hemispheric pathology during disease progression.

Our results point to the leftward lateralization of attentional weighting as a potential valid trait marker reflecting the intensity of the pathogenic mechanisms underlying Huntington's disease, which may remain constant during symptom

progression. First, we found the leftward bias quite consistently across the patient group assessed in our study. Second, there was no correlation with disease duration. Third, patients with higher CAG-triplet repeat length and earlier disease onset had a more pronounced leftward bias. A similar though weaker association has also been found by Ho *et al.* (2004) for the purely perceptual greyscales task. However, although applied in a larger sample of subjects, the greyscales task was unable to reliably prove a stronger leftward deviation in patients compared with controls. Thus, this task also seems to be less sensitive than the partial-report task used in the present study. Interestingly, in our study, the only sinistral patient showed an ameliorated leftward bias compared with those dextral patients with a comparable illness severity in terms of CAG-triplet repeat length and age at onset.

Spatially non-lateralized deficits of visual processing speed and WM storage capacity

Visual processing of Huntington's disease patients was, on average, slowed down to an extent (~ 5.5 letter/s) that they were unable to even process a quarter of the objects processed by the control subjects during the same time (~ 25.5). WM storage capacity or the number of objects that could consciously be identified and maintained was also decreased, with a mean value of >1 SD below that of the control group (some patients had a capacity of only one item). With regard to this parameter, however, there was considerable overlap with the control group, with 39% of the patients performing within the range of healthy subjects.

Given the processing speed value obtained for Huntington's patients, around 180 ms exposure duration would be necessary to perceive only one letter. This value corresponds to the patients' whole-report curves indicating that the mean values of one letter reported could be reached only with >150 ms exposure duration. To date, a comparable slowing of processing speed C has only been documented in two patients with visual simultanagnosia (Duncan *et al.*, 2003), a profound disturbance in simultaneously attending to more than one object presented in parallel (Balint, 1909; Wolpert, 1924; Coslett and Saffran, 1991). Since Duncan and colleagues found the symptoms of simultanagnosia to be related to the massively reduced processing speed, it would be important to test whether Huntington's disease patients demonstrate simultanagnosia in respective tests (e.g. overlapping figures).

In this regard, further similarities between Huntington's disease and simultanagnosia patients with respect to oculomotor, visuomotor and visuospatial behaviour are conspicuous. These include difficulties in initiating saccades, gaze-fixation abnormalities with intrusion of small jerky saccadic movements, undershooting of targets in saccades (Harper, 1991), deficits in spatial perception (dot counting and location judging; Ho *et al.*, 2003a) and problems in reading, writing and visuoconstruction (Brandt, 1991).

The speed reduction was clearly present bilaterally, within both hemi-fields. However, a tendency for a more pronounced speed reduction within the right hemi-field, contralateral to the assumed predominant left-sided pathology was present. Following the suggestion of Habekost and Rostrup (2005), this result could be explained by a bilateral atrophy of the putamen, which is more pronounced on the left side. On the other hand, the association with illness duration together with the known progressive cortical involvement in the course of Huntington's disease (Aylward *et al.*, 1998; Rosas *et al.*, 2002, 2005) suggests an alternative explanation. Reduced processing speed and storage capacity could be related to a progressive cortical thinning that proceeds along the posterior–anterior axis (Rosas *et al.*, 2002). According to the neural interpretation of TVA (Bundesen *et al.*, 2005), which is in agreement with a bulk of neurophysiological data from single-cell recordings, speed of visual stimulus processing is proportional to the number of cortical neurons representing a visual object. This assumption would predict that neuronal loss, indicated by grey matter atrophy, gives rise to a decline in processing speed.

The two TVA parameters, perceptual processing speed and visual WM storage capacity, may represent possible state markers reflecting the stage of disease progression. Both parameters were significantly related to illness duration and seemed to be increasingly affected during disease progression. In contrast to the spatial bias, no significant correlations were found with age at onset and the amount of the genetic defect. Therefore, the progressive decline of speed and WM storage capacity seems to be comparable across patients with different pathogenic intensities.

Noteworthy, the parameter *C* for processing speed had a perfect selectivity for distinguishing Huntington's disease patients from healthy controls: all patients performed below the range of the control subjects. Importantly, in spite of the extremely reduced performance in *each* patient, we nevertheless were able to differentiate quantitatively among different levels of impairment.

Although all patients of our study were under antihyperkinetic/neuroleptic medication, we did not find any evidence for a relationship between dosage (in chlorpromazine equivalents) and the TVA-based parameter estimates. Therefore, the massive reductions in both parameters cannot be explained by medication side-effects.

General considerations

As a critical methodological advantage for the assessment of patients with motor disorders affecting the upper extremities as an integral part of the disease, the whole-report experiment allowed measurement of processing speed without involving a manual response component. By measuring visual perceptual processing speed as a function of accuracy at different exposure durations, effects of impairments in motor accuracy and speed are excluded. Therefore, the extreme slowing of processing speed revealed in whole report cannot be attributed to dyskinesias or motor slowing.

Although genetic testing allows an early diagnosis of Huntington's disease today, the clinical assessment of symptoms is important to estimate the age of onset, the progression rate and the stage of the disease. Since attentional deficits may precede other neuropsychological impairments, they may contribute to a more precise prediction of onset and course of the illness in otherwise asymptomatic patients. In the clinical state, they may serve as indices of the stage of progression and, also, for example, for assessing the efficacy of pharmacological interventions. As we did not include pre-clinical carriers of the Huntington's disease gene mutation and used a cross-sectional design, neither the predictive validity nor the individual course of TVA parameters during the disease progression can be evaluated on the basis of our study. Nevertheless, our results are promising in suggesting TVA-based parameters to bear a potential as possible trait and state markers for Huntington's disease that should be further investigated in future studies, including structural and functional imaging.

Acknowledgements

We wish to thank I. Maurer, T. Sonnfeld, C. Lumma and C. Schrenk for assistance in data acquisition. We also wish to thank C. Bundesen, S. Kyllingsbæk and T. Habekost who provided outstanding theoretical expertise on the parametric analyses, as well as two anonymous reviewers for extremely helpful comments on an earlier draft of this paper. Last but not least we want to thank all patients who have participated in our study. This work was supported by grants from the Deutsche Forschungsgemeinschaft (DFG) to W.X.S. and H.J.M. (project Mu 773/6-1).

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