

# Focusing on the Cerebral Cortex in Huntington's Disease: Experience-Dependent Plasticity Deficits as the Cellular Basis of Dementia

Huntington's disease (HD) belongs to an expanding family of devastating neurological disorders caused by abnormally elongated CAG trinucleotide repeats which encode extended polyglutamine tracts in the disease proteins.<sup>1-6</sup> HD is characterised by extensive neurodegeneration in the striatum and the cortex.<sup>7,8</sup> The disease is classically known for its choreic and dystonic motor symptoms. However, cognitive deficits (dementia) and psychiatric manifestations (the most common of which is depression) represent major symptoms in HD, which usually precede the onset of motor abnormalities.<sup>9-12</sup>

This observation has led to an increased research effort concentrating in the examination of abnormal neurotransmission in areas involved in higher cognitive function such as the neocortex and the hippocampus. In accordance with the clinical picture, the genetic defect in HD could initially affect neurotransmission involved in higher cognitive function before any signs of neuronal loss in the striatum. So what is the evidence for abnormal neurotransmission in the HD neocortex and the hippocampus? Moreover, is there evidence of abnormal synaptic efficacy of neurotransmission in higher cognitive centres that could underlie dementia in HD?

Many studies using transgenic and knock-in mouse models of HD have shown that there is impaired synaptic transmission in corticostriatal and hippocampal circuitries.<sup>13-22</sup> More recently, impaired synaptic transmission has been reported in HD mouse neocortical neurons even before the onset of motor symptoms.<sup>23</sup> Evidence of cortical neuronal dysfunction has also been reported in HD patients, for example using transcranial magnetic stimulation of the motor cortex.<sup>24</sup>

Long-term changes in synaptic efficacy (synaptic plasticity) are thought to underlie higher cognitive functions such as learning and memory.<sup>25</sup> If cognitive function in HD is compromised before the onset of the motor symptoms then one could hypothesise that synaptic plasticity deficits may be the cellular basis of early symptomatology. Moreover, if higher cognitive functions are dependent on cortical functioning then a plausible hypothesis is that alterations in synaptic plasticity should be evident in the cerebral cortex of HD brains and correlate with the onset of dementia.

Initial evidence of abnormal synaptic plasticity in the hippocampus of R6/2 HD transgenic mice showed abnormalities in the form of long-term potentiation (LTP) and long-term depression (LTD) in the CA1 region of the hippocampus.<sup>26</sup> Interestingly, these synaptic plasticity deficits correlated with poor performance in a spatial memory task even before the onset of clear motor deficits. Similar impairment in hippocampal synaptic plasticity has also been reported in other HD mouse models.<sup>15,27</sup> A key regulator of synaptic plasticity, brain-derived neurotrophic factor (BDNF), has been shown to be decreased in the hippocampus of R6/1 HD mice (a transgenic line with a shorter CAG repeat length and later onset of symptoms than R6/2 mice) and correlated with the onset of cognitive deficits.<sup>28,29</sup> Furthermore, deficits of BDNF in the hippocampus and striatum are rescued by environmental enrichment, a form of cognitive and motor stimulation which

has been found to delay the onset and progression of HD in transgenic mice.<sup>28,30-32</sup>

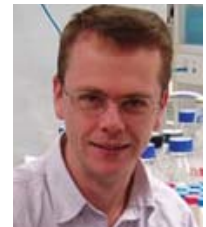
Interestingly, Cybulska-Klosowicz and colleagues showed that R6/1 HD mice show impaired functional cortical reorganisation – a form of experience-dependent plasticity – following a simple form of passive associative learning.<sup>33</sup> In normal rodents, a short period of classical conditioning causes cortical enlargement of the functional representation of the sensory modality (e.g. row of whiskers) that has been conditioned. However, in this study R6/1 HD mice showed a clear impairment to display an increase in the functional representation of the conditioned row of whiskers. Similarly, following a period of sensory deprivation, such as trimming a row of whiskers, the cortex displays a remarkable ability to reorganise as the functional representations of neighbouring intact whiskers take over the cortical region of those that have been deprived.<sup>34</sup> In this context, we showed, using 2-deoxyglucose metabolic labelling, that R6/1 HD mice which were sensory deprived failed to show cortical plasticity, in the form of map reorganisation, and that this cortical impairment correlated with a severe deficit to learn a sensory discrimination task.<sup>35</sup> It is interesting to note that the R6/1 mice used in the study were not yet displaying any motor symptoms, suggesting that cortical plasticity deficits and cognitive symptoms occur relatively early. More recently, Cummings and colleagues showed that cortical slices from R6/1 HD mice displayed abnormal short-term plasticity (exhibited as altered paired-pulse facilitation) and LTD.<sup>27</sup> Moreover, they showed a decrease in the cortical levels of both D1 and D2 dopamine receptors and found that *in vitro* administration of the D2 agonist, quinpirole, dramatically reversed the impairment in both short-term plasticity and LTD in the perirhinal cortex of R6/1 HD mice.

The above studies using transgenic mice that express the HD gene mutation suggest a functional impairment in cortical activity. Deficits in synaptic and structural plasticity could underlie the cognitive and psychiatric deficits observed in patients with HD. An interesting question is whether these cortical abnormalities are aetiologically involved in the striatal degeneration associated with the devastating motor symptoms characterising HD. One hypothesis is that cortical abnormalities, involving abnormal glutamatergic neurotransmission, might cause excitotoxic damage to striatal neurons via corticostriatal pathways. In other words, rather than medium spiny neurons dying via cell-autonomous 'suicide' they may be 'murdered' by corticostriatal afferents.<sup>36</sup> In this scenario, therapeutic interventions targeting the cortex could not only delay or ameliorate the cognitive and psychiatric abnormalities, but also the motor symptoms. Further evidence for the primary role of cortical pathology has been provided by the effect of environmental enrichment in salvaging cortical degeneration in HD mice,<sup>30</sup> as well as cortical transplantation experiments<sup>37</sup> and cortex-specific HD transgene expression in mice.<sup>38</sup>

In any case, the observation of early cortical dysfunction and neural plasticity deficits could provide a very useful biological marker that would be particularly useful in terms of monitoring both the progress of the dis-



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ease and the effects of potential therapeutic interventions. An attempt to replicate the animal studies described above at the human level, such as reliably demonstrating cortical plasticity impairments in HD gene carriers with the use of fMRI, would be an excellent starting point in the clinical application of these research discoveries.

## References

- La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH: *Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy*. Nature 1991;352:77-79.
- Koide R, Ikeuchi T, Onodera O, Tanaka H, Igarashi S, Endo K, Takahashi H, Kondo R, Ishikawa A, Hayashi T, et al.: *Unstable expansion of cag repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA)*. Nat Genet 1994;6:9-13.
- Orr HT, Chung MY, Banfi S, Kwiatkowski TJ, Jr., Servadio A, Beaudet AL, McCall AE, Duvick LA, Ranum LP, Zoghbi HY: *Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1*. Nat Genet 1993;4:221-226.
- Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, Kawakami H, Nakamura S, Nishimura M, Akiguchi I, et al.: *CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1*. Nat Genet 1994;8:221-228.
- Imbert G, Saudou F, Yvert G, Devys D, Trottier Y, Garnier JM, Weber C, Mandel JL, Cancel G, Abbas N, Durr A, Didierjean O, Stevanin G, Agid Y, Brice A: *Cloning of the gene for spinocerebellar ataxia 2 reveals a locus with high sensitivity to expanded CAG/glutamine repeats*. Nat Genet 1996;14:285-291.
- Zhuchenko O, Bailey J, Bonnen P, Ashizawa T, Stockton DW, Amos C, Dobyns WB, Subramony SH, Zoghbi HY, Lee CC: *Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1a-voltage-dependent calcium channel*. Nat Genet 1997;15:62-69.
- Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP, Jr.: *Neuropathological classification of Huntington's disease*. J Neuropathol Exp Neurol 1985;44:559-577.
- de la Monte SM, Vonsattel JP, Richardson EP, Jr.: *Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease*. J Neuropathol Exp Neurol 1988;47:516-525.
- Foroud T, Siemers E, Kleindorfer D, Bill DJ, Hodes ME, Norton JA, Conneally PM, Christian JC: *Cognitive scores in carriers of Huntington's disease gene compared to noncarriers*. Ann Neurol 1995;37:657-664.
- Kirkwood SC, Siemers E, Hodes ME, Conneally PM, Christian JC, Foroud T: *Subtle changes among presymptomatic carriers of the Huntington's disease gene*. J Neurol Neurosurg Psychiatry 2000;69:773-779.
- Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL: *Neuropsychiatric aspects of Huntington's disease*. J Neurol Neurosurg Psychiatry 2001;71:310-314.
- Berrios GE, Wagle AC, Markova IS, Wagle SA, Rosser A, Hodges JR: *Psychiatric symptoms in neurologically asymptomatic Huntington's disease gene carriers: A comparison with gene negative at risk subjects*. Acta Psychiatr Scand 2002;105:224-230.
- Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, Singaraja R, Smith DJ, Bissada N, McCutcheon K, Nasir J, Jamot L, Li XJ, Stevens ME, Rosemond E, Roder JC, Phillips AG, Ruben EM, Hersch SM, Hayden MR: *A yac mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration*. Neuron 1999;23:181-192.
- Levine MS, Klapstein GJ, Koppel A, Gruen E, Cepeda C, Vargas ME, Jokel ES, Carpenter EM, Zanjani H, Hurst RS, Efstratiadis A, Zeitlin S, Chesselet MF: *Enhanced sensitivity to N-Methyl-D-Aspartate receptor activation in transgenic and knockin mouse models of Huntington's disease*. J Neurosci Res 1999;58:515-532.
- Usdin MT, Shelbourne PF, Myers RM, Madison DV: *Impaired synaptic plasticity in mice carrying the Huntington's disease mutation*. Hum Mol Genet 1999;8:839-846.
- Cepeda C, Hurst RS, Calvert CR, Hernandez-Echeagaray E, Nguyen OK, Jocoy E, Christian LJ, Ariano MA, Levine MS: *Transient and progressive electrophysiological alterations in the corticostriatal pathway in a mouse model of Huntington's disease*. J Neurosci 2003;23:961-969.
- Cepeda C, Starling AJ, Wu N, Nguyen OK, Uzgil B, Soda T, Andre VM, Ariano MA, Levine MS: *Increased gabaergic function in mouse models of huntington's disease: Reversal by BDNF*. J Neurosci Res 2004;78:855-867.
- Starling AJ, Andre VM, Cepeda C, de Lima M, Chandler SH, Levine MS: *Alterations in N-Methyl-D-Aspartate receptor sensitivity and magnesium blockade occur early in development in the R6/2 mouse model of Huntington's disease*. J Neurosci Res 2005;82:377-386.
- Klapstein GJ, Fisher RS, Zanjani H, Cepeda C, Jokel ES, Chesselet MF, Levine MS: *Electrophysiological and morphological changes in striatal spiny neurons in R6/2 Huntington's disease transgenic mice*. J Neurophysiol 2001;86:2667-2677.
- Laforet GA, Sapp E, Chase K, McIntyre C, Boyce FM, Campbell M, Cadigan BA, Warzecki L, Tagle DA, Reddy PH, Cepeda C, Calvert CR, Jokel ES, Klapstein GJ, Ariano MA, Levine MS, DiFiglia M, Aronin N: *Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease*. J Neurosci 2001;21:9112-9123.
- Dalbem A, Silveira CV, Pedrosa MF, Breda RV, Werne Baes CV, Bartmann AP, da Costa JC: *Altered distribution of striatal activity-dependent synaptic plasticity in the 3-nitropropionic acid model of Huntington's disease*. Brain Res 2005;1047:148-158.
- Picconi B, Passino E, Sgobio C, Bonsi P, Barone I, Ghiglieri V, Pisani A, Bernardi G, Ammassari-Teule M, Calabresi P: *Plastic and behavioral abnormalities in experimental Huntington's disease: A crucial role for cholinergic interneurons*. Neurobiol Dis 2006;22:143-152.
- Andre VM, Cepeda C, Venegas A, Gomez Y, Levine MS: *Altered cortical glutamate receptor function in the R6/2 model of Huntington's disease*. J Neurophysiol 2006;95:2108-2119.
- Lorenzani C, Dinapoli L, Gilio F, Suppa A, Bagnato S, Curra A, Inghilleri M, Berardelli A: *Motor cortical excitability studied with repetitive transcranial magnetic stimulation in patients with Huntington's disease*. Clin Neurophysiol 2006;117:1677-1681.
- Bliss TV, Collingridge GL: *A synaptic model of memory: Long-term potentiation in the hippocampus*. Nature 1993;361:31-39.
- Murphy KP, Carter RJ, Lione LA, Mangiarini L, Mahal A, Bates GP, Dunnett SB, Morton AJ: *Abnormal synaptic plasticity and impaired spatial cognition in mice transgenic for exon 1 of the human Huntington's disease mutation*. J Neurosci 2000;20:5115-5123.
- Cummings DM, Milnerwood AJ, Dallerac GM, Waights V, Brown JY, Vatsavayai SC, Hirst MC, Murphy KP: *Aberrant cortical synaptic plasticity and dopaminergic dysfunction in a mouse model of Huntington's disease*. Hum Mol Genet 2006;15:2856-2868.
- Spires TL, Grote HE, Varshney NK, Cordery PM, van Dellen A, Blakemore C, Hannan AJ: *Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism*. J Neurosci 2004;24:2270-2276.
- Pang TY, Stam NC, Nithianantharajah J, Howard ML, Hannan AJ: *Differential effects of voluntary physical exercise on behavioral and brain-derived neurotrophic factor expression deficits in Huntington's disease transgenic mice*. Neuroscience 2006;141:569-584.
- van Dellen A, Blakemore C, Deacon R, York D, Hannan AJ: *Delaying the onset of Huntington's in mice*. Nature 2000;404:721-722.
- Hockly E, Cordery PM, Woodman B, Mahal A, van Dellen A, Blakemore C, Lewis CM, Hannan AJ, Bates GP: *Environmental enrichment slows disease progression in R6/2 Huntington's disease mice*. Ann Neurol 2002;51:235-242.
- Nithianantharajah J, Hannan AJ: *Enriched environments, experience-dependent plasticity and disorders of the nervous system*. Nat Rev Neurosci 2006;7:697-709.
- Cybulska-Klosowicz A, Mazarakis NK, Van Dellen A, Blakemore C, Hannan AJ, Kossut M: *Impaired learning-dependent cortical plasticity in Huntington's disease transgenic mice*. Neurobiol Dis 2004;17:427-434.
- Kossut M: *Experience-dependent changes in function and anatomy of adult barrel cortex*. Exp Brain Res 1998;123:110-116.
- Mazarakis NK, Cybulska-Klosowicz A, Grote H, Pang T, Van Dellen A, Kossut M, Blakemore C, Hannan AJ: *Deficits in experience-dependent cortical plasticity and sensory-discrimination learning in presymptomatic Huntington's disease mice*. J Neurosci 2005;25:3059-3066.
- van Dellen A, Grote HE, Hannan AJ: *Gene-environment interactions, neuronal dysfunction and pathological plasticity in Huntington's disease*. Clin Exp Pharmacol Physiol 2005;32:1007-1019.
- van Dellen A, Deacon R, York D, Blakemore C, Hannan AJ: *Anterior cingulate cortical transplantation in transgenic Huntington's disease mice*. Brain Res Bull 2001;56:313-318.
- Gu X, Li C, Wei W, Lo V, Gong S, Li SH, Iwasato T, Itoharu S, Li XJ, Mody I, Heintz N, Yang XW: *Pathological cell-cell interactions elicited by a neuropathogenic form of mutant huntingtin contribute to cortical pathogenesis in HD mice*. Neuron 2005;46:433-444.