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

Akshay Nair[1], Adeel Razi[2], Sarah Gregory[1], Robb Rutledge[1,3], Geraint Rees[1*], Sarah Tabrizi[1*]

(1) University College London, London, UK (2) Monash University, Melbourne, AUS (3) Yale University, New Haven, USA

Introduction:

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.

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).

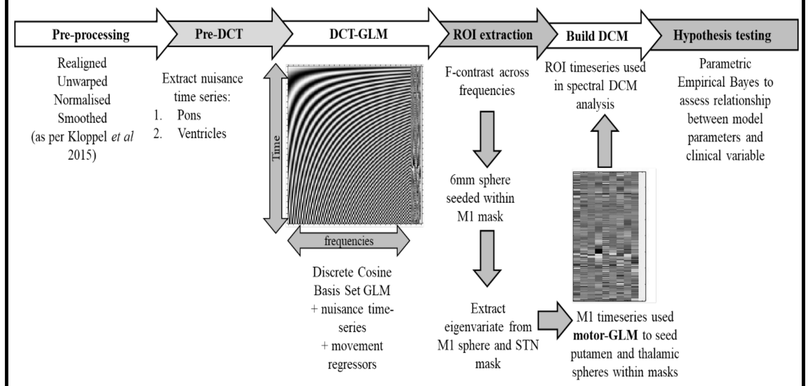
Methods: Overview

We used spectral dynamic casual modelling of resting state fMRI data to model effective connectivity in a model of these cortico-striatal pathways.

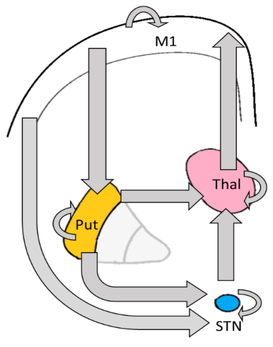
We used an advanced approach at the group level by combining **Parametric Empirical Bayes** and **Bayesian Model Reduction** procedure to generate large number of competing models and compare them by using Bayesian model comparison.

Using this fully Bayesian approach, associations between clinical measures and connectivity parameters emerge de novo from the data.

Methods: Neuroimaging pipeline

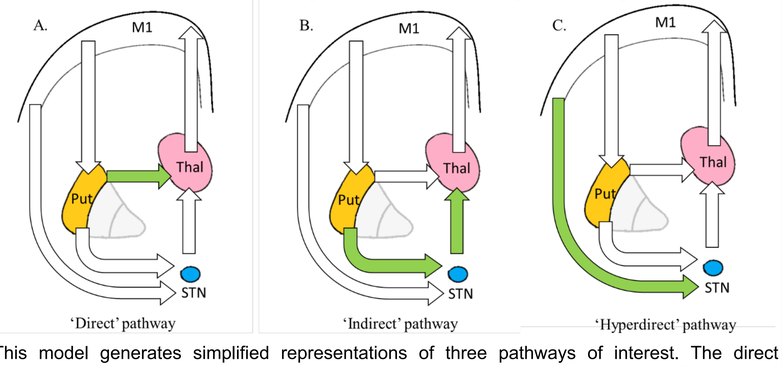


Methods: Connectivity matrix – 'A Matrix'



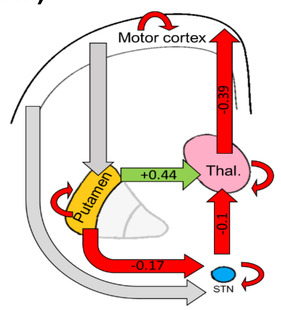
Schematic of the DCM A-matrix used in this study. Arrows looping back to the same node represent inhibitory self-connections specified in the DCM. The grey arrows describe the 'A' matrix in the DCM

Methods: Connectivity matrix – BG pathways



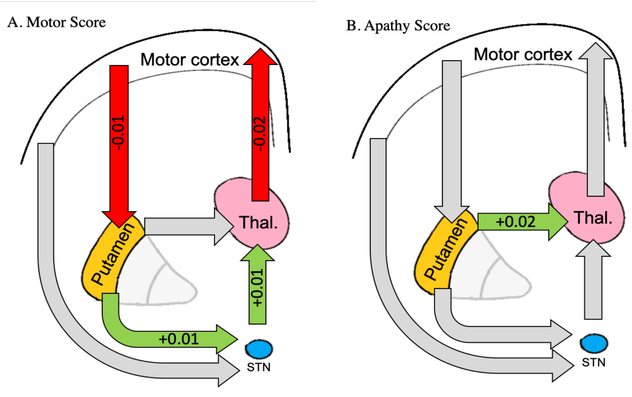
This model generates simplified representations of three pathways of interest. The direct pathway (A) is composed of the connection between putamen and thalamus. The indirect pathway components (B) are the putamen-STN connection and the STN-thalamic connection. Finally, the hyperdirect pathway (C) composes of a connection from the motor cortex to the STN.

Results: At rest, the network seems to be trying to prevent movement (remember – this is resting state data)



Schematic showing the average parameter values in the modelled network, across all 94 HD subjects, for between node connections. Red arrows indicate suppression of activity, green arrows indicate excitation and grey arrows indicate non-significant connections. Coloured arrows represent connections with a posterior probability of >0.99 for being greater than 0. Overall, the network activity shows a suppression of M1 activity which may be expected given that subjects are explicitly trying to remain still.

Results: Altered connectivity basal ganglia connectivity associated with total motor scores and apathy scores:



Association between inter-node connectivity parameters and (A) Total Motor Score and (B) Baltimore Apathy Score. 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.

Conclusion:

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.