



Orienting of spatial attention in Huntington's Disease

Maryline Couette^{a,b,c,*}, Anne-Catherine Bachoud-Levi^{a,b,d},
Pierre Brugieres^a, Eric Sieroff^e, Paolo Bartolomeo^{c,*}

^a INSERM U841-Equipe 1, "Neuropsychologie Interventionnelle", Faculté de Médecine de Paris XII, Créteil, France

^b AP-HP, Groupe Hospitalier Henri Mondor-Albert Chenevier, Pôle Neurolocomoteur, Créteil, France

^c INSERM-UPMC UMR S 610, and Department of Neurology, AP-HP, IFR 70, Hôpital de la Salpêtrière, Paris, France

^d Ecole Normale Supérieure, Département d'Etudes Cognitives, Paris, France

^e Laboratoire de Psychologie et Neurosciences Cognitives, CNRS, FRE 2987, Université Paris 5, Paris, France

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Abstract

To explore the functioning of spatial attention in Huntington's Disease (HD), 14 HD patients and 14 age-matched controls performed a cued response time (RT) task with peripheral cues. In Experiment 1, cues were not informative about the future target location, thus eliciting a purely exogenous orienting of attention. At short stimulus-onset asynchrony (SOA), controls showed an initial facilitation for cued locations, later replaced by a cost (inhibition of return, IOR). Patients had a larger and more persistent validity effect, with delayed IOR, resulting from a larger cost for uncued targets. This suggests an impairment of attentional disengaging from cued locations. In Experiment 2, 80% of the cues were valid, thus inducing an initially exogenous, and later endogenous, attentional shift towards the cued box. The validity effect was larger in patients than in controls, again as a result of a disproportionate cost for uncued targets. In Experiment 3, 80% of the cues were invalid, thus inviting participants to endogenously re-orient attention towards the uncued box. Patients could take advantage of invalid cues to re-orient their attention towards the uncued targets but at a longer SOA than controls, thus suggesting that endogenous orienting is preserved in HD, but slowed down by the disengage deficit. The disengage deficit correlated with several radiological and biological markers of HD, thus suggesting a causal relationship between HD and attentional impairments. Cued RT tasks are promising tools for the clinical monitoring of HD and of its potential treatments.

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1. Introduction

Huntington's Disease (HD) is a rare neurodegenerative genetic disease whose natural evolution is poorly understood. Its genetic basis is a pathological increase of the CAG repeats of IT 15 gene located on chromosome 4. HD entails intellectual deficits, motor disorders and psychiatric troubles. Evaluation and follow-up are difficult because of the entanglement of motor, psychiatric and cognitive disorders. The disease leads unavoidably towards dementia and death in approximately 20 years. At

present, there is no validated treatment and current therapeutic trials are calling for markers of efficacy. Neural degeneration affects the striatum bilaterally before the appearance of the first symptoms (Bamford, Caine, Kido, Cox, & Shoulson, 1995). Degeneration follows two evolutionary gradients: a postero-anterior gradient with a primary damage in posterior regions of the putamen, and an oblique gradient, which begins in dorso-medial regions of caudate nuclei and putamen and extends until ventrolateral regions (Vonsattel et al., 1985). With the evolution of the disease, an extra-striatal atrophy takes place in regions classically connected to the striatum like the globus pallidus, the substantia nigra pars reticulata, the thalamus, the limbic system, the cerebellum and the cortex. However, recent neuroimaging studies reported cortical impairment even in the early stages of the disease (Douaud et al., 2006; Kassubek, Bernhard, et al., 2004; Kassubek, Gaus, & Landwehrmeyer, 2004; Kassubek, Juengling, et al., 2004; Thieben et al., 2002), with an impli-

* Corresponding authors at: Neuropsychologie des lésions cérébrales focales, INSERM-UPMC UMR S 610, Pavillon Claude Bernard, Hôpital Salpêtrière, 47 bd de l'Hôpital, F-75013 Paris, France. Tel.: +33 1 42 16 00 25/58; fax: +33 1 42 16 41 95.

E-mail addresses: maryline.couette@gmail.com (M. Couette), paolo.bartolomeo@chups.jussieu.fr (P. Bartolomeo).

cation of insular and parietal regions. Fronto-parietal networks are important for the operations of spatial attention (Corbetta & Shulman, 2002; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Gitelman et al., 1999; Thiebaut de Schotten et al., 2005), so it would not be surprising if HD patients displayed spatial attention disorders.

Indeed, in a longitudinal follow-up of a cohort of 22 HD patients (Bachoud-Lévi et al., 2001), several tests exploring attentional processes (both spatial and non-spatial; Stroop, digit cancellation, Trail Making Test A) resulted to be reliable markers of cognitive decline (Bachoud-Lévi et al., 2001). Using a battery tapping several aspects of non-spatial attention, Sprengelmeyer, Lange, and Hömberg (1995) found that HD patients performed poorly on tasks of vigilance, divided attention, response flexibility and response inhibition, and concluded that attentional impairments in HD could in large part account for cognitive disorders in this disease (Sprengelmeyer et al., 1995). They showed a relative preservation of the alerting system, because patients were able to decrease their response times (RTs) when an acoustic signal preceded the target. However, patients exhibited a deficit of sustained attention, expressed by a high rate of omissions on each experiment. Sprengelmeyer et al. (1995) also used a “divided attention” experiment consisting of three tasks: a speeded visual detection task, an auditory task in which participants had to respond when two sounds of the same frequency occurred one after another, and a double task requiring the performance of both tasks at the same time. Patients performed correctly each of the two component tasks, but they were slowed to detect visual targets in the double task condition, which suggested an executive deficit in switching attention between modalities.

Posner (1980) developed a response time (RT) paradigm to explore orienting of spatial attention. According to the spotlight metaphor of attention, processing of stimuli located inside the attentional focus is facilitated, thus leading to RT benefits, while processing of stimuli outside the focus is inhibited, thus determining an RT cost. According to Posner (1980), orienting of attention toward a given stimulus implies three mechanisms: (1) disengaging the attentional spotlight from the previous stimulus, (2) moving and (3) engaging to the new target. Spatial attention can either be exogenously captured by an external salient stimulus, or it can be endogenously oriented by the subject himself towards an external or internal stimulus. Refinements of the model have proposed different forms of attention for exogenous and endogenous orienting (Klein & Shore, 2000; Lupiáñez et al., 2004). The different components of such processes can be explored by using the manual RT paradigm developed by Posner (1980). Participants are presented with three boxes horizontally arranged on a screen. They fixate the central box and respond by pressing a key to a target (an asterisk) appearing in one lateral box. Before the occurrence of the target, the occurrence of a cue designates one of the lateral boxes. The cue can either be “central” (for example an arrow appearing in the central box and pointing to one of the lateral boxes) or “peripheral” (a brief brightening of one lateral box). In “valid” trials, the target can appear inside the previously cued box (valid cue); in “invalid” trials the wrong box is cued. In “neutral” trials, used to discrimi-

nate between RT costs and benefits, the central box may be cued. An advantage for cued over uncued targets, or validity effect, suggests that the cue elicits an attentional orienting toward the cued location, which speed up the processing of targets appearing inside the cued box and slows down responses to targets appearing elsewhere. Importantly, the degree of predictiveness of cues influences the attentional processes involved. When a majority of cues are valid, most cues correctly predict the site of the upcoming target and are thus spatially informative. When the cue is non-informative, the target appears with equal probability in the cued or in the uncued location. Peripheral non-informative cues attract attention automatically, or exogenously (Jonides, 1981; Müller & Rabbitt, 1989). This exogenous attentional shift (revealed by a cue validity effect) is typically observed for short stimulus-onset asynchronies (SOAs) between cue and target. For SOAs longer than about 300 ms, a cost is observed for validly cued targets (Posner & Cohen, 1984). This phenomenon is often labelled inhibition of return (IOR; Posner, Rafal, Choate, & Vaughan, 1985). IOR is traditionally interpreted as an inhibition of attention to return to a previously inspected location, but its meaning, mechanisms and interpretation are currently debated (Lupiáñez, Klein, & Bartolomeo, 2006). When most cues (e.g. 80%) are invalid, they prompt an initial exogenous orienting towards the cued box, later followed by an inhibition of this exogenous shift, to be replaced by an endogenous shift towards the uncued box (Posner, Cohen, & Rafal, 1982). Thus, for long enough SOAs this condition explores endogenous orienting in relative isolation (Bartolomeo, Decaix, & Siéoff, 2007; Bartolomeo, Siéoff, Decaix, & Chokron, 2001; Lupiáñez et al., 2004).

Using a vibrotactile choice RT task, Georgiou, Bradshaw, Phillips, and Chiu (1997) showed that HD patients were impaired in allocating their attentional resources and to shift their attentional focus from a cued location to another location. This could be related to an inability to suppress reflexive saccades to sudden visual stimuli and to a delayed initiation of voluntary saccades in HD (Lasker & Zee, 1997). Finke, Bublak, Dose, Müller, and Schneider (2006) used a visual report task in which participants had to identify target letters accompanied or not by distractors. Using a mathematical model of weighting of attention along the two hemi-fields for each stimulus, they found that HD patients showed a deficit in the allocation of attentional weights. In addition, patients demonstrated reduced perceptual processing speed and reduced capacity of visual working memory.

Fielding, Georgiou-Karistianis, Bradshaw, et al. (2006) reported an accelerated time course of IOR in a saccadic RT paradigm with peripheral non-informative cues. Saccadic IOR was present as early as 150 ms after cue onset. Saccadic trajectories were abnormally influenced by the presence of distractors (Fielding, Georgiou-Karistianis, Millist, & White, 2006), with exogenous saccades deviating leftwards irrespective of target locations, and endogenous saccades deviating towards the left if directed upward, and towards the right if directed downward.

Asymmetries of attentional processes have also been described in HD. Georgiou-Karistianis, Churchyard, Chiu, and Bradshaw (2002) showed that HD patients were slower when

a pre-cue tactile stimulation appeared on the left finger relative to the right. Other asymmetries of visuo-spatial performance reported in HD patients include signs of visual neglect for the left (Ho, Manly, et al., 2003) or the right space (Ho et al., 2004). In particular, leftwards shifts on line bisection correlated with reduced density in the angular gyrus bilaterally, consistent with the implication of the inferior parietal lobule and its connections in bisection-related tasks (Fink, Marshall, Weiss, Toni, & Zilles, 2002; Thiebaut de Schotten et al., 2005).

These results suggest the interest of studying visuo-spatial performance in HD by using sensitive RT tasks, such as the Posner paradigm (Posner, 1980) which is widely used to assess lateral shifts of spatial attention in brain-damaged patients (Bartolomeo et al., 2001). In order to disentangle exogenous and endogenous contributions to patients' performance, we used a covert attention task with peripheral visual cues and different cue–target relationships (Bartolomeo et al., 2001; Posner, 1980; Posner et al., 1982). In three different experiments, cues predicted the correct location of the target with 80%, 50% or 20% accuracy, respectively. In this way, exogenous and endogenous orienting can be studied in relative isolation from one another, by using the same visual stimuli. A neutral condition, in which the central box was cued, was used to discriminate between cue-induced benefits and costs. The use of three different time intervals between cue and target appearance (stimulus-onset asynchronies or SOA), at 100, 500 and 1000 ms, allowed us to explore the time course of these processes. For example, in the present settings IOR is expected in controls starting from 500-ms SOA. Endogenous re-orienting to uncued targets in the 20% validity experiment should also occur by 500-ms SOA, but it may be delayed in brain-damaged patients (Bartolomeo et al., 2001). Thus, comparisons were planned in controls and patients between RTs to validly and invalidly cued targets at the

intermediate, 500-ms SOA. To explore the clinical implications of the observed patterns of RT performance, correlations were calculated with clinical parameters, such as scores on the Unified Huntington's Disease Rating Scale (UHDRS) (Huntington Study Group, 1996), the Mattis Dementia Rating Scale (MDRS) (Mattis, 1976), the Total Functional Capacity (TFC) (Huntington Study Group, 1996), as well as with radiological measures of caudate atrophy.

2. Methods

2.1. Participants

Fourteen patients with mild HD (6 females) and 14 age-matched controls (9 females) participated in the study. All patients had no previous neurological or psychiatric history other than HD. HD diagnosis was genetically confirmed. The control subjects had no neurological or psychiatric disorders and were matched to the patients for age (patients: mean age 48.43 years, range 36–59; controls: mean age 44.78 years, range 34–55; $t=1.34$; $p=0.19$) and educational level (patients: 13.29 years of schooling, range 9–20; controls: 14.50 years, range 10–20; $t=-0.94$; $p=0.35$). Participants were recruited among the out-clinic patients and controls within the follow-up program of predictive biomarkers of HD that was approved by the ethics committee of the Henri-Mondor Hospital. All participants gave informed consent. Demographic and clinical data are summarised in Table 1.

2.2. Apparatus and stimuli

Stimulus presentation and response collection were controlled by the Psychlab software (Gum, 1996). The computer used for this study was an Apple Ibook 300 MHz.

Three black empty squares boxes (10-mm long and 0.34-mm thick side) were presented on a white background. The boxes were horizontally arranged; the distance between boxes was 30 mm. The central box was located in the centre of the screen, and contained a black rectangular fixation point (1.02 mm $\times$ 1.34 mm). Cues consisted of a 300 ms thickening (from 0.34 to 0.68 mm) of the contour of one box. The target was an asterisk (4.40 mm diameter), which appeared inside one of the lateral boxes, at a retinal eccentricity of about 3.83°.

Table 1
Demographic and clinical data for HD patients, with the % of saccades made during the RT tasks

Patient	Sex/age/years of schooling/hand preference	Disease duration (years)	CAG repeats	Bicaudate ratio (%)	MDRS	UHDRS motor	TFC	Medication	% Saccades
P01	M/58/20/R	8	43	21.5	122	38	11	Venlafaxine, Lorazepam, Risperidone	12.79
P02	M/48/9/R	3	43	19	125	22	13	Buspirone, Milnacipran, Mianserine, Paroxetine, Pimozide	39.14
P03	F/45/15/R	3	43	19.5	122	16	13	None	15.57
P04	M/50/15/R	4	42	18	134	17	13	Venlafaxine, Chlorazepate	9.60
P05	F/60/10/R	8	46	16	128	40	10	Citalopram	8.16
P06	M/54/15/R	8	43	25	126	68	9	Carbamazepine, Citalopram, Bromazepam	16.58
P07	F/43/16/R	8	45	24.81	133	64	7	Paroxetine, Mianserine	16.33
P08	F/45/11/R	2	45	NA	137	5	13	Fluoxetine	18.69
P09	M/59/13/R	7	40	NA	131	7	11	Haloperidol, Valpromide	3.2
P10	M/39/9/R	7	47	23.44	122	32	10	Paroxetine, Olanzapine	8.67
P11	F/50/13/R	3	42	16.50	141	10	13	None	1.18
P12	F/49/16/R	2	41	18.00	142	8	13	Sertraline, Lithium, Lormetazepam	5.22
P13	M/42/15/L	6	46	NA	122	62	11	Venlafaxine, Olanzapine	15.07
P14	M/36/9/R	4	NA	NA	123	28	11	Amitriptyline, Olanzapine	9.51

MDRS = Mattis Dementia Rating Scale; TFC = Total Functional Capacity; NA = not available.

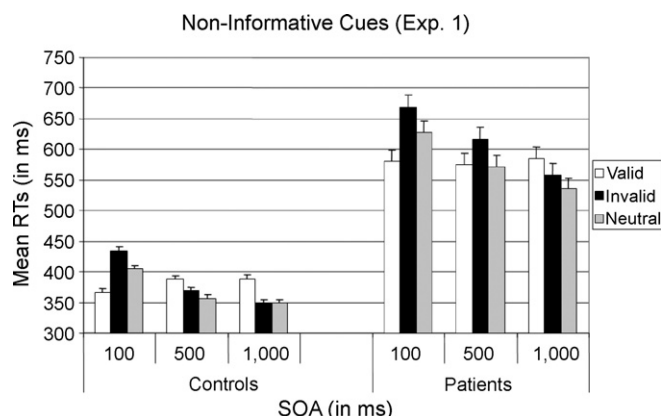


Fig. 1. Response times for controls and patients in Experiment 1 (non-predictive cues). Error bars denote standard errors.

2.3. Procedure

Participants sat in front of a computer monitor at a distance of 50 cm. Each trial began with the appearance of the three boxes for 500 ms. Then the cue was presented for 300 ms. The target appeared at a variable SOA (100, 500 or 1000 ms) from the cue, and stayed visible on the screen until the subject gave a response. Trials were separated by a white screen of 1000 ms. Participants were instructed to maintain fixation on the fixation point and to respond to the target as quickly and accurately as possible by pressing the space bar of the keyboard with the index finger of their preferred hand. In order to minimize the amplitude of the motor response, participants kept their responding finger close to the space bar. Eye movements were monitored by an experimenter using a mirror positioned near the presentation screen. If an eye movement occurred, the experimenter marked the trial with a mouse click. Marked trials were subsequently discarded from analysis. Before each experiment, participants were informed about the percentage of valid trials (50%, 80% or 20%). They were instructed to respond exclusively to the target, without paying attention to the cues. In a further experiment, considered as a neutral condition, the cue appeared on the central box. Experiment 1 (50% valid cues) and the neutral condition consisted of three blocks of 84 trials preceded by 12 practice trials. Experiments 2–3 (respectively 80% or 20% valid cues) consisted of three blocks of 90 trials preceded by 12 practice trials. The order of experiments followed a Latin square distribution.

2.4. Analysis of results

After exclusion of practice trials and of trials contaminated by eye movements (controls: 0.35%; patients: 12.84%; see Table 1 for percentages of saccades in individual patients), RTs were submitted to a trimming procedure to eliminate outliers. RTs exceeding the range of 2.5S.D. from each participant's mean RT were discarded from analysis. In the whole, this resulted in the exclusion of 15.75% of responses for controls and of 27.69% for patients. For each experiment and each group of participants, mean RTs were entered in a repeated-measures analysis of variance (ANOVA), with group (controls, patients) as between-group factors and side (left and right), cue (valid, invalid and neutral) and SOA (100, 500 and 1000 ms) as within-group factors.

3. Results

Mean RTs for patients and controls in each experimental condition are reported in Table 2 and Figs. 1–3.

3.1. Experiment 1: non-informative cues

In the first experiment the cue was not informative about the location of the target. The cue could appear in the cued or

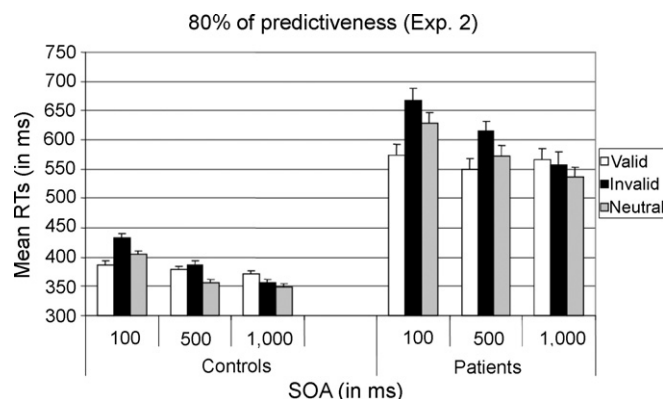


Fig. 2. Response times for controls and patients in Experiment 2 (80% predictive cues). Error bars denote standard errors.

in the uncued box with equal probabilities and thus elicited an exogenous orienting of attention (Müller & Rabbitt, 1989). In normal subjects, this exogenous effect typically results in a cue validity effect observed at short SOAs. For longer SOAs, RTs become longer for valid trials than for invalid trials (IOR). To explore the time course of IOR in HD patients, comparisons between groups were planned for the cue validity effects at the longer SOAs.

Results of Experiment 1 are displayed in Fig. 1. There was a main effect of each factor except for side, $F(1, 26) = 1.74$; $p = 0.20$. Patients had slower RTs (591 ms) than controls (378 ms), $F(1, 26) = 35.01$; $p < 0.001$. The cue factor affected RTs, $F(2, 52) = 5.66$; $p < 0.01$, because participants were slower for invalid trials than for valid trials by 22 ms, $F(1, 26) = 4.84$; $p < 0.05$. Performance with neutral cues indicated that there was a 27-ms attentional cost associated with invalid trials for both patients and controls, $F(1, 26) = 11.72$; $p < 0.01$. Attentional cost and validity effect were thus similar in amount, suggesting that the cue validity effect mainly resulted from a cost for invalid trials, rather than from an advantage for valid trials. The SOA factor also affected RTs, $F(2, 52) = 26.99$; $p < 0.001$, because participants took advantage of increasing SOAs to speed up their RTs. There was a significant interaction between SOA and cue, $F(4, 104) = 24.30$; $p < 0.001$, because a 79-ms validity effect at 100-ms SOA, $F(1, 26) = 35.89$; $p < 0.001$, reverted to a 27-ms

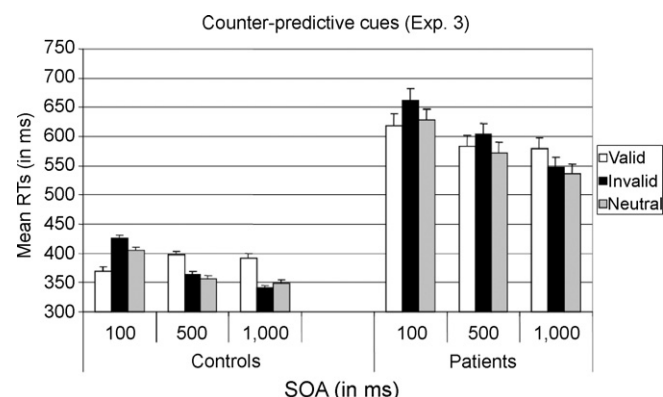


Fig. 3. Response times for controls and patients in Experiment 3 (counter-predictive cues). Error bars denote standard errors.

Table 2
Mean RTs (in ms) and relative S.D.s (reported in parentheses) for HD patients and controls in Experiments 1–3 and in the neutral condition

	Left						Right					
	Valid			Invalid			Valid			Invalid		
	SOA = 100 ms	SOA = 500 ms	SOA = 1000 ms	SOA = 100 ms	SOA = 500 ms	SOA = 1000 ms	SOA = 100 ms	SOA = 500 ms	SOA = 1000 ms	SOA = 100 ms	SOA = 500 ms	SOA = 1000 ms
Experiment 1 (50% cue predictiveness)												
HD	575 (128)	566 (133)	550 (101)	702 (209)	608 (148)	557 (149)	583 (169)	575 (111)	616 (125)	639 (176)	623 (157)	579 (169)
Controls	380 (45)	385 (44)	386 (52)	436 (45)	366 (38)	349 (34)	353 (54)	387 (43)	389 (40)	431 (51)	373 (45)	348 (40)
Experiment 2 (80% cue predictiveness)												
HD	579 (138)	550 (104)	552 (120)	672 (198)	591 (118)	604 (185)	569 (152)	547 (122)	582 (142)	618 (164)	584 (123)	591 (212)
Controls	403 (55)	386 (48)	371 (34)	439 (61)	389 (45)	355 (42)	370 (48)	371 (47)	370 (30)	433 (64)	383 (59)	357 (52)
Experiment 3 (20% cue predictiveness)												
HD	627 (221)	574 (147)	599 (166)	681 (175)	623 (185)	540 (128)	598 (204)	593 (175)	576 (149)	642 (153)	597 (153)	552 (126)
Controls	392 (54)	395 (56)	394 (45)	424 (43)	368 (37)	337 (29)	350 (40)	397 (34)	389 (47)	425 (43)	360 (42)	343 (30)
	Left			Right								
	SOA = 100 ms	SOA = 500 ms	SOA = 1000 ms	SOA = 100 ms	SOA = 500 ms	SOA = 1000 ms	SOA = 100 ms	SOA = 500 ms	SOA = 1000 ms	SOA = 100 ms	SOA = 500 ms	SOA = 1000 ms
Neutral condition												
HD		612(126)		571 (142)		528 (119)		645(144)		571 (129)		546 (142)
Controls		400(43)		356 (41)		352 (45)		411(40)		357 (36)		345 (29)

inverse validity effect at 1000-ms SOA, $F(1, 26) = 5.20$; $p < 0.05$. SOA also interacted with the side of target presentation, $F(2, 52) = 5.47$; $p < 0.01$, because at 1000-ms SOA RTs were faster to left-sided targets than to right-sided targets, $F(1, 26) = 5.79$; $p < 0.05$. This RT asymmetry was only present in HD patients, $F(1, 26) = 12.83$; $p < 0.01$ (see Table 2), which led to an interaction of side and SOA with the group, $F(2, 52) = 4.34$; $p = 0.02$. No other effect or interaction reached significance. Planned comparisons showed a cue validity effect at 500-ms SOA for patients, $F(1, 26) = 6.87$; $p < 0.05$, but not for controls, $F < 1$, who, as expected, started to develop IOR at this intermediate SOA (see Fig. 1). At 1000-ms SOA, controls developed a 40-ms IOR, $F(1, 26) = 5.5$; $p < 0.05$, whereas there was no reliable evidence of IOR for patients, $F < 1$. Overall, the RT pattern displayed in Fig. 1 suggests that the disengage deficit demonstrated by HD patients for invalid trials masked IOR by inflating the RTs for invalid trials.

3.2. Experiment 2: 80% cue predictiveness

In this experiment, the target appeared in the cued box in 80% of trials. The cues were thus informative about the future location of the target and were expected to induce an exogenous attentional shift towards the cued box at short SOA, later replaced by an endogenous shift towards the same cued box.

As in Experiment 1, the results of Experiment 2 (Fig. 2) demonstrated an effect of group, $F(1, 26) = 33.58$; $p < 0.001$, because patients responded slower (583 ms) than controls (380 ms). The side of target appearance did not affect RTs, nor did it interact with other factors, all F 's < 1.08 . The interaction between group and cue was marginally significant, $F(2, 52) = 3.02$; $p < 0.06$, because there was a 47-ms cue validity effect for patients, $F(1, 26) = 20.23$; $p < 0.001$, but only a non-significant 14-ms cue validity effect for controls, $F(1, 26) = 1.90$; $p = 0.18$, again consistent with a larger attentional cost for HD patients. RTs decreased with increasing SOA, $F(2, 52) = 25.06$; $p < 0.001$. SOA interacted with cue, $F(4, 104) = 5.60$; $p < 0.001$, because the cue validity effect decreased with increasing SOA, suggesting the development of IOR despite the informativeness of cues.¹ No other effect or interaction reached significance. Planned comparisons demonstrated a validity effect at 500-ms SOA for patients, $F(1, 26) = 14.24$; $p < 0.01$, but not for controls, $F < 1$. At 1000-ms SOA, the validity effect became non-significant for patients, $F(1, 26) = 2.67$; $p = 0.11$. This suggests that HD patients had difficulties in disengaging their attention from the cued boxes in order to re-engage it to the target appearing at the uncued box, consistent with the disengage deficit demonstrated in Experiment 1. Also consistent with the hypothesis of a disengage deficit of attention in HD, there was an attentional cost (invalid minus neutral condition) at 1000-ms SOA for patients, $F(1, 26) = 6.49$; $p < 0.05$, but not for controls, $F < 1$.

¹ IOR always occurs after a peripheral cue. When most cues are valid, it is often, but not always, masked by endogenous facilitation (Lupianez et al., 2004, 2006).

3.3. Experiment 3: 20% cue predictiveness

In this experiment, only 20% of the cues were valid. Participants were thus invited to endogenously orient their attention towards the box opposite to the cued one. Because this strategic re-orienting is time-consuming, this condition typically induces an advantage for valid trials (validity effect) at short SOAs, reflecting initial exogenous orienting towards the cued box, followed by an inverted validity effect (advantage of invalid trials over valid trials) at long SOAs (Bartolomeo et al., 2001; Bartolomeo, Decaix, et al., 2007; Posner et al., 1982).

As in the preceding experiments, results (Fig. 3) showed a main effect of group, $F(1, 26) = 32.85$; $p < 0.001$, because patients had longer RTs (592 ms) than controls (377 ms). The cue factor influenced the RTs, $F(2, 52) = 4.57$; $p < 0.05$, because there was a 17-ms attentional cost for invalid versus neutral trials, $F(1, 26) = 7.11$; $p < 0.05$. Similar to the precedent experiments, participants took advantage of increasing SOAs to decrease their RTs, $F(2, 52) = 31.80$; $p < 0.001$. There was a marginally significant interaction of SOA with group, $F(2, 52) = 3.10$; $p = 0.053$, because patients' RTs tended to decrease more steeply than controls' with increasing SOAs. Cue validity interacted with SOA, $F(4, 104) = 20.24$; $p < 0.001$. As expected, the initial advantage for valid trials, $F(1, 26) = 23.63$; $p < 0.001$, reverted to a cost at longer SOAs, $F(1, 26) = 26.60$; $p < 0.001$, because participants endogenously re-oriented their attention towards the uncued box, consistent with previous reports (Bartolomeo et al., 2001; Posner et al., 1982). Importantly, however, the inversion of the cue validity effect already occurred at 500-ms SOA for controls, $F(1, 26) = 4.67$; $p < 0.05$, but only at 1000-ms SOA for patients, $F(1, 26) = 10.8$; $p < 0.01$ (see Fig. 3). This resulted in a marginally significant interaction between group, cue and SOA, $F(4, 104) = 2.26$; $p = 0.067$. The inversion of the validity effect at 1000-ms SOA for patients suggests that they could take advantage of the counter-predictive cues to re-orient their attention to the uncued box, but did so more slowly than controls, who showed this effect already at 500-ms SOA. No other effect or interaction reached significance. In particular, the side factor did not alter RTs, $F < 1$.

3.4. Correlations with neuroimaging and clinical data

3.4.1. Bicaudate index

The severity of caudate nuclei atrophy is a well-known biological index of disease progression in HD, and correlates with cerebral atrophy (Barr, Heinze, Dobben, Valvassori, & Sugar, 1978). Caudate atrophy can be quantitatively estimated using the bicaudate ratio, i.e. the distance between the ratio of the distance between the heads of the caudate nuclei, calculated from serial sagittal MRI scans, and the distance between the outer tables of the skull at the same level (Barr et al., 1978). We calculated the correlations between the cue validity effect (RT to valid trials minus RT to invalid trials) and the bicaudate ratio for the 10 patients who had a MRI during the study (see Table 3).

A positive correlation emerged for Experiment 1 (non-informative cues) at 500-ms SOA, $r = +0.73$, $p < 0.05$. Thus, the disengage deficit in HD increased with increasing severity of

Table 3
Correlations between cue validity effects and clinical data in HD patients

	CAG repeats	Bicaudate ratio	MDRS	Age at onset	Disease duration	UHDRS motor	Rigidity	Chorea	Bradykinesia	TFC
Experiment 1: non-informative cues										
100-ms SOA	0.15	0.22	−0.39	−0.14	0.09	0.06	−0.11	0.02	0.15	−0.07
500-ms SOA	0.59	0.74*	−0.73*	−0.42	0.74*	0.63*	0.11	0.44	0.49	−0.62
1000-ms SOA	0.10	0.16	−0.63	0.18	0.26	0.11	0.14	0.22	0.32	−0.03
Experiment 2: 80% predictive cues										
100-ms SOA	−0.16	0.14	−0.44	0.18	−0.03	−0.07	−0.20	−0.16	0.04	0.17
500-ms SOA	0.68*	0.13	−0.58	−0.34	0.31	0.02	0.03	−0.03	−0.03	−0.17
1000-ms SOA	0.32	0.44	−0.65*	−0.14	0.35	0.35	0.25	−0.10	0.34	−0.23
Experiment 3: counter-predictive cues										
100-ms SOA	0.49	0.60	−0.23	−0.63	0.37	0.47	0.29	0.15	0.34	−0.49
500-ms SOA	0.24	0.19	0.01	−0.4	0.08	0.02	−0.32	−0.26	−0.34	−0.12
1000-ms SOA	0.24	0.09	−0.09	0.11	0.45	0.24	−0.28	0.03	0.04	−0.25

* $p < 0.05$ (two-tailed); MDRS = Mattis Dementia Rating Scale; TFC = Total Functional Capacity; rigidity and maximal chorea scores are relative to the upper limb used for motor response in the RT tasks.

caudate atrophy. There was also a marginally significant correlation between the same measures for Experiment 3 (20% predictive cues) at 100-ms SOA, $r = +0.59$, $p = 0.07$, suggesting that the slowing in endogenously re-orienting attention after a counter-predictive cue increased with the amount of caudate atrophy.

3.4.2. Clinical correlations

We calculated the correlations between the validity effects and biological/clinical measures such as the number of CAG sequences, the age at symptom onset, the disease duration, the MDRS, the TFC and several scores from the UHDRS (motor score, rigidity, bradykinesia and maximal chorea scores relative to the upper limb used for motor response in the RT tasks). Again, correlations occurred between some of these measures and cue validity effects in Experiment 1 at 500-ms SOA. The cue validity effect on this condition increased with increasing severity of global cognitive functioning as assessed by the MDRS ($r = -0.73$, $p < 0.05$), with disease duration ($r = 0.74$, $p < 0.05$), and with UHDRS motor score and TFC (motor score: $r = 0.63$, $p < 0.05$; TFC: $r = -0.62$, $p < 0.06$). However, no significant correlation occurred between cue validity effects and UHDRS scores for rigidity, chorea and bradykinesia, suggesting that these factors did not directly determine patients' performance. Finally, the cue validity effect in Experiment 2 (80% valid cues) correlated with the severity of cognitive impairment at 1000-ms SOA, $r = -0.65$, $p < 0.05$.

4. Discussion

We used a speeded target detection task to explore the orienting of spatial attention in HD patients. In different experiments, peripheral cues predicted the future location of the target with 80%, 50% or 20% accuracy. In this way, exogenous and endogenous orienting can be studied in relative isolation from one another, by using the same visual stimuli. For all the experiments, patients were able to decrease their RTs with increasing SOA, similar to controls. This pattern of performance suggests a relative preservation of alerting capacities in HD, consistent

with previous results (Sprenklemeier et al., 1995). The increased validity effect shown by HD patients in Experiment 1 (non-informative cues) with respect to controls may reflect a deficit of attentional disengagement (Posner, Walker, Friedrich, & Rafal, 1984). Consistent with this interpretation, IOR appeared to arise later in patients (1000-ms SOA) than in controls (500-ms SOA), as if patients' attention could not disengage from the cued location as fast as controls'.

Contrary to these results, Fielding, Georgiou-Karistianis, Bradshaw, et al. (2006) found IOR as early as 150 ms after cue occurrence in HD patients. Important differences in task procedures may explain this discrepancy. For example, the time of cue presentation was much longer in the present study (300 ms) than in the Fielding et al.'s study (50 ms); shorter cue presentation times presumably facilitate attentional disengagement from cues and may thus speed up the occurrence of IOR. More importantly, Fielding et al. used a saccadic RT task, in which participants had first to inhibit reflexive saccades toward the peripheral cues, then to produce a saccade toward the target. On the other hand, in the present study participants had to maintain fixation and to produce manual responses to the targets. Manual and saccadic IOR are likely to be subserved by partially distinct mechanisms: cortical and collicular for manual IOR, exclusively collicular for saccadic IOR (Sumner, 2006). The cortical component of IOR might thus have influenced the present results, for example by delaying IOR as a consequence of a disengage deficit, more than the saccadic RTs explored by Fielding et al.

The disengage deficit demonstrated by the present patients across all three experiments contrasts with the results of a previous study employing central cues (arrows), which induced normal cue validity effects in HD patients (Tsai, Lasker, & Zee, 1995). The present study used, instead, peripheral cues, which could be more effective in revealing a disengage deficit due to their capturing power on exogenous attention (Yantis & Jonides, 1990). Consistent with the present results, a study which employed a vibrotactile RT task showed that HD patients were impaired in shifting their attentional focus from a cued location to another location (Georgiou et al., 1997).

Since this study uses a timed manual response to examine spatial attention, patients' motor deficits might in principle have influenced the results. This possibility is, however, unlikely. First, patients' responding finger was placed close to the response bar, thus minimizing the amplitude of the required movement and hence the risk of contamination from chorea; second, whereas motor impairments might have introduced general noise in the RTs, they were unlikely to influence the specific patterns of performance related to cue validity effects that were observed; third, no correlation between brachial chorea, rigidity or bradykinesia and validity effects reached significance.

In the present Experiment 3 counter-predictive cues were used, which tap processes, such as inhibition of automatic but inappropriate responses and task switching, which are characteristically impaired in HD (Aron et al., 2003). At the intermediate SOA, 500 ms, the initial cue validity effect, expression of exogenous attentional capture by the cue, was reversed for controls, but still persisted for HD patients. This suggests a slowing of the endogenous processes of re-orienting, again consistent with a disengage deficit entailing an abnormal persistence of attention on the cued location. A directional analogue of this slowing of endogenous orienting has been reported in patients with left neglect (Bartolomeo et al., 2001). These patients were able to endogenously counteract their disengage deficit from right-sided (invalid) cues to left-sided targets, but only at a longer SOA than controls.

RT paradigms are known to be sensitive to asymmetries of performance, which can be demonstrated in brain-damaged patients even in the absence of signs of visuo-spatial neglect on paper-and-pencil tests (Posner et al., 1984; Siéoff, Decaix, Chokron, & Bartolomeo, 2007). The present results showed some evidence of RT asymmetry in HD patients, who responded faster to left targets than to right targets at 1000-ms SOA in Experiment 1. This left-side advantage is consistent with reports of "pseudoneglect" in HD patients (Ho et al., 2004), and with evidence indicating that neurodegeneration in HD can be asymmetric, affecting, at least in the beginning, predominantly left-sided structures (Kipps et al., 2005; Mühlau et al., 2007; Paulsen et al., 2004; Rosas et al., 2001). Note, however, that the observed RT asymmetry differed substantially from the disengage deficit of parietal patients, which typically consists in large cue validity effects for contralesional targets at short SOAs (Losier & Klein, 2001). The disengage deficit shown by the present HD patients appeared to be, instead, independent of the side of presentation of cues and targets.

The study of covert spatial attention in HD is especially difficult, because HD patients are generally poor in controlling inappropriate saccades to peripheral stimuli (Blekher et al., 2006; Golding, Danchaivijitr, Hodgson, Tabrizi, & Kennard, 2006; Winograd-Gurvich et al., 2003). In the present study we were careful to exclude from RT analysis trials contaminated by saccades. This procedure renders all the more convincing the conclusion for the presence of a disengagement deficit of covert attention in the present series of patients, but can raise concerns about the amount of the excluded trials. For example, for Patient 2 almost 40% of trials were to be excluded because of inappropriate saccades (see Table 1). However, further ANOVAs

conducted on the RTs after excluding this patient led to the same pattern of effects and interactions described in Section 3.

Another peculiar difficulty faced by behavioural studies in HD is the frequent presence of a general cognitive impairment (Bachoud-Lévi et al., 2001; Brandt, 1991; Ho, Sahakian, et al., 2003; Lange, Sahakian, Quinn, Marsden, & Robbins, 1995; Montoya, Price, Menear, & Lepage, 2006; Snowden, Craufurd, Griffiths, Thompson, & Neary, 2001). In the present series, all the patients but three were impaired on the MDRS. This might raise the concern that these patients approached the task differently from controls, e.g. concerning their ability to retain information regarding the percentage of valid trials throughout each task. Contrary to this possibility, we note that HD patients' pattern of performance at 1000-ms SOA was influenced by the cue–target relationships (decreased IOR with predictive cues in Experiment 2 as compared the non-predictive cues used in Experiment 1). Thus, patients were adequately coping with the different percentages of valid and invalid trials in each experiment. Moreover, evidence from normal participants indicates that explicit memory of the task instructions may not even be necessary to the development of these "strategic" effects resulting from the proportion of valid to invalid cues, as demonstrated by the fact that such effects can be demonstrated by participants ignorant of these proportions, and unable to describe them at debriefing (Bartolomeo, Decaix, et al., 2007; Bartolomeo, Zieren, Vohn, Dubois, & Sturm, 2007). These considerations suggest that the correlations found between MDRS scores and cue validity effects reflect similar effects of HD progression on these variables, rather than a causal relationship between them.

In conclusion, the present results, obtained by using a cued RT paradigm with peripheral cues and different cue–target contingencies, indicated that HD patients' attentional processing of visuo-spatial stimuli may be slowed, with a tendency for attention to remain on peripherally cued locations. This resulted in a slowing of disengagement processes, which delayed the occurrence of both exogenous processes such as IOR and endogenous strategies such as re-orienting towards uncued locations where the target is expected to appear. Attentional impairments should be systematically evaluated in HD patients, because there may have direct and important clinical implications. For example, deficits of visual attention may play a role in the increased risk of traffic collisions in HD (Rebok, Bylsma, Keyl, Brandt, & Folstein, 1995). In the present study, the outcome of RT tasks correlated with biological measures of disease severity, thus suggesting the clinical interest of such tasks in assessing the patients' neuropsychological status and the efficacy of potential treatments, whether pharmacological or surgical (Bachoud-Lévi et al., 2000).

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