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Short communication

Impulsivity trait in the early symptomatic BACHD transgenic rat model of Huntington disease

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HIGHLIGHTS

- Different forms of impulsivity were assessed in early symptomatic BACHD rats (line TG5), a transgenic rat model of Huntington's disease (HD).
- BACHD rats showed high levels of choice impulsivity favoring "smaller, sooner" over "larger/later" rewards (delay discounting task).
- BACHD rats also exhibited a lack of behavioral inhibition indicated by bursts and premature responses in a DRL task assessing action impulsivity.
- Our study is the first to provide evidence of deficits in impulse control in a rodent model of HD.
- These results are relevant to psychiatric alterations in early symptomatic HD patients. They increase the face-validity of the BACHD rat model.

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ABSTRACT

Impulsivity trait was characterized in 3–5 months old BACHD rats, a transgenic model of Huntington disease, using (1) the delay discounting task to assess cognitive/choice impulsivity, and (2) the Differential Reinforcement of Low Rate of Responding task to evaluate motor/action impulsivity. Transgenic animals showed a high level of choice impulsivity and, to a lesser extent, action impulsivity. Our results provide the first evidence that the transgenic BACHD rat (TG5 line) displays impulsivity disorder as early as 3 months old, as described in early symptomatic HD patients, thus adding to the face validity of the rat model.

Impulsiveness is a behavioral trait that refers to the tendency to engage in inappropriate or maladaptive behaviors. Impulsivity is not a unitary trait, but embraces two categories of behavior: motor or action impulsivity, defined as the inability to withhold a prepotent motor response, and cognitive or choice impulsivity, which is the inability to weight and/or to use all consequences of events (see Ref. [8] for review). Impulsivity, poor risk assessment and altered behavioral inhibition are frequently encountered personality traits in many neuropsychiatric disorders and in neurodegenerative diseases such as Parkinson's (see Ref. [23] and Huntington's diseases (HD; [7]).

HD is an autosomal dominantly inherited, progressive neurodegenerative disorder caused by an expansion of the polyglutamine repeat of variable length (>38CAG repeats) in exon 1 of the gene encoding the protein huntingtin (HTT) [11]. HD results first in neurodegeneration of medium spiny neurons of the striatum [20], and in atrophy of cortical and limbic structures as the disease progresses [16]. Cognitive/psychiatric disorders, including perseveration, lack of insight, distractibility, and impulsivity, affect HD patients before motor symptoms [14,17] and have thus an early deleterious impact on the quality of HD patient's life.

Modeling the complexity of the psychiatric symptoms of preclinical HD in a rodent model is therefore important for increasing our understanding of the neurobiological mechanisms underly-

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ing the HD neuropathology. However, certain behavioral processes (e.g. impulsivity trait) are typically more challenging to evaluate in mice [22]. Therefore, we aimed at investigating impulse control disorders in a recently generated transgenic rat model of HD, using a human bacterial artificial chromosome (BAC) which contains the full-length HTT genomic sequence with 97CAG/CAA repeats and all regulatory elements [25]. Primary characterization of BACHD rats demonstrated an early progressive HD-like phenotype with motor dyscontrol and emotional impairment [25]. To determine impulsivity traits in these rats, we used two different paradigms, the delay discounting task (DD), and the Differential Reinforcement of Low Rate of Responding task (DRL), to assess respectively choice and action impulsivity. Animals were food deprived at 85% of their normal weight and all experiments were performed in accordance with the recommendations of the EEC and the French Ethics Committee for compliance and use of laboratory animals.

Impulsivity in the DD task is characterized by a preference for small, immediate rewards (SS: smaller, sooner) over larger, delayed rewards (LL: larger, later). The task design was modified from [18] and run in operant chambers with 2 levers each side of a food magazine (Coulbourn Instruments, USA). Three months old naive male WT ($n = 16$) and BACHD ($n = 7$) rats were trained to lever-press for food on a daily schedule. A 30 min-session of magazine training with 30 pellets (45 mg food pellets, Bioserv) delivered using a VI60 (range from 30 to 90 s) was followed by lever-press sessions under a continuous reinforcement schedule (CRF) until 50 reinforcements were earned in 30 min, one session for each lever (Coulbourn Instruments, USA). The animals were then trained for 8 sessions to discriminate between a small (1 pellet) and a large (3 pellets) reward associated with the left or the right lever (counterbalanced between rats). Five blocks of 12 trials (2 forced choices and 10 free choices) were run during each session. Each 60-s trial began with a 10-s illumination of the food magazine during which a nose poke into the magazine extinguished the light and triggered extension of either a single lever (forced-choice trials) or both levers simultaneously (free-choice trials) for a maximum of 10 s. Once a lever was pressed and food delivered, both levers were retracted for the remainder of the trial. At the end of training, WT and BACHD animals chose the large reward in more than 90% of free trials, with no genotype difference or genotype x training session interaction (Fs < 2.33, ns). Animals were then trained for 12 sessions in the delay discounting task. Each session and trial organization was kept the same except that delays were introduced between lever pressing and the large reward delivery. Each block started with two forced-choice trials to expose the rats with the delays in effect for that block, followed by 10 free-choice trials. The delay duration increased between each block of trials (0, 4, 8, 16, 32 s), but remained constant within each block. The averaged choice for the large reward (LL choice) was calculated for each delay across all blocks of the 12 sessions. Contrast analyses of variance (ANOVAs) as well as Fisher Exact Tests, with an alpha level of 0.05, were used for statistical assessments. As the delays increased, BACHD and WT rats shifted progressively their choices to the immediate small reward (Fig. 1A; $F_{(4,84)} = 65.03$, $P < .001$). BACHD rats shifted more rapidly to the immediate small reward than WT rats (genotype: $F_{(1,21)} = 6.20$, $P < .05$; genotype x delay interaction: $F_{(4,84)} = 5.01$, $P < .01$). The higher proportion of impulsive rats (less than 50% choices for the large delayed reward) in BACHD compared to WT animals was confirmed for delays longer than 8s (Fig. 1B).

Impulsivity in the DRL task is characterized by the inability to withhold responses for a required amount of time. If the time between two responses (inter-response time, IRT) is less than t seconds, no reward is delivered and the timing contingency reset. WT ($n = 12$) and BACHD ($n = 11$), 5 months old, male naive rats were trained on magazine training (30 min, 30 pellets), and on a CRF session until a criterion of 50 reinforced lever presses earned in 30 min. Then, rats started a DRL-5s schedule for five sessions, during which a lever press resulted in a food pellet delivery only if at least 5 s had elapsed from the previous lever press. If the rat performed a premature lever press, the 5 s time period was reset. Animals were then trained for ten sessions on a DRL-10s schedule, during which the response had to be withheld for 10 s to obtain the reward. Each DRL session ended either after 60 min or 200 reinforcements were earned, whichever came first. Several indexes of performance were calculated and the results are presented in Fig. 2, for 5 sessions of DRL-5s (left panel) and 10 sessions of DRL-10s (right panel). First, the efficiency/impulsivity measured the ratio of correct/rewarded responses (>5 s or >10 s) to total responses. Then, inter-response times (IRTs) were classified according to a ratio of the DRL value as burst responses (responses during 0–1 s for DRL-5s and 0–2 s for DRL-10 s), premature responses (1–4s and 2–8 s for DRL-5s and -10s, respectively) and timing errors (4–5 s and 8–10 s for DRL-5s and -10s).

During the DRL-5 s, WT rats learnt the task and showed improvement of their efficiency accross sessions (Fig. 2A; $F_{(4,44)} = 13.02$,

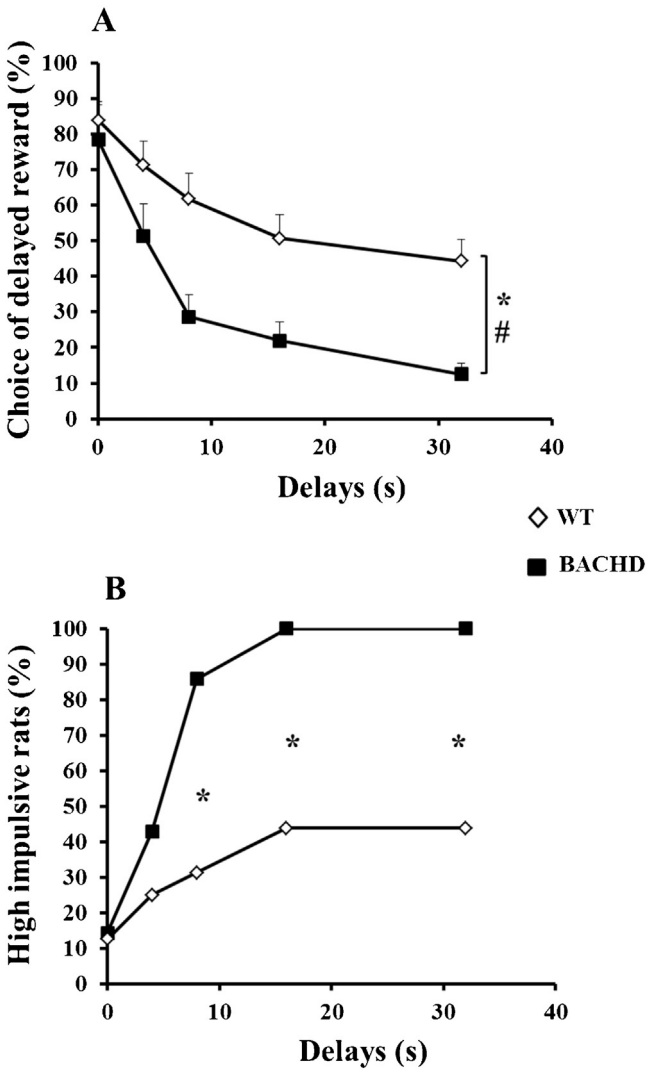

Fig. 1. Delay-discounting task showing higher choice impulsivity in BACHD rats compared to WT. (A) Mean + S.E.M percentage of choice of delayed reward across different delays. Genotype significant difference is indicated by (*) $P = 0.05$. Significant interaction is indicated by (#) $P < .01$. (B) Percentage of high impulsive (<50% choice of large reward choices) animals for the different delays (Fisher exact-tests: delay 8 s, $P = 0.022$; delay 16 s, $P = 0.026$; delay 32 s, $P = 0.02$).

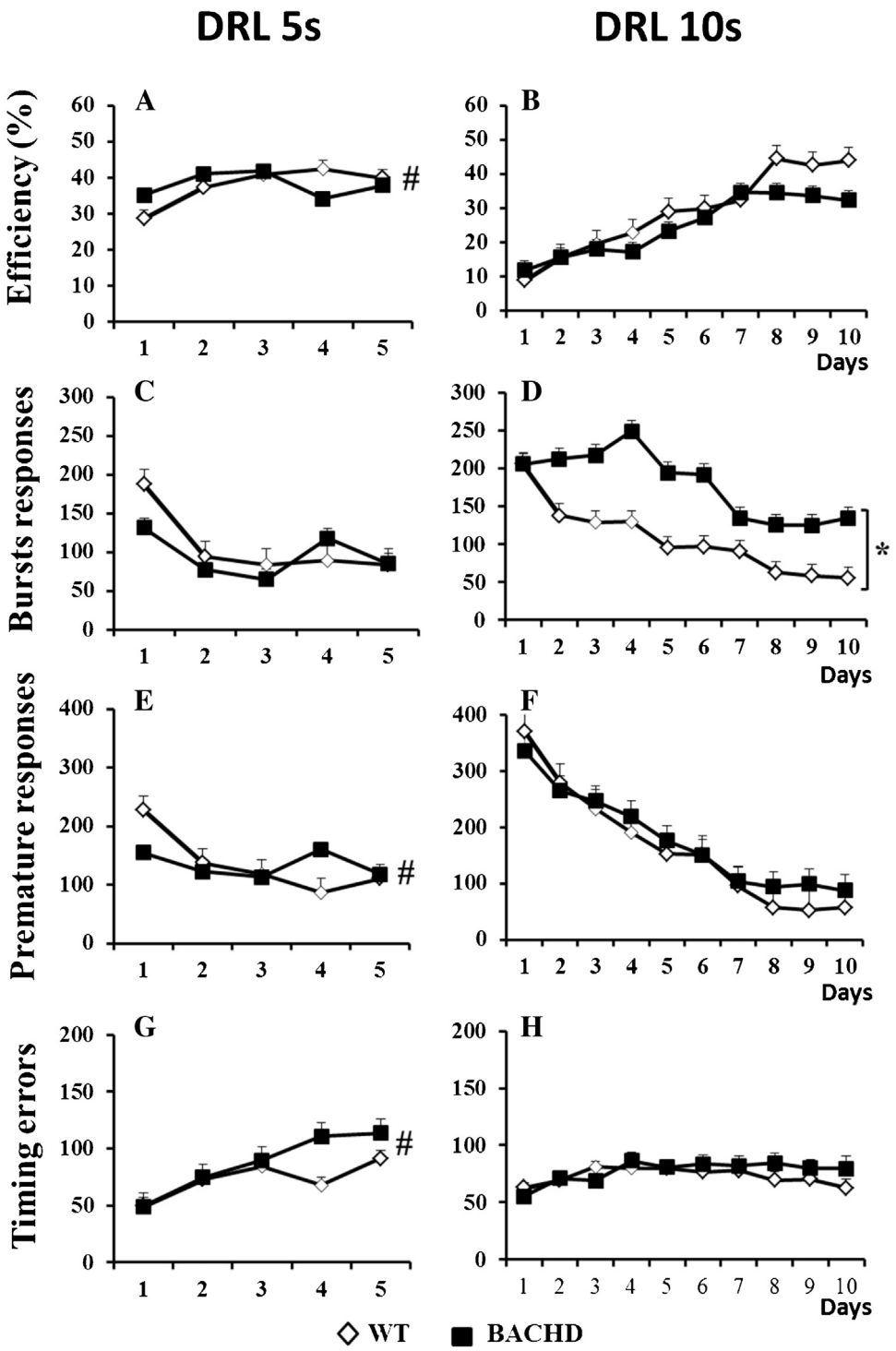

Fig. 2. Temporal characteristics of responding at DRL-5s (left panels) and -10s (right panels) schedules. (A and B) Percent efficiency (reinforced lever presses/total lever presses ×100) across DRL schedules; (C and D) Burst responses are those occurring <1 s (DRL-5s) and <2 s (DRL-10s) since the previous response; (E and F) Premature responses are those occurring 1–4s (DRL-5s) and 2–8s (DRL-10s) since the previous response; (G and H) Timing-error responses occurring at 4–5s (DRL-5s) and 8–10s (DRL-10s) since the previous response. Data are expressed as means + S.E.M. Genotype significant differences are indicated by (*) $P < 0.05$. Significant interactions are indicated by (#) $P < .05$.

$P < .001$) whereas BACHD rats did not ($F_{(4,40)} = 2.23$, ns); there was a significant genotype x session interaction ($F_{(4,84)} = 4.46$, $P < .005$) and no genotype difference ($F < 1$). The number of bursts responses decreased for both groups with session repetition (Fig. 2C; $F_{(4,84)} = 12.99$, $P < .001$) with no group x session interaction ($F_{(4,84)} = 2.16$, ns) and no genotype difference ($F < 1$). Both groups decreased their number of premature responses across sessions (Fig. 2E; ($F_{(4,44)} = 19.78$, $P < .001$ and $F_{(4,40)} = 2.94$, $P < .05$ respectively) with no genotype difference ($F < 1$). However, a significant genotype x session interaction (F4,84) = 8.79, $P < .001$) indicated that WT rats decreased their premature responses more rapidly than BACHD rats. Finally, BACHD rats increased more their timing errors than WT rats (Fig. 2G; $F_{(1,21)} = 4.23$, $P = .05$), with a significant genotype x session interaction ($F_{(4,84)} = 3.54$, $P < .05$).

When switching to the DRL-10s, both groups initially dropped their efficiency to then improve over the 10 training sessions (Fig. 2B; WT: $F(9,99) = 21.32$, $P < .001$; BACHD: $F(9,90) = 8.02$, $P < .001$), with no significant interaction between genotype and session ($F_{(9,189)} = 1.49$, ns) and no genotype effect ($F_{(1,21)} = 1.35$, ns). The number of bursts responses decreased with session repetition (Fig. 2H; $F_{(9,189)} = 9.44$, $P < .001$). However, BACHD transgenic rats exhibited a higher rate of burst responding compared to WT ($F_{(1,21)} = 4.53$, $P < .05$), with no genotype × session interaction ($F_{(9,189)} = 1.43$, ns). The number of premature responses decreased also significantly (Fig. 2F; $F_{(9,189)} = 66.12$, $P < .001$), but with no group difference and no genotype × session interaction (Fs < 1). There was a slight evolution of timing errors for both groups (Fig. 2D; $F(9,99) = 2.24$, $P < .05$ and $F(9,90) = 3.66$, $P < .01$ respectively), with no genotype difference ($F < 1$) and no genotype × session interaction ($F(9,189) = 1.76$, ns). Taken together, these results indicate that BACHD rats were nearly as efficient as WT in completing the DRL-5s and -10s tasks, with a less precise temporal discrimination and a higher rate of burst responses during the very first seconds following a reward.

These results demonstrate that HD pathology in 3–5 months old BACHD rats induced a high level of choice impulsivity and, to a lesser extent, action impulsivity. The DD paradigm describes primarily the devaluation of an event as the delay to that event increases and the failure to choose the larger delayed gratification as efficient self-control. Indeed, most decision-making procedures confront the individuals with several alternatives differing in cost and benefit. The increment of costs for the usually more-preferred larger reward leads to a discounting in the value of this option. The DRL paradigm describes the capacity to withhold actions during a fixed amount of time and mostly involves two cognitive/behavioral abilities: (1) behavioral inhibition or self-control indicated by bursts and premature responses. Burst responses, which follow immediately a rewarded lever-press, indicate perseverative responses induced by the failure to re-obtain an immediate feedback to their responses; (2) the temporal discrimination ability, which allows to know when the time t has elapsed, indicated by timing errors. BACHD rats exhibited a steep delay discounting curve in the DD showing a high level of cognitive/choice impulsivity. On the other hand, they show a nearly normal efficiency in the DRL, but timing errors and the high rate of burst responses when the delay increased indicate signs of motor impulsivity. These results could reflect an impairment in timing and/or working memory. In fact, both procedures (DD and DRL) are dependent upon limits on memory and sustained attention abilities. Deficits of these functions alter the ability to analyze all information about the possible alternatives and thus difficulties to evaluate future options, breaking the possibility to anticipate the consequences of actions and leading to incapacity to plan the most efficient behavior. Working memory deficits have previously been demonstrated in different tasks in early symptomatic HD patients [24,19]. However, the inability of BACHD rats to resist immediate rewards and/or to wait for larger rewards in DD rather suggests an impaired decision process, possibly due to the failure of the autonomous nervous system to mark negative outcomes [4] or to process correctly the cue/outcome contingencies through trial-to-trial feedback processing [10].

At the neurobiological level, lack of inhibitory control has been observed in several neuropathological disorders associated with abnormal dopaminergic transmission as deficit/hyperactivity disorder, Parkinson's Disease, Alzheimer's Disease and HD [2,15,14]. Furthermore, there is a strong correlation between dopamine receptors availability and the two different types of impulsivity: variation in striatal D2/D3 receptor levels is negatively correlated with impulsive action in rodents [6] and with impulsive choice and action in humans [9], whereas D1-like receptors appear to be most selectively involved in mediating impulsive choice in rats which may be explained by their differing locations within the prefrontal cortex (PFC), an area known to be involved in impulsive choice [12]. In BACHD rats, a decreased D2 receptor binding potential has been observed in the striatum, as well as an imbalance between the striatal striosome and matrix compartments [25]. Since these two compartments contain disproportionate amounts of D1 and D2 neurons, the striosome/matrix imbalance may influence the equilibrium of the inhibitory and excitatory output from the striatum to downstream neurons and thus have a behavioral impact that could account for BACHD rats' impulsivity. Furthermore, impulsivity, as well as compulsivity and flexibility, are closely interrelated executive processes in the context of inhibitory control mediated by the PFC [1]. However, according to the model proposed by Bechara in 2005 [3], willpower emerges from the dynamic interaction of two separate, but interacting, neural systems: an impulsive system, in which the amygdala is a critical neural structure involved in triggering the affective and emotional signals of immediate outcomes, and a reflective system, in which the ventral PFC is crucial in triggering the affective and emotional signals of long-term outcomes. Using a delay discounting paradigm, rats with inactivation and disconnection of the medial PFC and basolateral amygdala become more impulsive, showing preference for smaller immediate over larger delayed rewards [5]. Similarly, rats with amygdala lesions (basolateral nuclei) are more impulsive when rewards are delayed, preferring the immediate reward more quickly than controls [21]. In HD patients, both the prefronto-striatal circuit and the amygdala system seem to be dysfunctional [16]. In BACHD rats from 3 months of age, a high expression of mutant huntingtin (mhtt) aggregates was found in the neocortex and in limbic areas including the amygdala [25]. A dysfunctional prefronto-striatal/amygdala imbalance could thus account for the high level of choice impulsivity observed in BACHD rats, giving rise to behavioral inadaptability.

In sum, given the differences observed between WT and BACHD rats, it can be assumed that this transgenic rat model recapitulates some of the cognitive/psychiatric impairments already seen in HD patients. To our knowledge, our study is the first to provide evidence of deficits in impulse control in a rodent model of HD. This gap is surprising, due to the relevance of psychiatric alterations in the initial phases of HD and their deleterious impact on the quality of HD patient's life, but may be due to a lack of models until now that would permit testing of self-control. Taken together, our results indicate that presymptomatic/early symptomatic BACHD rats express a high level of impulsivity, impairments described in early symptomatic HD patients, which makes this rat model highly suitable for drug discovery purposes.

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