Supplementary information S2 | **Excitotoxicity and Huntington’s disease**

Observations from early studies with exogenous (glutamate1, kainate1 and ibotenate2) and endogenous excitotoxins (quinolinic acid3) led to the presumption that striatal excitotoxicity may take a leading role in the pathogenesis of Huntington’s disease. In line with this hypothesis, a human postmortem study revealed a robust loss of NMDA (N-methyl-D-aspartate) receptor binding in the striatum4. Correspondingly, striatal neurons exhibit a preferential abundance of NR2B subunit-containing NMDA receptors5, which predominate in the extrasynaptic areas6, where the activation of NMDA receptors is neurotoxic7. The high NR2B content, together with the innate sensitivity of the striatal mitochondria to a Ca²⁺-induced permeability transition8 and the massive glutamatergic input of the striatum from the cerebral cortex and the thalamus9, make this structure highly vulnerable to glutamatergic excitotoxicity. In contrast with normal huntingtin, which provides protection against NMDA receptor-induced neurotoxicity through binding to postsynaptic density protein-95 (PSD-95), mutated polyQ huntingtin aggravates NMDA toxicity by inhibiting this interaction10. Moreover, mutant huntingtin enhances the expression11 and phosphorylation of NR2B subunit-containing NMDA receptors12, further contributing to striatal hypersensitivity. The increased expression of extrasynaptic NMDA receptors in transgenic Huntington’s disease mice was recently reported, accompanied by decreased striatal cAMP response element-binding protein (CREB) signalling13 and subsequent deregulation of peroxisome proliferator activator receptor gamma coactivator-1alpha (PGC1α)14. As striatal hypersensitivity in Huntington’s disease is accompanied by a decreased glutamate uptake in transgenic animal models15 and in brains of patients with Huntington’s disease16, the possible therapeutic potential of the modulation of endogenous NMDA receptor regulatory pathways provides a fascinating target of research.