

Attentional Impairments in Huntington's Disease: A Specific Deficit for the Executive Conflict

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Objective: Huntington's disease (HD) is characterized by motor and cognitive impairments including memory, executive, and attentional functions. However, because earlier studies relied on multidetermined attentional tasks, uncertainty still abounds regarding the differential deficit across attentional subcomponents. Likewise, the evolution of these deficits during the successive stages of HD remains unclear. The present study simultaneously explored 3 distinct networks of attention (alerting, orienting, executive conflict) in preclinical and clinical HD. **Method:** Thirty-eight HD patients (18 preclinical) and 38 matched healthy controls completed the attention network test, an integrated and theoretically grounded task assessing the integrity of 3 attentional networks. **Results:** Preclinical HD was not characterized by any attentional deficit compared to controls. Conversely, clinical HD was associated with a differential deficit across the 3 attentional networks under investigation, showing preserved performance for alerting and orienting networks but massive and specific impairment for the executive conflict network. This indexes an impaired use of executive control to resolve the conflict between task-relevant stimuli and interfering task-irrelevant ones. **Conclusion:** Clinical HD does not lead to a global attentional deficit but rather to a specific impairment for the executive control of attention. Moreover, the absence of attentional deficits in preclinical HD suggests that these deficits are absent at the initial stages of the disease. In view of their impact on everyday life, attentional deficits should be considered in clinical contexts. Therapeutic programs improving the executive control of attention by neuropsychology and neuro-modulation should be promoted.

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General Scientific Summary

Huntington's disease (HD) centrally leads to motor dysfunction but is also characterized by cognitive deficits. Attentional abilities, while important for efficient cognitive functioning, have not been fully explored in HD, and their differential impairment between pre-clinical and clinical HD has not been determined. We measured attentional abilities in pre-clinical and clinical HD, with a task separately exploring alerting (i.e., sustaining a readiness state to be prepared for incoming stimuli), orienting (i.e., selecting the incoming information by engaging, disengaging, and shifting attentional resources) and executive control (i.e., top-down control of attention and conflict resolution) attentional networks. Results showed that clinical HD is associated with a specific impairment for executive control, while alerting and orienting are preserved. No deficits for attentional networks were observed in pre-clinical HD, suggesting that attentional deficits might differentiate the successive stages of HD, and that rehabilitation programs focusing on executive control should be developed in clinical HD.

Keywords: Huntington's disease, attentional networks, executive control, attention network test

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Huntington's disease (HD) is a genetic neurodegenerative disease mainly associated with massive motor impairments (Van Duijn, Kingma, & van der Mast, 2007). At the cerebral level, these movement disorders are related to progressive neurodegeneration in basal ganglia, particularly in the striatum and its spiny projections toward globus pallidus and substantia nigra (Fusco et al., 1999; Ross & Tabrizi, 2011; Sapp et al., 1997). However, the brain deficits go far beyond motor regions: White matter atrophy is observed from early disease stages (Reading et al., 2005), followed by marked brain atrophy in the thalamus, hypothalamus, and occipital cortex as well as in frontal regions (Eidelberg & Surmeier, 2011; Rosenblatt, 2007; Wolf & Klöppel, 2013). These cerebral modifications lead to wide-range cognitive impairments in preclinical (i.e., asymptomatic persons carrying the HD's gene) and clinical (i.e., symptomatic individuals presenting motor, cognitive, and/or psychiatric impairments) patients (Ross & Tabrizi, 2011; Sturrock & Leavitt, 2010). Accordingly, clinical HD patients exhibit impaired visuomotor (Aron et al., 2003; Say et al., 2011), memory (Lawrence et al., 1996), and executive (Beglinger et al., 2010; Beste, Saft, Andrich, Gold, & Falkenstein, 2008) processes. Yet evidence remains inconsistent in preclinical HD, particularly regarding executive impairments (Brandt et al., 2008; O'Rourke et al., 2011).

Of critical importance for practitioners, these cognitive alterations result in a significant burden for patients through lower educational and professional achievement, everyday occupational impairments, and reduced treatment compliance (Beglinger et al., 2012; Paulsen & Long, 2014). Therefore, a comprehensive understanding of these cognitive alterations is needed and would help clinicians to select appropriate therapeutic targets whose restoration may improve patients' everyday life. Moreover, such advances may help to identify potential neurocognitive biomarkers of disease progression acting as a tipping point in the preclinical to clinical transition (Stout et al., 2011). The discrepancies observed in earlier studies and the use of multidetermined neuropsychological tasks (Brandt et al., 2008) currently hamper the identification of such cognitive biomarkers. However, as recently proposed (Dumas, van den Bogaard, Middelkoop, & Roos, 2013), attentional processes are an underexplored but promising way to differentiate preclinical and clinical HD (Bachoud-Lévi et

al., 2001; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2004), thus constituting a potential candidate to become a cognitive biomarker.

Accordingly, a dissociated pattern with marked attentional dysfunction in clinical HD but preserved attentional processes in preclinical HD has been proposed. Whereas early works had spotted large-scale attentional dysfunctions in clinical HD (e.g., Sprengelmeyer, Lange, & Hömberg, 1995), recent ones have more specifically indicated impaired visuospatial (Bublak, Redel, & Finke, 2006), divided (Thompson et al., 2010), selective (Georgiou-Karistianis et al., 2012), and sustained (Duff et al., 2010) attention, thus confirming large-range attentional impairments in HD. Several studies have further illuminated that clinical HD is associated with preserved attention orientation (Beste et al., 2008) but impaired ability in the voluntarily disengagement of attentional focus (Couette, Bachoud-Levi, Brugieres, Sieroff, & Bartolomeo, 2008; Georgiou, Bradshaw, Phillips, & Chiu, 1996) and in the inhibitory control of attention (Henderson et al., 2011). This proposal that clinical HD would mostly be related to impairments for the executive control of attention is consistent with neuroimaging results, because this ability relies on the integrity of frontal regions and fronto-striatal circuits, known to be impaired in HD (Georgiou-Karistianis et al., 2012; Wolf & Klöppel, 2013).

In contrast, individuals with preclinical HD did not evidence such a deficit (Lemiere et al., 2004; Malejko et al., 2014), despite some inconsistent results (Verny et al., 2007; Wolf et al., 2011). Yet, most of these studies did not compare preclinical and clinical HD. Moreover, the four studies including such a comparison yielded inconsistent findings. On the one hand, two studies (Peretti et al., 2008; Peretti, Peretti, Chouinard, & Chouinard, 2010) depicted preserved exogenous but impaired endogenous attention in clinical and preclinical HD, which was interpreted as a specific deficit for voluntary attentional abilities. On the other hand, Hart et al. (2012) showed distinct performances in a sustained attention task, namely reduced attentional control in clinical HD with no deficit in preclinical HD. These results have been recently confirmed by a 3-year follow-up study showing a linear decrease of attentional performance in clinical HD over time, whereas preclinical HD patients were able to maintain

a preserved performance (Hart et al., 2015). Despite their useful insights, these studies focused on a specific and basic component of attention, so their generalizability toward other attentional subsystems remains unknown. More globally, earlier studies comparing preclinical and clinical HD did not control for psychopathological comorbidities (despite their influence on attention; Heeren, Maurage, & Philippot, 2015; Lyche, Jonassen, Stiles, Ulleberg, & Landrø, 2011). Finally, earlier studies did not propose an integrated task simultaneously evaluating the different attentional subcomponents. Using such an integrated task in preclinical and clinical HD would thus constitute an important step toward the understanding of this impairment.

The attention network test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002), based on a cognitive model of attention (Petersen & Posner, 2012; Posner & Petersen, 1990), constitutes an effective tool to simultaneously explore various attentional subcomponents. Indeed, it provides an integrated assessment of three independent networks: (a) *alerting*, that is, reaching and sustaining a global high sensitivity or readiness state to be prepared for incoming stimuli; (b) *orienting*, that is, selecting the incoming information by engaging, disengaging, and shifting the attentional resources from one stimulation to another; and (c) *executive conflict*, that is, top-down control of attention and conflict resolution. By evaluating these three components simultaneously, this task allows the direct exploration of the differential deficit across attentional subcomponents. This model has been reinforced by a neuroscience approach that identified specific brain circuits associated with each network: superior temporal and thalamic activations for alerting; superior parietal lobule and fusiform gyrus activations for orienting; and thalamic, cingulate and superior-inferior frontal gyri activations for executive conflict (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; MacLeod et al., 2010; Visintin et al., 2015).

The ANT has been widely used to characterize attentional deficits in neuropsychiatric (Maurage, de Timary, Billieux, Colignon, & Heeren, 2014; Orellana, Slachevsky, & Peña, 2012) and neurological (Fernández et al., 2011; Fernandez-Duque & Black, 2006; Urbanek et al., 2010) disorders but also recently in movement disorders such as Wilson's and Parkinson's diseases (associated to alerting and orienting impairments, respectively; Han et al., 2014; Zhou et al., 2012). This task is thus a reliable tool to explore the differential attentional impairments across neuropsychiatric and neurological syndromes, but it has not to date been applied to HD. The main aim of the present study was thus to measure attentional processes in preclinical and clinical HD with the ANT. In view of earlier studies showing executive functions deficits in clinical HD (Dumas et al., 2013) and suggesting a specific deficit for attentional control (Couette et al., 2008; Henderson et al., 2011), it can be hypothesized that clinical HD will be associated with attentional impairments, particularly for the executive conflict network. This hypothesis is reinforced by the fact that this attentional network mostly relies on thalamic and frontal areas (Fan et al., 2005), which are particularly affected by HD neurodegeneration (Eidelberg & Surmeier, 2011; Wolf & Klöppel, 2013). Conversely, preclinical HD might show a global preservation of attention, because attentional functions appear quite preserved in this population (Malejko et al., 2014).

Method

Participants

Thirty-eight individuals (15 women) with a genetically confirmed HD diagnostic (Huntington's disease participants [HDPs]) were recruited in four Belgian hospitals. Participants were first contacted by their general practitioner or neurologist, who explained the aims of the study. Then they were referred to the principal investigator. All participants were over 18 years of age, had a family history of HD, and completed a genetic blood test assessing the HD's cytosine–adenine–guanine (CAG) expansion. HD is characterized by elongated CAG repeat on at least one allele of the chromosome 4 on the Huntingtin gene (Roos, 2010). All participants presented an expansion of at least 36 CAG repeats. Among them, 18 were at preclinical stage (HDP–) and 20 were at clinical stage (HDP+). The disease stage was assessed according to Roos's (2010) criteria. Among those with HDP–, 15 were at the A2 stage (i.e., gene carrier, premanifest stage) and three were at the A3 stage (i.e., transition phase, ongoing changes at behavioral and motor levels). Among those with HDP+, 12 were at the B1 stage (i.e., Clinical Stage I, with initial neurological, cognitive, and psychiatric symptoms, with chorea being the most prominent symptom) and eight were at the B2 stage (i.e., Clinical Stage II, with generalized motor disturbance and increased cognitive–psychiatric symptoms). The mean illness duration among patients with HDP+ was 7.04 years ($SD = 5.57$). The mean number of CAG repeats of the longest allele was 41.8 ($SD = 3.20$) in HDP– and 43.74 ($SD = 3.89$) in HDP+. Moreover, a clinical evaluation of the psychological, social, and occupational abilities of the patients was conducted by a neurologist through the Clinical Global Impression scale (CGI; Guy, 1976), a widely used tool with a scale ranging from 1 (*normal*) to 7 (*among the most ill patients*). In HDP–, CGI scores were between 1 (*normal*) and 2 (*borderline*; $M = 1.20$, $SD = .41$). In HDP+, CGI scores were between 3 (*mildly ill*) and 5 (*markedly ill*; $M = 4.35$, $SD = .67$). Patients were matched for age, gender, and education with 38 control participants (CPs). Two subgroups of CP were determined (CP–, CP+), respectively matched with the HDP– and HDP+ groups. Groups' characteristics appear in Table 1. Exclusion criteria for both groups included major medical problems, neurological disease other than HD, and psychiatric disorder, as assessed through the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Education level was assessed according to the number of years of education completed since starting primary school.

Materials and Measurements

Questionnaires. Validated self-completion questionnaires were used to assess depression (the French version of the second edition of the Beck Depression Inventory; Beck, Steer, & Brown, 1998) and trait-anxiety (State and Trait Anxiety Inventory; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

Attentional task. The ANT was administered to determine the efficiency of three independent attentional networks: alerting, orienting, and executive control (Fan et al., 2002). Participants had to determine as fast and accurately as possible the direction of a central arrow (the target) by pressing the corresponding button (left or right) on a mouse. These targets were preceded by a cue,

Table 1

Demographic and Psychopathological Measures for Clinical (HDP+) and Preclinical (HDP-) Huntington's Disease Participants and Matched Controls (CP+ and CP-, Respectively)

Variable	Huntington's Disease Participants (HDP)			Control Participants (CP)		
	HDP+ (n = 20)	HDP- (n = 18)	All HDP (n = 38)	CP+ (n = 20)	CP- (n = 18)	All CP (n = 38)
Demographic measures						
Age: <i>M</i> (<i>SD</i>)	49.1 (11.3)	40.4 (14.3)	44.9 (13.4)	49.6 (15.7)	39.4 (15.0)	44.8 (16.0)
Gender ratio (F/M)	8/12	7/11	15/23	8/12	7/11	15/23
Educational level (in years): <i>M</i> (<i>SD</i>)	10.9 (3.6)	13.2 (2.7)	11.9 (3.3)	12.1 (2.8)	12.0 (4.2)	12.0 (3.5)
Psychopathological measures: <i>M</i> (<i>SD</i>)						
Beck Depression Inventory	13.4 (9.1)	12.2 (8.9)	12.8 (8.9)	11.9 (6.4)	10.8 (6.1)	11.4 (6.2)
Trait Anxiety Inventory	43.3 (10.4)	45.1 (11.3)	44.1 (10.7)	40.3 (8.5)	43.1 (8.8)	41.6 (8.7)

Note. F/M = female/male.

with four possible cue types (see Figure 1A): no cue, center cue (an asterisk replacing the fixation cross), double cue (two asterisks, respectively appearing above and below the fixation cross), or spatial cue (an asterisk appearing above or below the fixation cross and indicating the location of the upcoming target). Moreover, flankers were located on each side of the target, with three possible

flanker types (see Figure 1B): two arrows in the same direction as the target (congruent condition), two arrows in the opposite direction of the target (incongruent condition), or two lines (neutral condition). Each trial was as follows (see Figure 1C): (a) a central fixation cross (random duration, 400–600 ms); (b) a cue (100 ms); (c) a central fixation cross (400 ms); (d) a target and its flankers, appearing above or below the fixation cross (lasting until the participant responded or for 1,700 ms); (e) a central fixation cross (lasting for 3,500 ms minus the sum of the first fixation period's duration and the reaction time [RT]). RT (ms) and accuracy (percentage of correct responses) were recorded for each trial.

The ANT comprised 288 trials, divided in three blocks of 96 trials each (with a short break between blocks). There were 48 possible trials, based on the combination of four cues (no cue, center cue, double cue, spatial cue), three flankers (congruent, incongruent, neutral), two directions of the target arrow (left, right), and two localizations (upper or lower part of the screen). Trials were presented in a random order, and each possible trial was presented twice within a block. The task was programmed and presented using E-Prime 2 Professional (Psychology Software Tools, 2012).

Procedure

The task was completed individually in one 45-min session in a quiet, dimly lit room. Participants were provided with full details regarding the aims of the study and the procedure to be followed, and they signed the written informed consent. Each participant was then provided with the instructions on the computer screen. These instructions were emphasized by the experimenter, and then a training session consisting of 24 randomly selected trials began. Finally, the experimenter recalled the instructions and answered the remaining questions before starting the experiment. The distance between participants' eyes and the screen was 50 cm, and the target stimuli subtended a visual angle of about 4° in the horizontal field. After the experimental task, participants filled in the questionnaires and were debriefed individually. This study was approved by the Ethical Committee of the Université catholique de Louvain (Belgium) and conducted according to the Declaration of Helsinki (World Medical Association, 2013). Participants received compensation (25 euros) for their participation. This experiment was part of a larger project investigating neurocognitive and emotional deficits in HD (e.g., Maurage et al., 2016).

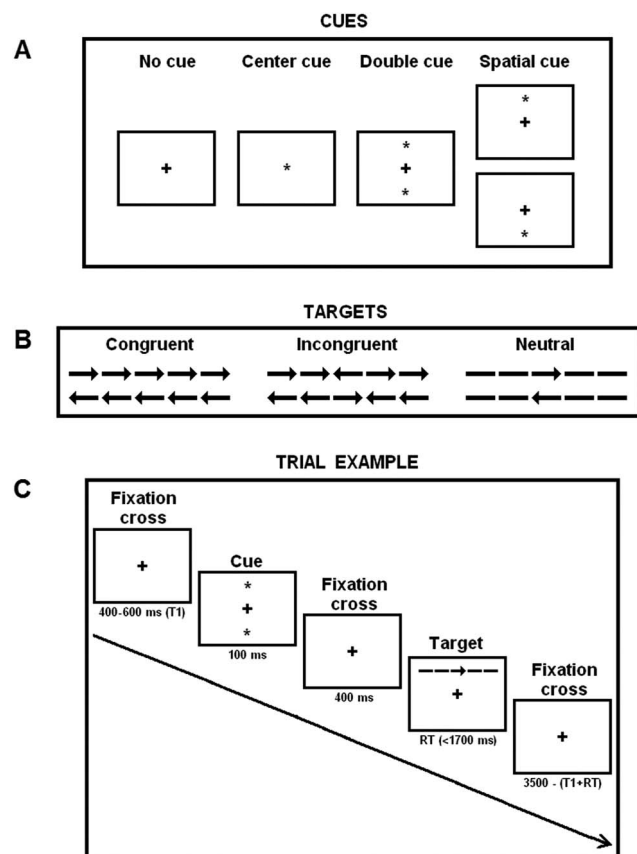


Figure 1. Description of the attention network test used to explore the three attentional networks (alerting, orienting, executive conflict) in Huntington's disease, presenting the four possible cues (Panel A), the six possible targets (Panel B), and a trial example (Panel C; i.e., neutral trial preceded by a double cue, the correct response being "right"). Adapted from Fan, McCandliss, Sommer, Raz, and Posner (2002).

Data Preparation and Analytic Plan

Power analysis. An a priori power analysis was conducted to determine the appropriate total sample size for testing hypotheses with the primary outcome variable. We expected, based on previous studies on cognition in preclinical and clinical HD (Finke et al., 2007; Harrington et al., 2014; Peretti et al., 2010; Wolf et al., 2011), a medium effect size of Cohen's $d = .50$. Setting alpha at .05, and power $(1 - \beta)$ at .80 on a repeated-measures design, the power analysis (G*Power 3.1.3; Faul, Erdfelder, Lang, & Buchner, 2007) indicated that a total sample size of 17 individuals per group would yield adequate power, thus confirming that the chosen design and sample size had enough statistical power to test our hypothesis.

Statistical analyses. We addressed outliers and errors in the experimental tasks as follows. First, trials with incorrect responses were excluded (5.58% of trials). Second, RTs lower than 200 ms or greater than 2,000 ms were removed from analyses (.007% of the remaining trials). Third, RTs of more than 2 SDs below or above each participant's mean for each experimental condition were excluded as outliers (.024% of the remaining trials). Data analyses were performed following the approach pioneered by Fan and his colleagues (Fan et al., 2002, 2009) and increasingly used by others (e.g., Heeren et al., 2014; Moriya & Tanno, 2009; Sommerfeldt et al., 2016; Tortella-Feliu et al., 2014). Because a preliminary analysis showed no difference in RT or accuracy according to the direction (left or right) and localization (upper or lower) of the arrow, these trials were thus merged, leading to 24 trials for each of the 12 experimental conditions (four cues \times three flankers).

Clinical HD groups were older than preclinical ones due to the progressive nature of HD-related disorders (see Table 1). Two types of analyses were thus conducted to explore the differential attentional impairment across the successive stages of the disease while taking this age difference (known to influence attentional processes; Deiber, Ibañez, Missonnier, Rodriguez, & Giannakopoulos, 2013; Mahoney, Verghese, Goldin, Lipton, & Holtzer, 2010) into account: (a) a direct comparison between HD subgroups (i.e., preclinical HDP- and clinical HDP+) with the inclusion of age as a covariate and (b) a comparison between each HD group (preclinical HDP- and clinical HDP+) and its respective control group (CP- and CP+), matched for age, gender, and education. First, for each subgroup comparison, general $2 \times 4 \times 3$ analyses of variance (ANOVAs) were performed separately for RT and accuracy with Group (HDP- vs. HDP+; HDP- vs. CP-; HDP+ vs. CP+) as between-subjects variable and Cue (no cue, central cue, double cue, spatial cue) and Flanker (congruent, incongruent, neutral) as within-subject variables.

We then computed the *alerting* effect by subtracting the mean (i.e., RT or accuracy score) for double-cue trials from the mean for no-cue trials (no cue - double cue), the *orienting* effect by subtracting the mean for spatial-cue trials from the mean result for center-cue trials (center cue - spatial cue), and the *executive conflict* effect by subtracting the mean for congruent trials (summed across cue types) from the mean for incongruent trials (Incongruent - Congruent). For both the alerting and orienting effects, greater subtraction scores for RT (and lower for accuracy) indicated greater efficiency. In contrast, greater subtraction scores for RT (and lower for accuracy) on executive conflict indicated

increased difficulty with executive control of attention (Fan et al., 2005). Consequently, a second general 2×3 ANOVA was performed separately for RT and accuracy with Group as between-subjects variable and Attention Network (alerting, orienting, executive conflict) as within-subject variable.

For each ANOVA, significant main effects and interactions were followed up by corrected post hoc independent-samples t tests. Independent-samples t tests were computed to explore group differences on control measures. Two-tailed Pearson's correlations were also performed to explore the links between experimental results and psychopathological variables. Because our main focus concerned the exploration of a potential deficit in HD, the Results section focuses on group comparison and the overall effects for each ANOVA (i.e., significant results not related to group differences) are reported in the online supplemental materials. Statistical analyses were performed using the SPSS 19 software package.

Results

Group Equivalence

HDP- versus HDP+: As shown in Table 1, no significant difference was identified for gender, $\chi^2(1, 38) = .005, p = .999$; education, $t(36) = 1.63, p = .118$; depression, $t(36) = .41, p = .684$; or anxiety, $t(36) = .53, p = .599$. However, age was related to a significant group difference, $t(36) = 2.09, p = .043$, HDP+ being significantly older than HDP-. Age was thus included as a covariate in the following HDP- versus HDP+ comparisons.

HDP- versus CP-: No significant difference was observed for age, $t(34) = .21, p = .835$; gender, $\chi^2(1, 38) < .001, p = .99$; education, $t(34) = .99, p = .329$; depression, $t(34) = .52, p = .606$; or anxiety, $t(34) = .61, p = .546$.

HDP+ versus CP+: No significant difference was described for age, $t(38) = .12, p = .905$; gender, $\chi^2(1, 38) = 0, p = 1$; education, $t(38) = 1.13, p = .266$; depression, $t(38) = .58, p = .565$; or anxiety, $t(38) = .98, p = .333$.

General Analysis

A 2 (groups: HDP- and HDP+/HDP- and CP-/HDP+ and CP+, respectively for the three subgroup comparison) \times 4 (cues: no cue, central cue, double cue, spatial cue) \times 3 (flankers: congruent, incongruent, neutral) ANOVA was performed separately for RT and accuracy in each subgroup comparison. The means and standard deviations for each group in each experimental condition are presented in Table 2.

Reaction Times

HDP- versus HDP+: A main group effect was identified, $F(1, 35) = 17.82, p < .001, \eta_p^2 = .38$, because HDP+ presented longer RTs than did HDP-. A Group \times Flanker interaction was also detected, $F(2, 70) = 4.26, p = .018, \eta_p^2 = .11$. A between-groups post hoc comparison showed that HDP+ presented longer RTs than did HDP- for congruent, $t(36) = 4.13, p < .001$; incongruent, $t(36) = 5.34, p < .001$; and neutral, $t(36) = 4.89, p < .001$, flankers. However, this group difference was significantly stronger for incongruent than for congruent, $t(17) = 2.67, p = .016$, and neutral, $t(17) = 2.54, p = .021$, flankers. Neither the Group \times

Table 2

Mean (and Standard Deviation) Reaction Time and Accuracy Measures for Clinical (HDP+) and Preclinical (HDP-) Huntington's Disease Participants and Matched Controls (CP+ and CP-, Respectively)

Variable	Huntington's Disease Participants (HDP)			Control Participants (CP)		
	HDP+ (n = 20)	HDP- (n = 18)	All HDP (n = 38)	CP+ (n = 20)	CP- (n = 18)	All CP (n = 38)
Congruent condition						
Reaction time (ms)						
No cue	850 (161)	663 (157)	761 (183)	612 (111)	608 (113)	610 (110)
Center cue	831 (156)	624 (154)	733 (185)	587 (114)	581 (126)	584 (118)
Double cue	809 (154)	612 (138)	715 (176)	569 (106)	571 (111)	570 (107)
Spatial cue	785 (140)	592 (136)	693 (168)	547 (107)	553 (115)	550 (109)
Accuracy (%)						
No cue	86.25 (15.60)	97.69 (4.78)	91.67 (13.00)	99.17 (2.18)	99.54 (1.35)	99.34 (1.82)
Center cue	90.62 (12.67)	97.68 (4.34)	93.97 (10.19)	99.58 (1.28)	99.77 (.98)	99.67 (1.14)
Double cue	91.87 (12.13)	98.15 (4.10)	94.85 (9.66)	99.79 (.93)	99.77 (.98)	99.78 (.94)
Spatial cue	90.21 (13.40)	98.61 (3.50)	94.19 (10.77)	99.79 (.93)	99.31 (2.14)	99.56 (1.62)
Incongruent condition						
Reaction time (ms)						
No cue	1,034 (153)	754 (151)	902 (206)	703 (134)	714 (133)	708 (132)
Center cue	1,008 (180)	742 (149)	882 (212)	708 (140)	717 (150)	712 (143)
Double cue	1,001 (181)	735 (157)	875 (215)	713 (128)	708 (157)	710 (140)
Spatial cue	967 (192)	688 (143)	835 (220)	642 (131)	662 (155)	651 (141)
Accuracy (%)						
No cue	71.25 (27.87)	92.59 (12.50)	81.36 (24.23)	95.21 (5.28)	97.92 (2.58)	96.49 (4.39)
Center cue	72.08 (28.58)	93.77 (10.52)	82.36 (24.31)	95.42 (6.18)	95.37 (7.94)	95.39 (6.97)
Double cue	74.38 (26.98)	96.53 (9.07)	84.87 (23.18)	96.87 (3.79)	96.06 (6.31)	96.49 (5.08)
Spatial cue	75.21 (27.85)	95.37 (7.13)	84.76 (22.93)	97.50 (3.42)	96.53 (4.57)	97.04 (3.98)
Neutral condition						
Reaction time (ms)						
No cue	834 (131)	652 (139)	748 (162)	610 (94)	604 (114)	607 (103)
Center cue	834 (129)	620 (139)	733 (171)	582 (109)	580 (123)	581 (114)
Double cue	814 (109)	606 (131)	715 (158)	584 (104)	566 (116)	575 (108)
Spatial cue	803 (137)	583 (157)	699 (183)	551 (105)	551 (114)	551 (108)
Accuracy (%)						
No cue	89.58 (13.62)	99.31 (2.14)	94.19 (11.03)	98.33 (2.10)	98.61 (2.02)	98.46 (2.04)
Center cue	89.58 (13.00)	98.15 (4.79)	93.64 (10.78)	99.17 (1.71)	99.77 (.98)	99.45 (1.43)
Double cue	87.50 (15.71)	98.38 (4.08)	92.65 (12.83)	99.58 (1.28)	99.31 (1.60)	99.45 (1.43)
Spatial cue	90.00 (12.78)	98.38 (3.54)	93.97 (10.37)	99.17 (2.18)	100 (.00)	99.56 (1.62)

Cue, $F(3, 105) = .27, p = .847$, nor the Group \times Cue \times Flanker, $F(6, 210) = .99, p = .433$, interactions were significant.

HDP- versus CP-: No main group effect was observed, $F(1, 34) = .74, p = .396$, nor was there any interaction with cue, $F(3, 102) = .96, p = .415$, or flanker, $F(2, 68) = .61, p = .546$, or a Group \times Cue \times Flanker interaction, $F(6, 204) = .08, p = .998$.

HDP+ versus CP+: A main group effect was described, $F(1, 38) = 43.88, p < .001, \eta_p^2 = .54$, because HDP+ presented longer RTs than did CP+. A Group \times Flanker interaction was also detected, $F(2, 76) = 7.01, p = .002, \eta_p^2 = .16$. A between-groups post hoc comparison showed that HDP+ presented longer RTs than did CP+ for congruent, $t(38) = 5.68, p < .001$; incongruent, $t(38) = 6.81, p < .001$; and neutral, $t(38) = 6.67, p < .001$, flankers. However, this group difference was significantly stronger for incongruent than for congruent, $t(19) = 2.81, p = .011$, and neutral, $t(19) = 2.93, p = .008$, flankers. No Group \times Cue, $F(3, 114) = .97, p = .409$, or Group \times Cue \times Flanker, $F(6, 228) = 1.76, p = .108$, interactions were detected.

Accuracy

HDP- versus HDP+: The analysis revealed a main group effect, $F(1, 35) = 10.28, p = .002, \eta_p^2 = .23$, because HDP+

presented lower accuracy scores than did HDP-. A Group \times Flanker interaction was also observed, $F(2, 70) = 8.65, p < .001, \eta_p^2 = .20$. A between-groups post hoc comparison showed that HDP+ presented lower accuracy than did HDP- for congruent, $t(36) = 2.65, p = .012$; incongruent, $t(36) = 3.18, p = .003$; and neutral, $t(36) = 3.03, p = .005$, flankers. However, this group difference was significantly stronger for incongruent than for congruent, $t(17) = 3.32, p = .004$, and neutral, $t(17) = 2.95, p = .009$, flankers. No Group \times Cue, $F(3, 105) = 1.09, p = .357$, or Group \times Cue \times Flanker, $F(6, 210) = .57, p = .754$, interactions were identified.

HDP- versus CP-: No main group effect was described, $F(1, 34) = 1.27, p = .268$, nor was there any interaction with cue, $F(3, 102) = 1.26, p = .292$, or flanker, $F(2, 68) = .27, p = .764$, or a Group \times Cue \times Flanker interaction, $F(6, 204) = 1.92, p = .079$.

HDP+ versus CP+: The analysis revealed a main group effect, $F(1, 38) = 13.88, p < .001, \eta_p^2 = .27$, because HDP+ presented lower accuracy scores than did CP+. A Group \times Flanker interaction was also observed, $F(2, 76) = 11.58, p < .001, \eta_p^2 = .23$. A between-groups post hoc comparison showed that HDP+ presented lower accuracy than did CP+ for congruent, $t(38) = 3.49, p = .002$; incongruent, $t(38) = 3.99, p < .001$; and neutral, $t(38) =$

3.64, $p = .002$, flankers, but this group difference was significantly stronger for incongruent than for congruent, $t(19) = 3.73$, $p = .001$, and neutral, $t(19) = 3.61$, $p = .002$, flankers. No Group \times Cue, $F(3, 114) = .79$, $p = .502$, or Group \times Cue \times Flanker, $F(6, 228) = 1.24$, $p = .287$, interactions were observed.

Attentional Networks Analyses

A 2 (groups: HDP⁻ and HDP⁺/HDP⁻ and CP⁻/HDP⁺ and CP⁺, respectively for the three subgroup comparison) \times 3 (attentional networks: alerting, orienting, executive conflict) ANOVA was performed separately for RT and accuracy in each subgroup comparison. These results are illustrated in Figure 2.

Reaction times. HDP⁻ versus HDP⁺: No main group effect was observed, $F(1, 35) = 2.13$, $p = .153$. However, a Group \times Attentional Networks interaction emerged, $F(2, 70) = 5.03$, $p = .009$, $\eta_p^2 = .13$. A between-groups post hoc comparison showed that, compared to HDP⁻, HDP⁺ presented higher RT subtraction scores for executive conflict, $t(36) = 2.76$, $p = .009$, but not for alerting, $t(36) = .87$, $p = .390$, or orienting, $t(36) = .24$, $p = .811$.

HDP⁻ versus CP⁻: No main group effect was described, $F(1, 34) < .001$, $p = .99$, nor was there any Group \times Attentional Networks interaction, $F(2, 68) = 1.03$, $p = .362$.

HDP⁺ versus CP⁺: The analysis revealed a main group effect, $F(1, 38) = 5.05$, $p = .03$, $\eta_p^2 = .12$, because HDP⁺ presented higher RT subtraction scores than did CP⁺. A Group \times Attentional Networks interaction was also identified, $F(2, 76) = 6.25$, $p = .003$, $\eta_p^2 = .14$. A between-groups post hoc comparison showed that, compared to CP⁺, HDP⁺ were impaired for executive conflict, $t(38) = 2.81$, $p = .011$, but not for alerting, $t(38) = .54$, $p = .592$, or orienting, $t(38) = .59$, $p = .559$.

Accuracy. HDP⁻ versus HDP⁺: A main group effect emerged, $F(1, 35) = 8.98$, $p = .005$, $\eta_p^2 = .21$, because HDP⁺ presented higher accuracy subtraction scores than did HDP⁻. A Group \times Attentional Networks interaction was also identified, $F(2, 70) = 8.38$, $p = .001$, $\eta_p^2 = .19$. A between-groups post hoc comparison showed that, compared to HDP⁻, HDP⁺ were impaired for executive conflict, $t(36) = 3.11$, $p = .004$, but not for alerting, $t(36) = .88$, $p = .385$, or orienting, $t(36) = .09$, $p = .929$.

HDP⁻ versus CP⁻: The analysis did not reveal a main group effect, $F(1, 34) = 1.13$, $p = .295$, nor was there any Group \times Attentional Networks interaction, $F(2, 68) = .35$, $p = .706$.

HDP⁺ versus CP⁺: A main group effect was observed, $F(1, 38) = 11.16$, $p = .002$, $\eta_p^2 = .23$, because HDP⁺ presented higher accuracy subtraction scores than did CP⁺. A Group \times Attentional Networks interaction was also revealed, $F(2, 76) = 9.48$, $p < .001$, $\eta_p^2 = .20$. A between-groups post hoc comparison showed that, compared to CP⁺, HDP⁺ were impaired for executive conflict, $t(38) = 3.73$, $p < .001$, but not for alerting, $t(38) = .85$, $p = .401$, or orienting, $t(38) = .22$, $p = .827$.

Complementary Analyses

Complementary analyses were conducted to explore the influence of confounding factors (i.e., psychopathological measures, HD characteristics, and fatigue) on the experimental results:

1. *Influence of psychopathological factors:* Pearson's correlations were conducted in all groups among psycho-

pathological factors (i.e., depression and anxiety measures) and experimental results (i.e., results for accuracy and RT in the three attentional networks). No significant correlation was observed (all $ps > .05$).

2. *Link in the HD groups between disease intensity indices (CGI score, number of CAG repeats, disease duration, and disease stage) and experimental results:* No significant correlation was observed for the number of CAG repeats and for disease duration ($p > .05$ for every correlation). However, for the CGI score as well as for disease stage, no significant correlations were observed for alerting and orienting (all $ps > .05$), but the extent of executive control impairment was significantly correlated with the CGI score (RT: $r = .37$, $p = .011$; accuracy: $r = .53$, $p < .001$) and with disease stage (RT: $r = .29$, $p = .038$; accuracy: $r = .23$, $p = .041$).
3. *Influence of fatigue factor:* Because fatigue might differently affect groups and influence the results, experimental data were divided in three successive blocks, that is, Block 1 (first 96 trials of the task), Block 2 (Trials 97–192), and Block 3 (Trials 193–288), and the ANOVAs related to attentional networks for each group comparison were recomputed with the inclusion of block as a three-level within-subject variable. As fully reported in the online supplemental materials, this analysis replicated the results observed in the initial ANOVA, and no significant main block effect or interaction with Group and Attentional Networks were observed on the results, showing that fatigue cannot account for the results.

Discussion

In this study, we proposed the first joint exploration of the three attentional networks in preclinical and clinical HD. We found that clinical HD does not lead to a global attentional deficit but rather to a specific impairment for executive control network, with preserved alerting and orienting networks. Clinical HD patients first showed globally increased RTs and reduced accuracy compared to preclinical HD patients and matched controls, indexing a general cognitive and visuomotor processing speed deficit, which is consistent with earlier results (Aron et al., 2003; Say et al., 2011). Of critical importance, the executive attentional subcomponent was significantly impaired in clinical HD, because these patients exhibited longer RTs for task-irrelevant stimuli than did preclinical patients and controls. Because this measure specifically reflects the RT delay provoked by the presence of nonpertinent flankers (in incongruent trials) compared to pertinent ones (in congruent trials), this indicates that those with clinical HD have difficulties to resolve the conflict between task-relevant information (i.e., the central arrow to be processed) and interfering distractors (i.e., the incongruent and irrelevant flankers). This RT delay is also present among controls, as observed earlier (Fan et al., 2009), but is significantly increased in clinical HD. Attentional deficits in clinical HD are thus related to a decreased ability to distinguish task-relevant and task-irrelevant stimuli, and to solve the conflict between these contradictory cues. This proposal is further reinforced by accuracy results showing reduced performance in clin-

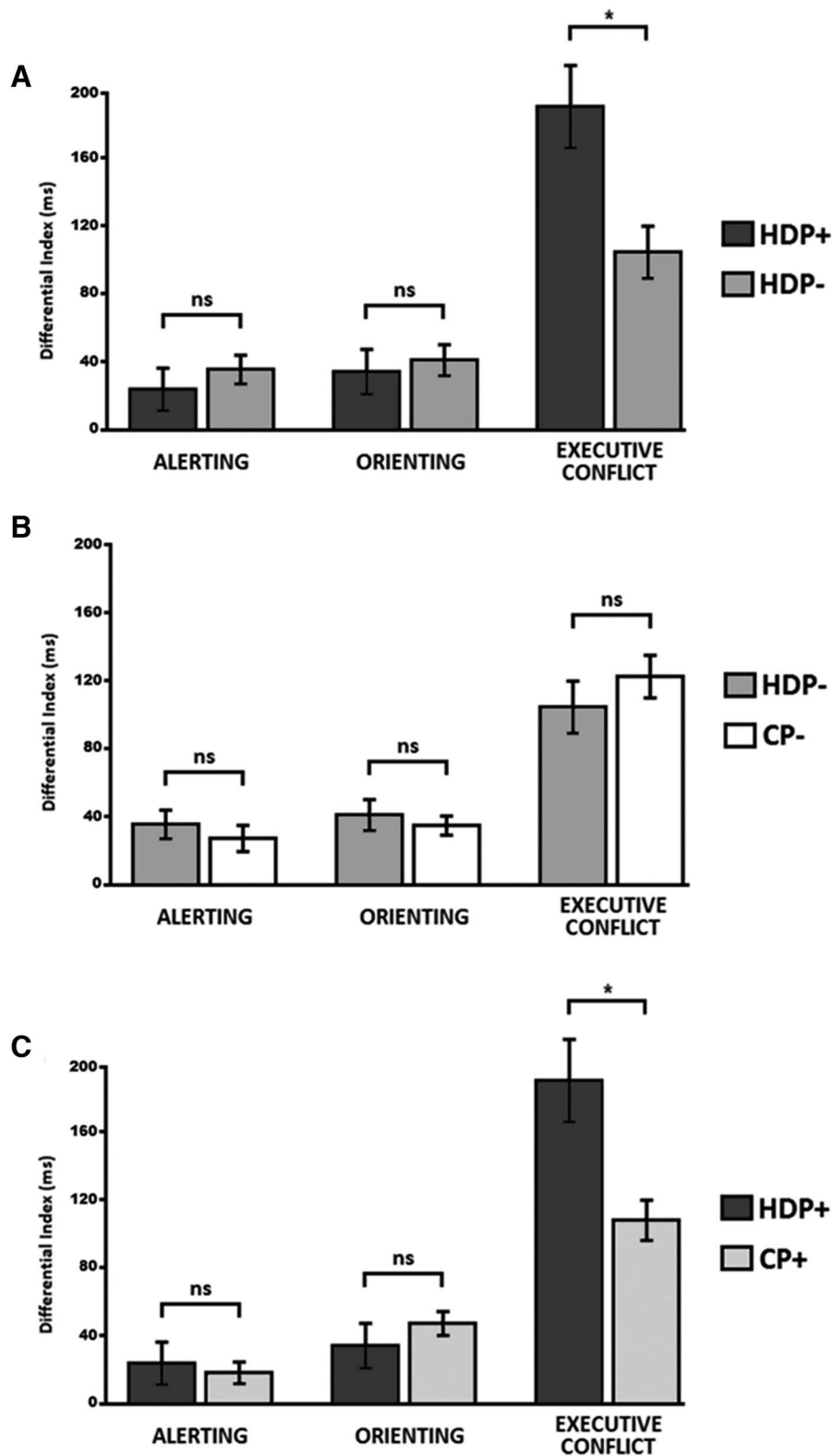


Figure 2. Clinical Huntington's disease participants (HDP+) and preclinical Huntington's disease participants (HDP-; Panel A), preclinical Huntington's disease participants (HDP-) and matched control participants (CP-; Panel B), and clinical Huntington's disease participants (HDP+) and matched control participants (CP+; Panel C) performance related to the indices computed on reaction times for the three attentional networks (alerting, orienting, executive conflict). Error bars represent standard errors of the mean. * $p < .05$.

ical HD for incongruent compared to congruent trials, which is in line with RT results and indexes a global deficit of the executive conflict network. Because HDP+ and CP+ groups were matched for demographical factors and because age was included as a covariate in the HD groups' comparison, this impairment cannot be explained by differences in these variables. Moreover, the control of comorbid psychopathological states and their absence of link with experimental results suggest that the deficit cannot be attributed to comorbid depressive or anxious symptomatology among HD patients.

It is important to note that this executive control deficit is not part of broader visuomotor or attentional impairments, which would encompass various subcomponents of attention. Indeed, alerting and orienting networks are preserved in clinical HD. These patients are thus still able to use their alerting network to increase their alertness or vigilance after a cue and to get ready for the processing of upcoming stimuli. Moreover, they have an intact ability to mobilize their orienting network following a spatial cue to move their attentional focus toward relevant information by successively disengaging attentional resources from a previous target and shifting them toward a new target. This differential deficit between preserved alerting or orienting and impaired executive conflict networks is not the mere consequence of a higher complexity for the executive control network, because earlier studies have shown a reverse pattern of deficits, notably in movement disorders. Indeed, Wilson's and Parkinson's diseases are related with preserved executive control network but impaired alerting (Han et al., 2014) or orienting (Zhou et al., 2012) networks, respectively, implying that the various pathologies leading to movement disorders are characterized by differential attentional deficits.

The present results are in line with previous ones showing impairments for cognitive subcomponents related to the executive conflict network, like attentional inhibitory control (Henderson et al., 2011), executive managing of the attentional resources (Peretti et al., 2008, 2010), or selective attention in clinical HD (Georgiou-Karistianis et al., 2012). Concerning alerting and orienting networks, previous results had led to mixed conclusions, some suggesting a preservation of these processes (Beste et al., 2008) and others showing impaired alertness (Duff et al., 2010; Hart et al., 2015) or orienting (Couette et al., 2008). However, the use of multidetermined tasks in these earlier studies cannot rule out the possibility that the observed deficits are related to the involvement of other attentional subcomponents (and potentially of executive control) in the task. The present study thus clarifies this debate by showing that alerting and orienting networks are preserved in clinical HD when a more specific measure is proposed.

Another central result of this study is the dissimilarity observed between preclinical and clinical HD, because attentional processes are preserved in preclinical HD, in line with most previous results (Hart et al., 2012, 2015; Lemiere et al., 2004; Malejko et al., 2014). However, because reduced brain activities during attentional tasks have been suggested in preclinical HD (Wolf et al., 2011), subtle attentional impairments might already be present at the cerebral level in preclinical HD while remaining undetectable by behavioral measures. The current study nevertheless clearly shows that the impairment observed for executive conflict in clinical HD is not related to the carrying of HD's gene but is rather the consequence of the neurodegenerative evolution observed at the clinical

stage, as further illustrated by the correlational analyses showing significant links between disease severity (i.e., CGI score and disease stage) and executive control deficits. By distinguishing preclinical and clinical patients, our results support the proposal that attentional processes might constitute a biomarker of disease stage in HD (Dumas et al., 2013), but future studies on broader samples are needed to determine whether the ANT can be used as an efficient complementary tool to determine disease stage.

Several issues also require further examination in follow-up research. First, our experimental design did not include other neuropsychological measures, and no data were collected regarding cognitive and executive functions in HD patients. The links between executive control and other executive deficits repeatedly reported in HD (Beglinger et al., 2010; Beste et al., 2008) should be further explored to clearly determine the interactions between the executive control impairment reported here and the other cognitive functions impaired in clinical HD patients. Second, although it can be postulated that the attentional impairments observed here in clinical HD are related to the brain changes appearing during the course of the disease, no cerebral measures were performed in the present study, and future neuroimaging works are thus needed to determine the brain correlates of the executive control deficit, particularly regarding thalamic, cingulate cortex, and superior-inferior frontal gyri, which are the key regions for executive control (Fan et al., 2005; Visintin et al., 2015). Eventually, although the preservation of alerting and orienting abilities in clinical HD excludes the hypothesis that executive control impairments might be the mere consequence of a far more global cognitive deficit, no measure of global intellectual functioning was performed, and it can thus not be excluded that the deficit observed for executive control might partly rely on more general cognitive disabilities in clinical HD.

Despite these limitations, the present results bare critical insights at both fundamental and clinical levels. At the fundamental level, they reinforce the experimental validity of the ANT theoretical model (Fan et al., 2002) by indicating that the three networks are independent because they can be differentially impaired. Our results, together with earlier ones, even constitute a convincing confirmation of this three-networks model in the field of movement disorders, because alerting, orienting, and executive conflict networks are respectively impaired in Wilson's (Han et al., 2014), Parkinson's (Zhou et al., 2012), and Huntington's diseases, each disease being related with a preservation of the two other networks (i.e., orienting and executive control in Wilson's disease, alerting and executive control in Parkinson's disease, alerting and orienting in HD). Beyond the ANT model (Petersen & Posner, 2012; Posner & Petersen, 1990), our results also bring some insights regarding the theoretical framework proposed by Stuss, Shallice, Alexander, and Picton (1995). According to this framework, the frontal lobe constitutes the chief structure of complex attentional processes. Indeed, this model (Stuss & Alexander, 2007; Stuss et al., 2005) is organized around an "anterior attentional system," relying on several frontal regions, which would manage three main attention-related subcomponents, namely energizing (i.e., initiating and sustaining attentional resources mobilization, relying on the superior medial frontal gyrus), task setting (i.e., establishing a stimulus-response link by associative learning, relying on the left lateral frontal gyrus), and monitoring (i.e., checking task accomplishment over time and ensuring its correct

execution, relying on the right lateral frontal gyrus). Although the present experimental design did not allow for exploring the brain correlates of attentional subcomponents, the massive deficit observed here in clinical HD for executive conflict abilities, known to rely on frontal networks, supports the proposal formulated by Stuss and colleagues that frontal cortex integrity is essential for efficient high-level attentional abilities and suggests that attentional deficits in HD might directly result from the frontal dysfunctions reported in this population (Eidelberg & Surmeier, 2011; Wolf & Klöppel, 2013). Conversely, the preservation of alerting and orienting networks in clinical HD also supports the hypothesis that lower level attentional subcomponents would involve regions other than the frontal ones (e.g., anterior cingulate cortex; Shallice, Stuss, Alexander, Picton, & Derkzen, 2008; Stuss & Alexander, 2007), which might be less damaged in clinical HD. A complementary explanation of the present results could be that, because alerting is centrally involved in the mobilization and sustaining of attentional resources, this network might be considered as part of the energizing system described in Stuss's (2005) theory. In this perspective, it can be hypothesized that the frontal areas involved in the alerting or energizing system (and particularly the superior medial frontal gyrus) might be less damaged in HD than are those underlying the executive control network and task setting or monitoring systems. Neuroimaging results have supported this proposal by showing preserved medial frontal gyrus structure in HD (Nopoulos et al., 2010), with conversely strongly impaired lateral frontal regions, even at the early stages of the disease (e.g., Matsui et al., 2014). However, neuroimaging studies further exploring the differential anatomical and functional deficits across the subcomponents of the frontal lobe should be conducted in HD to offer a more direct exploration of these proposals.

At the clinical level, our results underline the importance of cognitive deficits in clinical HD. In view of their role in daily life and treatment compliance (Beglinger et al., 2012; Paulsen & Long, 2014), rehabilitating attentional impairments might alleviate the disease's burden for patients and relatives. Earlier rehabilitation programs in HD were based on global attentional rehabilitation (Pira et al., 2014; Veenhuizen et al., 2011; Zinzi et al., 2007), but the present study makes the case for focusing these programs on the impaired attentional subcomponent (i.e., executive conflict), in line with what has been done in other populations (Serino et al., 2007; Thimm, Fink, Küst, Karbe, & Sturm, 2006). Moreover, because executive control mostly relies on frontal gyri, neuro-modulation (up to now used only for motor cortex stimulation in HD; Ljubisavljevic, Ismail, & Filipovic, 2013; Medina & Túnez, 2010) could efficiently increase frontal activation and improve executive control (Brunoni & Vanderhasselt, 2014).

In conclusion, this first exploration of attentional networks in HD using the ANT allowed us to identify a differential deficit between impaired executive control and preserved alerting and orienting networks in clinical HD. This constitutes a significant step toward the precise identification of cognitive deficits related to the successive stages of the disease. Moreover, the present results offer a sound basis for the development of specific rehabilitation programs focusing on impaired attentional subcomponents.

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