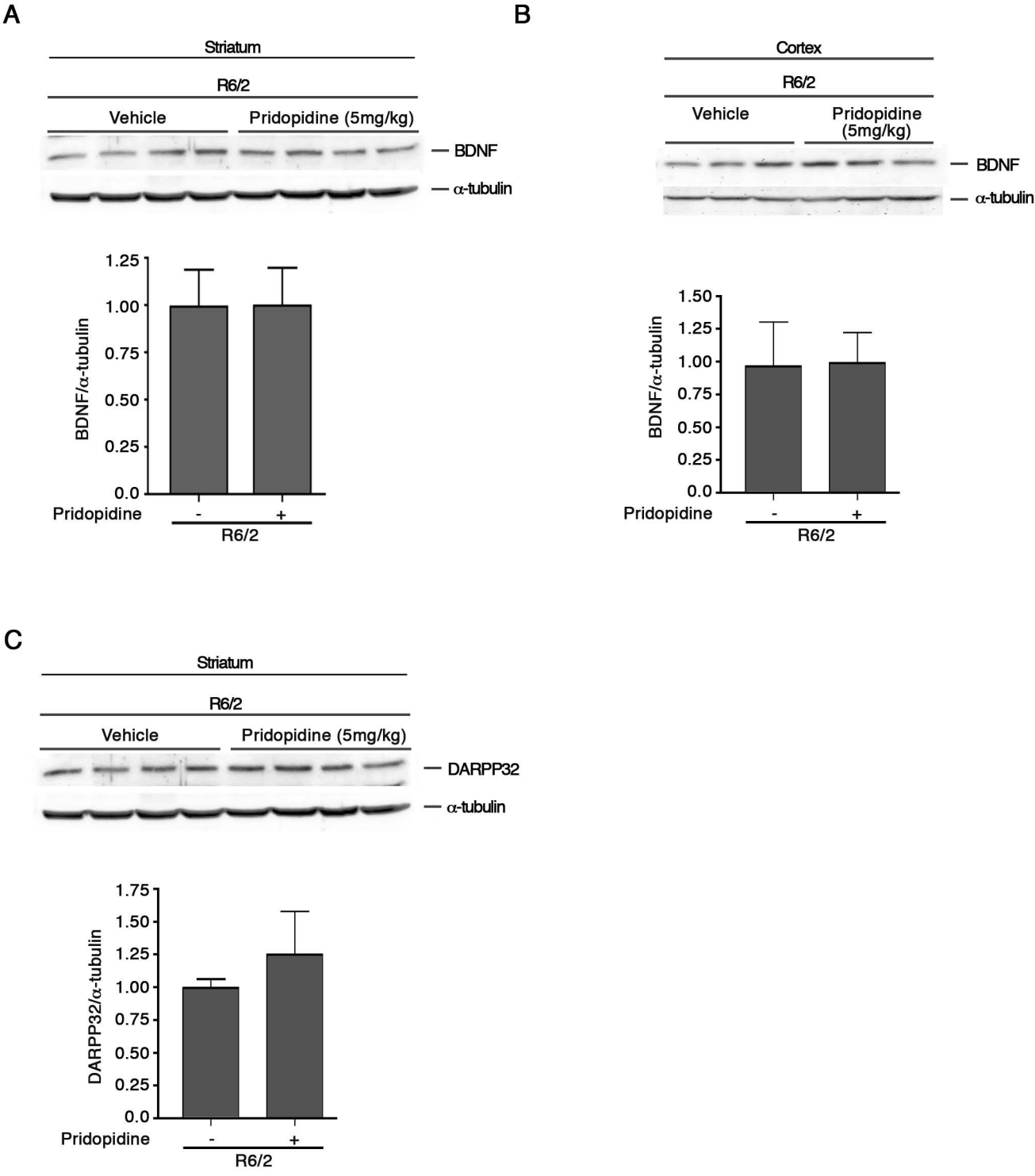
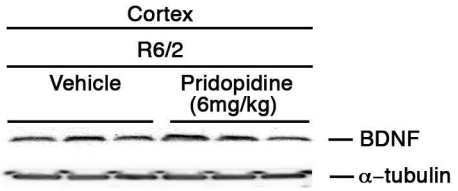
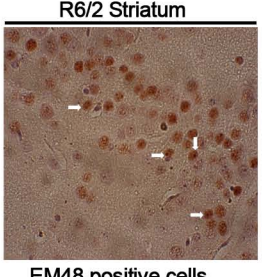
Supplementary Figure 1



Supplementary Figure 2

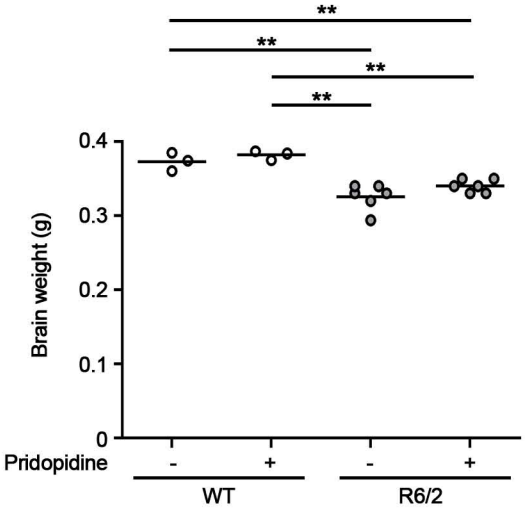


Supplementary Figure 3

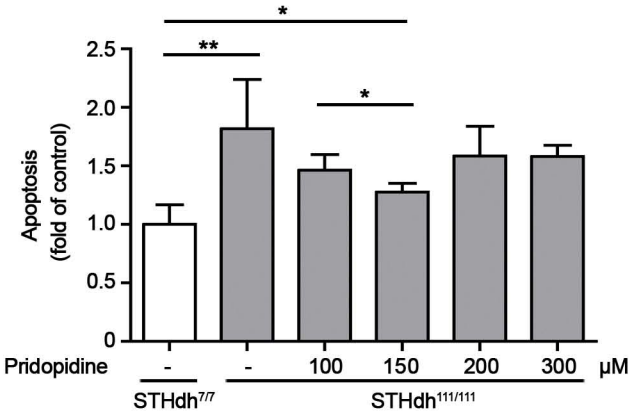


EM48 positive cells

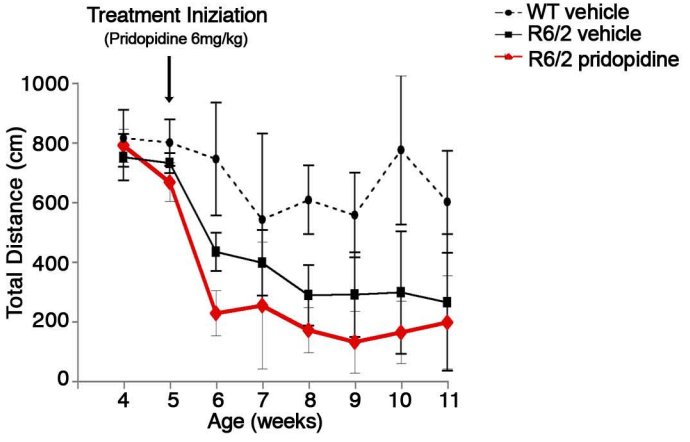
Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure 6



Supplementary Figure 1. Chronic administration of pridopidine at constant dose fails to enhance cerebral expression of both BDNF and DARPP32. (**A-B**) Representative Western Blottings and densitometric analyses of BDNF protein expression in striatal and cortical tissue of vehicle- and pridopidine-treated R6/2 mice. (**C**) Representative Western Blotting and densitometric analysis of DARPP32 in striatal tissues of the same mice. Data are represented as mean ± SD. n=5 for each group of mice.

Supplementary Figure 2. Change of pridopidine dose does not increase expression of BDNF in the cortex of R6/2 mice. Representative Western Blotting of BDNF protein expression in cortical tissue of vehicle- and pridopidine-treated R6/2 mice. Data are represented as mean ± SD, n=5 for each group of mice.

Supplementary Figure 3. mHtt aggregates are detectable at presymptomatic stage of the disease. Representative micrograph of EM48 positive cells from WT and R6/2 mouse striatum. Arrows indicate mHtt aggregates.

Supplementary Figure 4. Chronic administration of pridopidine fails to prevent loss of brain weight in R6/2 mice. Average brain weight of vehicle- and pridopidine -treated WT and R6/2 mice. Vehicle- and pridopidine-treated WT mice n=5 for each group; vehicle-treated R6/2 mice n=7; pridopidine-treated mice n=7, **, $p<0.001$ (Non-parametric Mann Whitey U)

Supplementary Figure 5. Pridopidine (150μM) resulted to be the effective dose in protecting HD cells from apoptosis. Apoptosis in striatal-derived cell lines cultured for six hours in serum-free medium in presence or absence of different concentrations of pridopidine. Data are represented as the mean ± SD of

two independent experiments performed in quadruplicate**.** *, $p<0.05$; **, $p<0.001$ (non parametric Mann Whitney U)

Supplementary Figure 6. Chronic administration of pridopidine (6mg/kg) induces hypokinesia in R6/2 mice. General locomotor activity in the open field in the R6/2, before and after treatment and WT littermates. Each data point represents the average performance ± SD of 3 mice for each group.