Fronto-striatal circuits for cognitive flexibility in far from onset Huntington's Disease: Evidence from the Young Adult Study.

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Introduction

Cognitive flexibility refers to the ability to shift attention to select behaviourally relevant stimuli in a given context. Cognitive flexibility is vital for adaptive decision-making in everyday life. Indeed, studies using the CANTAB Intra-Extra Dimensional Set Shift Task (IED) to assess Huntington's Disease (HD) have shown impairments at all phases of HD[1,2,3], including in the premanifest (pre-HD) stage[2]. Performance on tests of cognitive flexibility is sensitive to disruption of fronto-striatal circuitry[4,5]. It is well established that the neurodegeneration in both HD and pre-HD is especially severe in the striatum[6] and that fronto-striatal circuits are the earliest to show degeneration in HD[7]. We used resting-state fMRI to examine the association between the functional connectivity in predefined fronto-striatal circuits[4,5] and separate performance on the extra dimensional (ED) shift stage of the CANTAB IED to examine whether similar circuits are involved in far from onset premanifest HD.

Methods

Participants: 51 right-handed premanifest HD participants (age 29.22 (5.71), 23.89 (5.95) years from onset) and 53 healthy controls (HC) (age 28.85 (5.50)) matched for age, sex and IQ were included. Task: The CANTAB IED is a test of cognitive flexibility that consists of 9 stages. Stages 1-7 are learning stages that involve learning which is the correct stimulus and simple reversals. Stage 8 is the crucial stage, as it requires an extradimensional set shift. In stages 1-7 the shapes were the stimuli of interest, whereas in stage 8 this shifts to the lines. Data acquisition: 3T Siemens Prisma scanner, 64 channel head coil. The resting-state T2*-weighted images were acquired with a TR=3360ms and TE=30ms; field of view=192mm2, flip angle of 90°, 48 slices of 2.5mm thickness. The T1-weighted images were acquired using a 3D MPRAGE sequence with a TR=2530ms and TE=3.34ms; inversion time of 1100ms, flip angle of 7°, field of view=256mm2.

Pre-processing: All images were pre-processed in SPM12. Images were slice-time corrected, realigned, co-registered, normalised to MNI space using the DARTEL deformation parameters, and smoothing was performed using a 6mm Gaussian kernel. We specified eight regions of interest based on previously identified coordinates[4,5]. These were the left and right caudate, ventral striatum, dorsolateral prefrontal cortex (pFC) and ventrolateral pFC. A 6mm sphere was created at each coordinate. Noise from white matter, cerebrospinal fluid and movement signals were regressed out and we applied a linear detrending and a bandpass filter between 0.01 and 0.08. Pearson's correlations between each of the 8 ROIs was conducted and we standardised the data using a Fisher z-transform. Analysis: These values from the standardised weighted connectivity matrices were used to perform the correlation analyses with ED errors in SPSS 26 and a Benjamini-Hochberg correction was applied.

Results and Discussion

Our behavioural results showed that the pre-HD group made significantly more ED shift errors compared to the controls, but there were no significant differences between the groups for pre-ED errors. These results suggest that the pre-HD group successfully formed attentional sets and achieved reversal learning but had a specific impairment in shifting attentional control between stimulus dimensions when compared to controls.

In the HCs we found that functional connectivity between left ventral striatum and right ventrolateral PFC associated with ED errors. This result provides further evidence for the involvement of fronto-striatal networks in cognitive flexibility, specifically between the prefrontal cortex and the ventral striatum, in healthy individuals.

The pre-HD group showed an alternative circuit, specifically between left caudate and left dorsolateral PFC was associated with ED errors. It is possible that the involvement of the dorsolateral PFC with the caudate in the pre-HD group represents an inefficient strategy based on increased searching for over-elaborate, and hence counterproductive, rules or solutions governing performance in the IED task rather than responding appropriately to reinforcing feedback. However, further research to formally test this hypothesis would be required.

Conclusion

The CANTAB IED is sensitive to impairments in cognitive flexibility in HD even in far from onset premanifest groups. The pre-HD group showed alternative fronto-striatal circuit, associated with attentional set shifting compared to controls, potentially representing a form of functional reorganisation, which, while effective for most pre-HD participants in preserving performance is maladaptive in a small number of the most affected pre-HD participants. The intrinsic functional connectivity at rest in relation to performance on this test of cognitive flexibility may thus provide a potential neuroimaging biomarker of individual variability in cognitive flexibility in pre-HD early in disease progression.

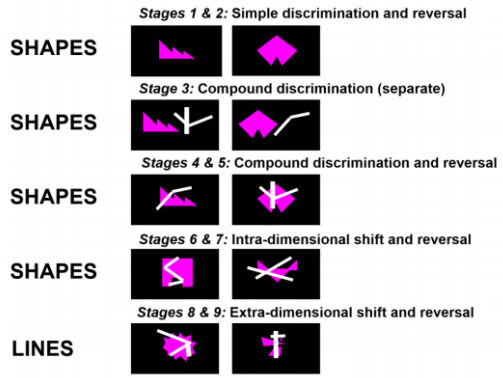

Figure 1 Schematic of the Cambridge Neuropsychological Test Automated Battery (CANTAB) Intra-Extra Dimensional Set-Shift (IED) Task.

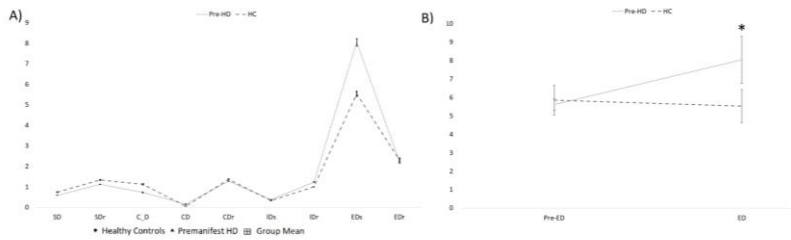

Figure 2 Performance on the Cambridge Neuropsychological Test Automated Battery (CANTAB) Intra-Extra Dimensional Set-Shift (IED) Task. (A) The mean number of errors by learning stage on the IED task. Error bars represent standard error of the mean. *p < 0.05. CD, superimposed compound discrimination; C_D, separated compound discrimination; CDr, superimposed compound discrimination reversal; EDs, extradimensional shift; EDr, extradimensional shift reversal; IDs, intradimensional shift; IDr, intradimensional shift reversal; SD, simple discrimination; SDr, simple discrimination reversal.
(B) A line graph displaying the mean pre-ED and ED errors in each group. Error bars represent standard error of the mean.
ED, extradimensional; HC, healthy controls; HD, Huntington's disease.

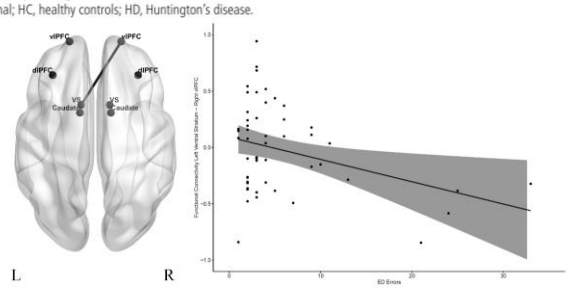

Figure 3 Scatterplot between functional connectivity and ED errors in the HC group. The scatterplot between ED errors and functional connectivity between the left ventral striatum and the right ventrolateral PFC.

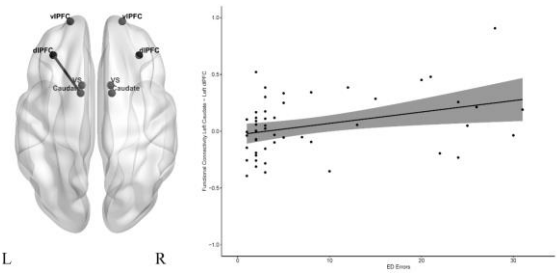

Figure 4 Functional connectivity and ED errors in premanifest HD group. The scatterplot between ED errors and functional connectivity between the left caudate and left dorsolateral PFC.

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