Accepted Manuscript

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PII: S0166-4328(13)00440-3
DOI: <http://dx.doi.org/doi:10.1016/j.bbr.2013.07.041>
Reference: BBR 8411

To appear in: *Behavioural Brain Research*

Received date: 20-6-2013
Revised date: 19-7-2013
Accepted date: 23-7-2013

Please cite this article as: Mo C, Renoir T, Pang TYC, Hannan AJ, Short-term memory acquisition in female Huntington's disease mice is vulnerable to acute stress, *Behavioural Brain Research* (2013), <http://dx.doi.org/10.1016/j.bbr.2013.07.041>

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**Short-term memory acquisition in female Huntington's disease mice
is vulnerable to acute stress**

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Running title: Stress and memory in Huntington's disease mice

Key words: Huntington's disease, short-term memory, acute stress, sexual dimorphism, corticosterone, Y-maze

ABSTRACT:

Huntington's disease (HD) is a neurodegenerative disorder marked by cognitive, psychiatric and motor decline, and is modifiable by unidentified environmental factors. We examined the effects of stress on cognitive function in R6/1 HD transgenic mice. Utilising the Y-maze to assess short-term memory, we report that only female HD mice displayed vulnerability to one hour of confinement stress reflected by impaired memory acquisition. This could not be attributed to a different corticosterone response or exploratory behaviour in the task. This is the first demonstration of increased stress susceptibility in an animal model of HD involving a direct negative impact on cognitive function.

Huntington's disease (HD) is an autosomal dominant neurodegenerative condition caused by a trinucleotide CAG repeat expansion, encoding an expanded polyglutamine tract, in exon 1 of the *huntingtin* gene. The pre-motor symptomatic stages of the disease are commonly characterized by cognitive deficits such as impaired attention, working memory, verbal fluency and executive functioning [1, 2]. Cognitive dysfunction has been demonstrated in a variety of rodent models of HD [3, 4], including R6/1 transgenic mice, which develop cognitive deficits in tests of short-term and long-term learning and memory [5, 6]. The onset of HD is largely determined by the length of the triplet repeat mutation, however, there is also an environmental component [7]. We have previously demonstrated that memory impairments in R6/1 HD mice can be rescued by interventions such as increased physical activity through wheel-running [6] and cognitive and sensory stimulation through environmental enrichment [5]. However, the influence of negative environmental factors on HD cognitive deficits has not been investigated.

It is well established that stressful events can influence cognitive performance, with possible differential effects of glucocorticoids on memory consolidation and memory retrieval [8, 9]. Sex differences have been reported in the context of acute stress-induced memory impairment, using spatial tasks such as the water maze and the Y-maze [10, 11]. Relevant to neurodegenerative disorders, immobilization stress has been shown to exacerbate memory deficits in a mouse model of Alzheimer's disease [12]. However, the influence of acute stress on HD cognitive deficits has not been investigated. Coping with stress is mediated through activation of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent release of stress hormones such as cortisol (corticosterone in rodents). Neuropathology of the HPA axis in HD patients is evident from a correlative increase in urinary cortisol levels with disease progression [13] and exaggerated circadian cortisol patterns [14]. HD mouse models also

reflect abnormalities such as elevated baseline corticosterone levels and impaired down-regulation after an acute stressor [13, 15].

Despite this evidence for an abnormal stress response in HD, there has not been further investigation into stress as a negative environmental modulator of HD. In the present study, we hypothesized that memory function in HD mice will be more susceptible to disruption by an acute stress, and that this would be associated with a dysfunctional corticosterone response. The Y-maze is a short-term memory, exploratory-driven task which is sensitive to stress [11]. It also has the advantage of using a simple and rapid training session (without food deprivation), making it a suitable test to assess the effect of a single exposure to stress on memory function. Notably the Y-maze is a behavioural test in which R6/1 HD mice showed an early cognitive deficit, prior locomotor impairment [5]. Indeed, R6/1 HD animals have been previously shown to be intact in the novel object recognition test but impaired in hippocampal-dependent short-term memory tests [5] such as Y-maze (at 12 weeks of age). The Y-maze was therefore the most suitable test to assess the effect of acute stress on short-term memory. Our verified hypothesis was that acute stress would bring forward the onset of cognitive-impairment in HD mice (without altering WT animals).

We investigated the effects of a 1-hour confinement stress on Y-maze performance in male and female R6/1 HD mice and their wild-type (WT) littermates. Exposure to confinement stress immediately prior to the training trial (PreStress, Fig.1A) versus during the inter-trial interval of Y-maze testing (InterStress, Fig.2A) was tested to study potential stress effects on both memory acquisition and retrieval respectively. In order to test the hypothesis that only the performance of HD (but not WT) mice will be affected by a mild stressor, we used confinement in a well-ventilated plastic container (dimensions: 6Wx5Lx5H cm) as an acute

stress paradigm. Alternative possible acute stressors used in previous studies on WT rodents include restraint stress, cold exposure or electric foot shock. However, those more stressful paradigms have been previously shown to change WT animal performance in memory tests such as the Y-maze [11, 16]. As expected [17], animals subjected to confinement stress protocol showed increase serum corticosterone levels, compared to control non-stressed mice (Fig.3A).

When confinement stress was administered immediately prior to the training trial (PreStress), female HD mice displayed impaired novel preference (as measured by novel-arm preference index [18]) compared to non-stress control animals (Fig 1B). Indeed, 3-way ANOVA analysis of the novel-preference index during the 5-min trial revealed a significant genotype x stress x sex interaction ($F_{1,70}=5.61$, $p<0.05$). Interestingly, this disruption in Y-maze performance was not observed in wild-type mice, thus demonstrating a HD-specific susceptibility to stress-induced memory impairment. However, if administered during the inter-trial interval of Y-maze testing (InterStress), there was no effect of confinement on novel-arm preference ($F_{1,66}=0.24$, $p=0.627$), regardless of the genotype (Fig.2B). Overall, our results suggest that, compared to WT animals, HD mice are more vulnerable to the negative effect of stress on short-term memory only when confinement stress is administered prior to the training trial. This observation is consistent with the female HD-specific depressive-like behavioural phenotype elicited by exposure to acute stressors such as forced-swim and novelty-suppressed feeding [19, 20]. Female HD mice thus appear hyper-responsive to the detrimental effects of acute stress, in both affective-related responses and in memory acquisition.

Previous studies by our group found HD female-specific abnormalities in stress-related behaviours [19, 20]. In the present study, male HD mice showed no preference for the novel arm in the non-stress condition (Fig. 1B & Fig. 2B). This early cognitive deficit in male HD mice meant that we could not assess any potential negative effects of confinement stress on short-term memory in this group. When male and female data were pooled together, R6/1 HD mice have been previously shown to develop a deficit in the Y-maze by 12 weeks of age [5]. However, when the sexes are analysed separately (in our present study), we now show that the Y-maze deficit in R6/1 HD males appears as early as 8 weeks of age. An earlier onset of the Y-maze deficit in R6/1 HD male mice corroborates with sexually dimorphic pathologies in other HD rodent models [21-23]. Furthermore, a large epidemiological study revealed an earlier mean age of diagnosis in male HD patients [24], supporting that the onset of symptoms in HD may be sexually dimorphic. In contrast, no sex differences in HD mice were reported in the Morris water-maze [25]. Our present results suggest a vulnerability to stress in HD females. In innately stressful tests such as the water-maze, this vulnerability may have shifted the female HD phenotype in line with the otherwise earlier deficit in HD males. Corticosterone elevation in the Y-maze test is low compared to that of the water-maze [10]. Therefore, less stressful cognitive tests may be more suitable for revealing sex differences in the HD phenotype.

One explanation for the Y-maze impairment in PreStressed female HD mice could have been an eventual stress-induced reduction in exploration, thus impairing memory acquisition. However, there was no effect of PreStress on total distance travelled during the 10-min training (Fig. 1C) and the 5-min test (Fig. 1D) trials. Exploration during the subsequent 5-min testing was not affected either ($F_{1,66}=2.19$, $p=0.092$) when stress was administered during the inter-trial interval of Y-maze testing (InterStress, Fig. 2C).

Another explanation of our behavioural results could be high levels of glucocorticoids, which can be detrimental to Y-maze performance [8], in HD compared to WT female mice. We therefore measured serum corticosterone levels after 5-min, 10-min and 1-hour of confinement and compared them to baseline levels (EIA kit, Cayman Chemical Company, Ann Arbor, MI). An overall effect of stress was found, indicating that all groups showed elevations in corticosterone during confinement. However the corticosterone profile in female HD mice was no different to female WT animals (Fig. 3A). There was no sex x genotype interaction ($F_{1,76}=3.45$, $p=0.07$). This suggests that the corticosterone response during confinement was not exaggerated in female HD mice. Since previous work has shown that female R6/1 HD mice have a delayed decline in corticosterone levels post-stress [15], we therefore analysed corticosterone levels after 10-min of Y-maze exposure. However, we found no effect of the genotype at this time-point representing memory acquisition (Fig. 3A). We also did not find any effect of genotype when measuring serum corticosterone levels in mice exposed to both stress and Y-maze (Stress+Y-maze, Fig 3B) indicating that, at least during our behavioural time-point of interest (Y-maze acquisition), confinement did not induce the expected sustained elevation in corticosterone in female HD mice. The discrepancy between our present findings and those reported following forced-swim stress [15] could be due to the different intensity and duration of the stressors or the age and progression of R6/1 mice at the time of testing (12 weeks compared to 8 weeks of age). Taken together with the similar corticosterone response to WT mice during 1-hour confinement (Fig 3A), this provides further evidence that HPA-axis function cannot explain the susceptibility of female HD mice to stress-induced memory impairment.

Confinement stress and Y-maze exposure revealed overall sex differences in serum corticosterone response. The increase in corticosterone levels during confinement (Fig. 3A)

and after Y-maze exposure alone (Fig. 3B) was more pronounced in female (WT and HD) mice when compared to male animals. Other stressors such as training in the water maze also elicited an exaggerated corticosterone response in females when compared to males [10], although there were no sex differences in rats after Y-maze exposure [11]. Specifically, the 10-min Y-maze exposure and 10-min of confinement elevated corticosterone to higher levels compared to males (Fig. 3). Only female animals showed a significant reduction from 10-min confinement compared to the end of confinement (10-min vs 1-hour of confinement, $p < 0.05$, Fig. 3A.). This could indicate that the profile in females not only shows an earlier peak, but a more rapid return to baseline levels compared to males. The latter was reported in female WT compared to male WT animals after a 10-min forced swim [15].

Our hypothesis for female HD susceptibility to stress was confirmed with the Y-maze test where confinement stress induced a deficit in memory acquisition in female HD mice, but not WT controls (Fig 1B). We have considered using another acute stressor (e.g. swim stress, restraint). However, in light of our verified hypothesis of HD-specific vulnerability to acute stress, we believe that our choice of stressor (i.e. as mild as possible so as not to impair wild-type animals) was the most suitable for this study. Also, since swimming performance has been shown to be altered in 8-week-old female HD mice [20], the use of swim stress would have been a potential confound. Our present female HD-specific deficit was not due to stress effects on exploration in the Y-maze (Fig. 1C & 1D) and surprisingly did not correlate with a corticosterone abnormality during or after the stressor (Fig. 3). Potential candidates to explain this susceptibility may be found in other HD pathologies which interact with the stress system. For example, hippocampal and cortical noradrenaline levels are reduced in female HD mice [20] and Y-maze memory acquisition specifically requires a functional beta-adrenergic system [26]. Confinement stress may act to exacerbate a baseline noradrenergic deficit, leading to impaired performance in HD female mice. Another potential mediator of

our behavioural findings is the serotonergic system. Only female HD mice showed supersensitive 5-HT_{1A} receptors at 8 weeks of age [20]. 5-HT_{1A} receptor function supports spatial learning [27] and stress has also been shown to alter its expression and function [28]. Therefore, modulating 5-HT_{1A} and/or beta-adrenergic receptors may be an avenue to counteract the detrimental effects of confinement stress on memory in female HD mice.

In conclusion, we present the first evidence demonstrating that memory acquisition in HD mice can be disrupted by prior exposure to acute stress. This is of significance because despite a strong correlation between age of onset and the length of the trinucleotide repeat mutation, environmental factors can affect onset in HD patients [7, 29] and mice [30]. Here we propose not only that stress is a negative modulator of cognitive function in HD but that the HD mutation confers a vulnerability to acute stress since the mutation-negative (wild-type) mice were able to cope with a mild, 1-hour stressor. Stress is particularly relevant to HD families as there are self-reports of distress from genetic discrimination [31]. A susceptibility to stress may contribute to the higher rates of depression and suicide in HD gene-positive individuals [32, 33]. HD pathophysiologies such as a dysfunctional monoamine system may explain the stress-induced memory impairment in the current study. Our data further reveals gene-environment interactions in HD, demonstrating that a negative environmental factor can directly impair cognitive performance in an animal model. Whether acute stress can have longer term consequences on the development of cognitive deficits in HD mice still remained to be studied. Also it would be interesting to know the effect of prolonged (tonic) mild stress on memory function and also other HD symptoms such as motor and affective disorders. Whether HD animals would worsen symptomatically with prolonged stress, or develop adaptive mechanisms would depend on factors such as the nature

and severity of the stressor. Wild-type animals have been shown to adapt physiologically and behaviourally to predictable chronic stressors [34]. Based on our current findings of HD-specific susceptibility, we hypothesize that the HD brain may also lack these adaptive mechanisms and would therefore exhibit accelerated disease onset and/or progression under chronic stress.

Acknowledgements

AJH is an ARC Future Fellow (FT3) and Honorary NHMRC Senior Research Fellow. CM is a University of Melbourne Australian Postgraduate Award Scholar. The Florey Institute of Neuroscience and Mental Health acknowledge the support from the Victorian Government and in particular the funding from the Operational Infrastructure Support Grant.

Figure 1:

Figure 1: Effects of 1-hour confinement stress on Y-maze memory acquisition (PreStress) in HD and WT mice. **(A)** Schematic of PreStress experimental design where 1-hour confinement immediately preceded memory acquisition **(B)** Analysis of Y-maze performance (expressed as novel-arm preference index) during the testing trial showed a significant genotype x stress x sex interaction ($F_{1,70}=5.61$, $p<0.05$). Stressed female HD (but not WT) mice showed a lower novel-arm preference index when compared to non-stress control animals ($p=0.030$). Non-stress male but not female HD mice show a deficit in short-term memory in the Y-maze by 8 weeks of age ($p<0.05$). **(C)** Exploratory activity during the 10-min trial showed no effect of stress ($F_{1,70}=2.04$, $p=0.157$) or genotype ($F_{1,70}=2.47$, $p=0.120$). There was a stress x sex interaction ($F_{1,70}=7.21$, $p<0.01$) but no significant post-hoc comparisons. **(D)** Analysis of the distance travelled during the 5-min trial revealed no overall effects or interactions. Novel-arm preference index = [time spent in novel arm/average time spent in other arms], where an index of 1 indicates no preference. All data were analysed by 3-way ANOVA (for main factors of sex, genotype and stress exposure) and followed by a Fisher's LSD post-hoc test where * $p<0.05$, ** $p<0.01$, *** $p<0.001$. Values represent means ($\pm$ SEM) of $n=7-12$ mice per group.

Figure 2:

Figure 2: Effects of 1-hour confinement stress on Y-maze memory retrieval (InterStress) in HD and WT mice. **(A)** Schematic of confinement and Y-maze experimental design where 1-hour confinement occurred during the inter-trial interval. **(B)** Looking at the effect of InterStress on Y-maze performance (expressed as novel-arm preference index), there was a significant genotype x sex interaction ($F_{1,66}=4.29$, $p<0.05$). In both stress- and non-stress conditions, HD males showed reduced novel preference ($p<0.05$). Overall, novel-arm preference was not affected by confinement stress when administered during the 1-hour inter-trial interval of the Y-maze ($F_{1,66}=0.24$, $p=0.627$). **(C)** Exploratory activity was not affected by confinement during the subsequent 5-min testing trial ($F_{1,66}=2.19$, $p=0.092$). Novel-arm preference index = [time spent in Novel arm/average time spent in other arms], where an index of 1 indicates no preference. All data were analysed by 3-way ANOVA (for main factors of sex, genotype and stress exposure) and followed by a Fisher's LSD post-hoc test where * $p<0.05$, ** $p<0.01$, *** $p<0.001$). Values represent means ($\pm$ SEM) of $n=7-12$ mice per group.

Figure 3:

Figure 3: Influence of sex and genotype on the effects of acute stress- and Y-maze- induced corticosterone release. **(A)** Overall, statistical analysis of the corticosterone response to confinement revealed no difference between female HD and WT mice. Serum corticosterone (expressed in ng/ml) was increased after 5 and 10 min spent in confinement, as well as at the end of 1-hour of confinement period when compared to baseline levels ($F_{3,76}=35.77$, $p<0.001$). There was no sex x genotype interaction ($F_{1,76}=3.45$, $p=0.07$). There was a significant overall sex effect ($F_{1,76}=7.33$, $p<0.01$) and sex x stress interaction ($F_{3,76}=4.36$,

$p < 0.01$). Regardless of the genotype, post-hoc analyses showed a significant difference between 10-min and 1-hour confinement only in female mice ($p < 0.01$). **(B)** Serum corticosterone levels were also similar between female HD and WT mice post-stress after Y-maze acquisition. Exposure to both Y-maze alone (Y-maze 10min) and Y-maze preceded by 1-hour confinement stress (Stress+Y-maze) elevated corticosterone compared to baseline levels ($F_{2,54} = 61.13$, $p < 0.001$). There was no effect of genotype ($F_{1,54} = 0.19$, $p = 0.664$) but an effect of sex ($F_{1,54} = 12.98$, $p < 0.001$). Furthermore, there was a significant interaction between sex and stress condition ($F_{2,54} = 6.71$, $p < 0.01$). Indeed, 10-min Y-maze elicited a higher corticosterone release in females and Pre-stress blunted the Y-maze-induced elevation (post-hocs for Female WT, $p = 0.028$ and Female HD, $p = 0.002$). There was also a genotype x sex interaction ($F_{2,54} = 5.66$, $p < 0.05$) but no significant post-hoc comparisons. Values represent means ($\pm$ SEM) of $n = 4-9$ mice per group. Significant interactions were followed by a Fisher's LSD post-hoc test where * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to control, + $p < 0.05$, ++ $p < 0.01$, +++ $p < 0.001$ comparisons between treatment groups, # $p < 0.01$ effect of stress.

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Highlights:

- short-term memory deficit (assessed in the Y-maze) appears earlier in R6/1 HD males
- acute stress induced memory impairment only in HD female animals
- however, stress-induced corticosterone release was not exaggerated in female HD mice

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Title:

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Date:

2013-09-15

Citation:

Mo, C., Renoir, T., Pang, T. Y. C. & Hannan, A. J. (2013). Short-term memory acquisition in female Huntington's disease mice is vulnerable to acute stress. *BEHAVIOURAL BRAIN RESEARCH*, 253, pp.318-322. <https://doi.org/10.1016/j.bbr.2013.07.041>.

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