#3101 Title: Imbalanced basal ganglia connectivity is associated with motor deficits and apathy in Huntington's disease: First evidence from human *in vivo* neuroimaging

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Background:

The gating of movement in humans is thought to depend on activity within the cortico-striato-thalamic loops. Within these loops, emerging from the cells of the striatum, run two opponent pathways – the *direct* and *indirect* pathway. Both are complex and polysynaptic but the overall effect of activity within these pathways is to encourage and inhibit movement respectively. In Huntington's disease (HD), the preferential early loss of striatal neurons forming the indirect pathway is thought to lead to disinhibition that gives rise to the characteristic motor features of the condition. But early HD is also specifically associated with apathy, a failure to engage in goal-directed movement. We hypothesised that in HD, motor signs and apathy may be selectively correlated with indirect and direct pathway dysfunction respectively.

Methods:

Using a novel technique for estimating dynamic effective connectivity of the basal ganglia, we tested both of these hypotheses *in vivo* for the first time in a large cohort of patients with prodromal HD (n = 94). We used spectral dynamic casual modelling of resting state fMRI data to model effective connectivity in a model of these cortico-striatal pathways. We used an advanced approach at the group level by combining Parametric Empirical Bayes and Bayesian Model Reduction procedure to generate large number of competing models and compare them by using Bayesian model comparison.

Results:

With this fully Bayesian approach, associations between clinical measures and connectivity parameters emerge *de novo* from the data. We found very strong evidence (posterior probability > 0.99) to support both of our hypotheses. Firstly, more severe motor signs in HD were associated with altered connectivity in the indirect pathway and by comparison, loss of goal-direct behaviour or apathy, was associated with changes in the direct pathway component of our model.

Conclusions:

The empirical evidence we provide here is the first *in vivo* demonstration that imbalanced basal ganglia connectivity may play an important role in the pathogenesis of some of commonest and disabling features of HD and may have important implications for therapeutics.