Chapter 8

Reduced functional brain connectivity prior to disease onset in Huntington's Disease

Eve M Dumas[1], Simon JA van den Bogaard[1], Ellen P Hart[1], Roelof P Soeter[2], Mark A van Buchem[2], Jeroen van der Grond[2], Serge ARB Rombouts[2,3,4], Raymund AC Roos[1], on behalf of the TRACK-HD investigator group

1. Deparment of neurology, Leiden University Medical Center, The Netherlands
2. Department of Radiology, Leiden University Medical Center, The Netherlands
3. Leiden Institute for Brain and Cognition (LIBC)
4. Institute of Psychology, Leiden University

submitted

Abstract

Background

Huntington's disease (HD) is characterised by both regional and generalised neuronal cell loss in the brain. Investigating functional brain connectivity patterns in rest in HD has the potential to broaden the understanding of brain functionality in relation to disease progression. This study aims to establish whether brain connectivity during rest is different in premanifest and manifest HD as compared to controls.

Methods

At the Leiden University Medical Centre study site of the TRACK-HD study, 20 early HD patients (disease stage 1 and 2), 28 premanifest gene carriers and 28 healthy controls underwent 3T MRI scanning. Standard and high-resolution T_1-weighted images and a resting state fMRI scan were acquired. Using FSL, group differences in resting state connectivity were examined for eight networks of interest using a dual regression method. With a voxelwise correction for localised atrophy, group differences in functional connectivity were examined.

Results

Brain connectivity of the left middle frontal and pre-central gyrus, and right post central gyrus with the medial visual network was reduced in premanifest and manifest HD as compared to controls ($0.05>p>0.0001$). In manifest HD connectivity of numerous widespread brain regions with the default mode network and the executive control network were reduced ($0.05>p>0.0001$).

Discussion

Brain regions that show reduced intrinsic functional connectivity are present in premanifest gene carriers and to a much larger extent in manifest HD patients. These differences are present even when the potential influence of atrophy is taken into account. Resting state fMRI can potentially be used for early disease detection in the premanifest phase of HD and for monitoring of disease modifying compounds.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterised by progressive motor-, behavioural- and cognitive-dysfunction. The expansion of the HTT gene on chromosome 4 is eventually responsible for neuronal loss and dysfunction throughout the brain[1;2]. Previous studies have demonstrated that atrophy of both the deep grey matter structures and of the cortex are apparent in patients with HD, and also to a lesser degree in HD gene carriers prior to disease onset[3-6]. These premanifest gene carriers, who do not show symptoms of the disease but are certain of eventual disease onset, have also been found to show reduced integrity of white matter[7-9]. In patients with HD, both extensive white matter integrity loss and atrophy of white matter has been shown[9-11].

Clinical assessments in multiple functional domains have extensively objectified the impairments reported by patients and their companions[12-15]. Also in premanifest gene carriers numerous tests of functioning have shown diminished performance[16-18]. In an effort to bridge the gap between the observed clinical deteriorations and structural brain deficits, a number of studies have applied clinical assessments whilst observation of brain activity was performed using functional magnetic resonance imaging (fMRI).

Four task-based fMRI studies in manifest HD demonstrated a fairly homogenous profile, with reductions in brain activation in numerous cortical and sub-cortical brain regions[19-22]. However the results from the limited number of task-based fMRI studies in premanifest HD report a more heterogeneous pattern. Increased activation in several brain regions was found in premanifest gene carriers far from expected disease onset, and reduced activation was reported in premanifest gene carriers close to expected disease onset[23;24]. These task-based fMRI studies all challenged the brain during the MRI scanning yielding assessment and performance dependent results. An alternative approach is to examine the brain connectivity patterns without taxation.

Brain function depends on large-scale brain interactions[25]. Functional brain connectivity patterns can be examined at rest with fMRI and this approach is recognised as an important step towards understanding functional brain networks[26]. Hence, recent reports have incorporated resting state (RS) fMRI to examine the brain during both normal aging and disease[27-30]. Currently the earliest detectable brain changes in HD are atrophy of subcortical grey matter structures[17;31]. Given that cell loss presents as the result of a pathologic cascade it is plausible to expect functional brain changes prior to cell loss. In carriers of the APOE-4 gene, alterations in intrinsic functional connectivity have been observed even in the absence of changes in brain structure[32]. Such interactions have not been studied in premanifest HD. Functional brain changes may also occur in HD, either prior to, or as a result of brain atrophy. RS fMRI has the potential to give insight into

potential functional changes. RS fMRI could be implemented for early disease detection and could evaluate the effect of future neuroprotective or therapeutic compounds. This study aims to establish whether functional brain connectivity at rest is altered in both premanifest HD gene carriers and early manifest patients.

Methods

Participants

At the Leiden University Medical Centre study site of the TRACK-HD study, subjects participating in the longitudinal TRACK-HD study underwent MRI scanning including fMRI during the baseline visit. Of the 90 participants included, 11 did not undergo the additional fMRI scan due to time constraints. Furthermore after quality control of the fMRI data, both visually and by means of the scan analysis reports generated during post-processing of the MRI data, three manifest HD participants were excluded from the analysis because of excessive motion (>4mm). In total 20 stage 1 and 2 HD patients, 28 premanifest gene carriers and 28 healthy controls were included in the fMRI analysis (table 1).

Inclusion criteria for HD patients included a positive genetic test for the *HTT* gene with 40 or more CAG repeats; the presence of motor disturbances defined as more than five points on the Unified Huntington's Disease Rating Scale – total motor score (UHDRS-TMS), and a Total Functional Capacity score (TFC) greater than or equal to seven points, thereby only including patients in the earliest two disease stages[33]. Inclusion criteria for premanifest gene carriers consisted of a positive genetic test with 40 or more CAG repeats, and the absence of motor disturbances with five or less points on the UHDRS-TMS. Finally, a burden of pathology score ((CAG repeat length -35.5) x age) greater than 250[34] was required. Age- and gender-matched gene-negative relatives of HD gene carriers and unaffected spouses were included as healthy controls. Exclusion criteria for all participants included previous significant head injury, any other neurological or major psychiatric disorder, or unwillingness to undergo MRI scanning. The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre. All participants gave written informed consent. For full details of study parameters see Tabrizi *et al*. (2009)[31].

During further medical history taking, handedness was recorded by means of the Edinburgh Inventory 2nd version (Oldfield, 1970). For early HD patients, the rater's estimate of disease onset was determined, based on the rater's observations, reports by the patients and information from companions or relatives. With this information the current disease duration was calculated. For premanifest gene carriers the estimated number of years until disease onset was calculated based on their current age and CAG repeat length, by means of the formula developed by Langbehn *et al*. (2004)[35].

MRI protocol

MRI acquisition was performed on a 3 Tesla whole body scanner (Philips Achieva, Healthcare, Best, The Netherlands) with an eight channel receive array head coil. An anatomical T_1-weighted scan was acquired using an ultrafast gradient echo 3D acquisition sequence with the following imaging parameters: repetition time (TR) = 7.7 ms, echo time (TE) = 3.5 ms, field-of-view = 24 x 24 x 16.4 cm, matrix size 224 x 224, with a duration of 9 minutes. For post-processing registration purposes, a high resolution T_1-weighted scan, with the following parameters was collected; repetition time (TR) = 2200 ms, echo time (TE) = 30 ms, field-of-view = 220 x220x168 mm, flip angle = 80°, matrix size= 112x109mm, with a duration of 46 seconds. A RS fMRI scan with the following parameters was also obtained: repetition time (TR) = 2200 ms, echo time (TE) = 30 ms, field-of-view = 220 x 220 x 10.4 cm, resolution = 1.96 x 1.96 x 2, no slice gap, flip angle = 80°, matrix size 80 x 79, with a duration of 7.5 minutes. To reduce unnecessary sensory input that could influence the results, participants were not allowed to listen to music during the RS fMRI scan, and to ensure a wakeful disposition participants were asked to keep their eyes open with normal background light.

Pre-processing for RS fMRI analysis

Pre-processing of the RS fMRI data using the standard procedure was carried out using FSL 4.1.8[36]. The following steps were preformed: head motion correction[37], brain extraction[38], spatial smoothing using a Gaussian kernel of 5 mm full width at half maximum (FWHM). All volumes were normalised based on mean intensity and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, FWHM = 100s). The middle (reference scan) of each individuals RS fMRI time series was affine registered to MNI152 standard space (Montreal Neurological Institute, Montreal, QC, Cananda): initially, it was registered to the high resolution T_1-weighted scan. This high resolution T_1-weighted scan was subsequently registered to the anatomical T_1-weighted scan. Finally, the anatomical scan was registered to MNI152 standard space. By first registering the functional data to the high resolution scan and then to the anatomical T_1-weighted scan allows for better registration of the data. These three registration matrices were combined to obtain a matrix for transforming fMRI data from native space to standard space, using interpolation to 2x2x2 mm voxels. Visual quality control was performed to ensure correct registration.

Statistical analyses

Statistical analysis of group demographic was compared using SPSS (version 17, SPSS, USA). Where appropriate either Analysis of Variance or Chi-squared tests were applied. Resting state connectivity was examined using a dual regression method[32;39;40]. In doing so the similarity of the haemodynamic response patterns (fMRI signal) for each brain voxel was compared to the fMRI signal in eight pre-defined, well established, networks

of interest (NOIs)[41]. These networks encompass over 80% of the entire brain volume. The NOIs represent spatial template maps corresponding to medial visual (NOI1), lateral visual (NOI2), auditory (NOI3), sensorimotor (NOI4), the default mode (NOI5), executive control (NOI6), visual-spatial memory (NOI7), and working memory (NOI8) networks.

First, a spatial regression was applied: The eight NOIs and a CSF mask were used as spatial regressors in a general linear model (GLM) to obtain the nine corresponding dynamic patterns of fMRI signal fluctuations in each network from each individual's RS fMRI scan. Next, these nine time series, together with six motion correction parameters derived during preprocessing (three translations and three rotations) were used as temporal regressors in a second (temporal) GLM. For each voxel, the z-score corresponding to each of these 15 temporal regressors was obtained. A GLM was applied, resulting in spatial z-score maps for each individual's RS fMRI scan, for each NOI. This dual-regression method thereby generated eight z-scores maps reflecting the connectivity strength of each voxel in the brain to each of the eight NOIs. A voxel with a high z-score demonstrated a highly similar pattern of fMRI fluctuation to the voxels in the NOI.

These z-score maps were constructed to compare the groups. The group statistical analysis was performed to determine which brain regions showed statistically significant differences in connectivity to any of the NOIs between groups by applying three independent sample t-tests. This was performed with a voxel-wise correction for localised grey matter concentration to rule-out any potentially confounding impact of local structural loss on brain connectivity, as described by Oakes *et al*. (2007)[42]. In short, per individual the anatomical T_1-weighted scans were processed to provide voxel-based intensity maps of grey matter concentration, which were included as a voxel-wise covariate in the mixed effects model group analysis. Non-parametric permutation based statistical inference was used with 5000 repeated permutations per NOI for the comparisons; controls vs premanifest, controls vs manifest HD and premanifest vs manifest HD. Correction for multiple comparisons was applied using threshold free cluster enhancement based correction whereby all results under the threshold of $p<0.05$ were considered statistically significant[43]. This provided spatial information per NOI of brain regions demonstrating different connectivity patterns between the study groups.

Results

The groups did not differ in terms of age, gender, handedness and education level. Early HD patients had significantly higher UHDRS motor scores, CAG repeat lengths and lower TFC scores than premanifest gene carriers and/or healthy controls.

Table 1: Group characteristics of the study groups

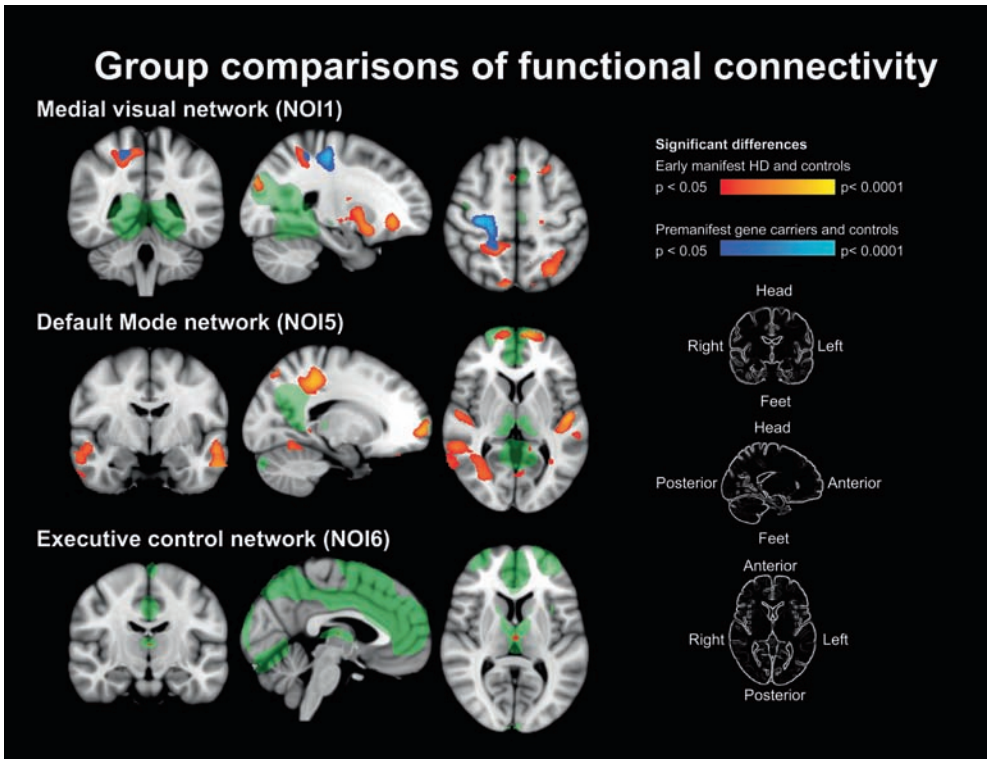
	Healthy controls	Premanifest gene carriers	Early HD patients
N	28	28	20
Gender M/F	13/15	11/17	5/15
Age (years) Mean (SD)	48.5 (8.5)	43.21 (8.2)	46.5 (10.6)
CAG repeat length Mean (SD)	n/a	42.5 (2.5)	44.1 (2.6)[§]
Total Functional Capacity Mean (SD)	12.9 (1.9)	12.6 (0.8)	10.2 (1.9)*[§]
UHDRS - Motor Mean (SD)	2.5 (2.5)	2.4 (1.4)	20.3 (11.0)*[§]
Expected disease onset (years) Mean (SD)	n/a	11,6 (4.4)	n/a
Disease duration (years) Mean (SD)	n/a	n/a	6.8 (7.4)

N = number of participants, SD = Standard deviation, n/a = not applicable, UHDRS – Motor = Unified Huntington's Disease Rating Scale – total motor score, * significantly different to controls at $p< 0.05$, [§] significantly different to premanifest gene carriers at $p< 0.05$.

In both premanifest gene carriers and early manifest HD the same regions in the left frontal lobe and the right parietal lobe displayed reduced connectivity with the NOI1 (medial visual network), as compared to controls ($0.05>p>0.0001$). The area in the left frontal lobe comprised the grey matter near the pre-central and middle-frontal gyri. The area in the parietal lobe was localised in the post-central gyrus (figure 1). Premanifest gene carriers only, also displayed reduced connectivity bi-laterally of the cingulate gyrus with NOI1 compared to the controls. This area of reduced connectivity was not found in the early HD group. The manifest HD group demonstrated additional areas of reduced connectivity with NOI1 that were not observed in the premanifest gene carrier group. These areas were located bi-laterally within the superior occipital lobe, within a large field in the deep grey matter, including the putamen, globus pallidus, thalamus, and bi-laterally in the cortex of the frontal orbital region (figures 1).

The connectivity of the left parietal lobe, the pre-frontal cortex in both hemispheres, and regions of grey and white matter in the both temporal lobes with NOI5 (the default mode network) was reduced in early HD only as compared to controls ($0.05>p>0.0001$) (figure 1). Connectivity of a small region in the thalamus and the left supramarginal gyrus with NOI6 (executive control network) was reduced in manifest HD as compared to controls ($0.05>p>0.0001$) (figure 1). No differences between any of the study groups were found in the connectivity with the other NOIs.

Figure 1. Group comparisons of functional brain connectivity shown in three orientations.



Green areas show the voxels encompassing the network of interest (NOI) with which the connectivity decreases are present. Blue - light blue areas show the areas of reduced connectivity with the NOI between premanifest gene carriers and controls, red-yellow areas show the areas of reduced connectivity with the NOI between early manifest HD and controls. Some are of blue and red overlap is present, here the functional connectivity is reduced in both premanifest and manifest HD.

Discussion

Reductions in intrinsic functional connectivity are apparent in both premanifest gene carriers and patients with early HD. The earliest areas to show a reduction in connectivity are regions within the left frontal and right parietal and bilateral visual lobes. These areas also demonstrated reduced connectivity in the early manifest group. Further connectivity reductions were also apparent in many other brain regions in early HD such as subcortical grey matter and the occipital lobes. These observed differences to healthy controls are not explained by brain atrophy.

In premanifest gene carriers our findings show reduced connectivity of the medial visual network (NOI1) with the left frontal, right parietal and bilateral cingulate gyrus during rest. The only known other report of RS fMRI in HD is a methodological report

describing the stability and suitability of RS fMRI over a one year follow up period in premanifest gene carriers. No group differences in any of their prespecified interregional fMRI correlations were found[44]. The prespecified two seed regions used for interregional correlation were different to the networks applied in the current paper, and this methodological dissimilarity may explain the variation in outcome. Carriers of genes resulting in neurological diseases other than HD have been found to show aberrant intrinsic functional connectivity in the absence of disease signs[32;45], thus supporting the occurrence of functional brain changes prior to a disease manifestation. Results from other studies using task based fMRI in HD also support our findings[23;24;46-48]. These studies show disrupted activation (either increased or decreased) in areas that do not form an identical spatial match to our results, but do show great similarity of involved brain areas. Some regions with altering between region connections in this study, such as the left frontal lobe, specifically in the middle frontal gyri and pre-central gyrus, have also shown locally decreased task related fMRI activation[23;24;46-48]. Task based fMRI studies also demonstrated the implication of the post central gyrus[48], and the bilateral cingulated cortex[23;24;48]. Further support for our finding is found in results using a different imaging technique that measures blood perfusion during rest. Cerebral blood flow was found to be altered in premanifest gene carriers in prefrontal brain regions[49]. Our results demonstrate that early reductions in intrinsic functional connectivity are present prior to the clinical manifestation of HD. This is an important finding as therapeutic interventions may wish to monitor the functional impact of a compound on the brain in the absence of clinical outcome measures.

In the early HD group, our findings of reduced connectivity encompass more and larger regions in the brain than of premanifest gene carriers. Some, but not all of these regions have previously been shown to show disturbed activation during task based fMRI. The disrupted activation was reported in the same brain areas with which we found reductions in connectivity of the medial visual network (NOI1); left frontal lobe[20;50], right parietal lobe[20;50], superior occipital[20] and frontal orbital[22] regions in both hemispheres, and specific subcortical structures such as the putamen[22;48]. However, no previous literature describes involvement of the globus pallidus, or thalamus. The brain regions demonstrating reduced connectivity with the default mode network (NOI5) were also reported to show altered activation during performance, such as with the left parietal[50], and bilateral prefrontal cortices[21;48] and temporal lobes[22]. The reduction of connectivity of the left supermarginal gyrus and thalami with the executive control network (NOI6) during rest, does not find support in other studies of connectivity or brain activation during task execution. Despite the different nature of RS fMRI versus task based fMRI, our current findings do seem complementary to the task-based fMRI results. With RS fMRI overall brain connectivity is examined that is not limited to task related brain regions, and we have demonstrated that the connectivity of multiple brain networks is affected in HD.

The brain regions demonstrating reduced connectivity as compared to healthy controls showed overlap between premanifest gene carriers and early HD patients, possibly indicating progressive functional deficits. The regions demonstrating reduced connectivity generally occur bilaterally and throughout the brain, especially in manifest HD.

It is unknown whether reduced connectivity patterns reflect connectivity that is limited or non-existent due to neuronal death or whether such results reflect intact but abnormally functioning neurons in HD. The results from this current study suggest that the latter may be a more accurate reflection, given that atrophy reflects (advanced) volume loss as a result of neuronal death, and that our results remain valid when taking into consideration MRI detectable regional atrophy. Therefore, it is not likely that reductions in functional connectivity can be explained solely by neuronal death in HD.

The strengths of this study lay in the comprehensive and exploratory nature of the fMRI analysis. As this study was performed in a single sample of strictly selected premanifest and early manifest HD the results reflect varying stages of disease progression. Furthermore, by taking atrophy into consideration the potential influence of cell loss on connectivity results was reduced. Examination of brain networks encompassing almost the entire brain allowed for a hypothesis generating approach. Therefore the brain regions found to display reduced connectivity may be targeted in future studies of HD. The limitations of this study lay in the potential for the influence of motion artefacts due to chorea. However, every effort was made to prevent motion during scanning and furthermore strict quality control was applied to prohibit the inclusion of poor quality scans. This resulted in the exclusion of three scans from the manifest HD group. Also, the influence of excessive motion was reduced by including a strictly selected early HD group where chorea is generally limited. Other limitations are the novelty of the technique and the cross-sectional design. To further understand if connectivity patterns are indeed affected by the progressive nature of this degenerative disease, study reproduction and longitudinal follow-up is essential in all study groups. Longitudinal follow-up using RS fMRI has the advantage over task-based fMRI that it is easier to standardise for cross-site, cross-cultural studies. In the multi-site follow up of the TRACK-HD study the evaluation of RS fMRI as a biomarker for HD is ongoing.

In conclusion, we have demonstrated that in the absence of processes that put demand on the brain, the HD brain functions differently. These findings are not explained by the presence of cerebral atrophy. We have shown that these functional differences are present not only after disease manifestation but also in the preceding ‘premanifest’ phase. Functional connectivity measures can potentially be used for early disease detection and for monitoring of disease modifying compounds.

References

1. van den Bogaard S, Dumas E, van der Grond J, et al. MRI biomarkers in Huntington's disease. Front Biosci (Elite Ed) 2012;4:1910-25
2. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol 2011;10:83-98
3. van den Bogaard SJ, Dumas EM, Acharya TP, et al. Early atrophy of pallidum and accumbens nucleus in Huntington's disease. J Neurol 2010;258:412-20
4. Tabrizi SJ, Scahill RI, Durr A, et al. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. Lancet Neurol 2011;10:31-42
5. Rosas HD, Liu AK, Hersch S, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 2002;58:695-701
6. Aylward EH, Codori AM, Rosenblatt A, et al. Rate of caudate atrophy in presymptomatic and symptomatic stages of Huntington's disease. Mov Disord 2000;15:552-60
7. Rosas HD, Tuch DS, Hevelone ND, et al. Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. Mov Disord 2006;21:1317-25
8. Reading SA, Yassa MA, Bakker A, et al. Regional white matter change in pre-symptomatic Huntington's disease: a diffusion tensor imaging study. Psychiatry Res 2005;140:55-62
9. Dumas EM, van den Bogaard SJ, Ruber ME, et al. Early changes in white matter pathways of the sensorimotor cortex in premanifest Huntington's disease. Hum Brain Mapp 2012;33:203-12
10. Beglinger LJ, Nopoulos PC, Jorge RE, et al. White matter volume and cognitive dysfunction in early Huntington's disease. Cogn Behav Neurol 2005;18:102-07
11. Weaver KE, Richards TL, Liang O, et al. Longitudinal diffusion tensor imaging in Huntington's Disease. Exp Neurol 2009;216:525-29
12. Snowden J, Craufurd D, Griffiths H, et al. Longitudinal evaluation of cognitive disorder in Huntington's disease. J Int Neuropsychol Soc 2001;7:33-44
13. Caine ED, Hunt RD, Weingartner H, et al. Huntington's dementia. Clinical and neuropsychological features. Arch Gen Psychiatry 1978;35:377-84
14. Ho AK, Sahakian BJ, Brown RG, et al. Profile of cognitive progression in early Huntington's disease. Neurology 2003;61:1702-06
15. Kirkwood SC, Su JL, Conneally P, et al. Progression of symptoms in the early and middle stages of Huntington disease. Arch Neurol 2001;58:273-78
16. Brandt J, Shpritz B, Codori AM, et al. Neuropsychological manifestations of the genetic mutation for Huntington's disease in presymptomatic individuals. Journal of the International Neuropsychological Society 8(7)()(pp 918-924), 2002 Date of Publication: Nov 2002 2002;918-24
17. Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. J Neurol Neurosurg Psychiatry 2008;79:874-80
18. Solomon AC, Stout JC, Weaver M, et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord 2008;23:1830-36
19. Wolf RC, Vasic N, Schonfeldt-Lecuona C, et al. Cortical dysfunction in patients with Huntington's disease during working memory performance. Hum Brain Mapp 2009 Jan;30(1):327-39
20. Clark VP, Lai S, Deckel AW. Altered functional MRI responses in Huntington's disease. Neuroreport 2002;13:703-06
21. Thiruvady DR, Georgiou-Karistianis N, Egan GF, et al. Functional connectivity of the prefrontal cortex in Huntington's disease. J Neurol Neurosurg Psychiatry 2007;78:127-33
22. Kim JS, Reading SA, Brashers-Krug T, et al. Functional MRI study of a serial reaction time task in Huntington's disease. Psychiatry Res 2004;131:23-30
23. Zimbelman JL, Paulsen JS, Mikos A, et al. fMRI detection of early neural dysfunction in preclinical Huntington's disease. J Int Neuropsychol Soc 2007;13:758-69
24. Paulsen JS, Zimbelman JL, Hinton SC, et al. fMRI biomarker of early neuronal dysfunction in presymptomatic

Huntington's Disease. AJNR Am J Neuroradiol 2004;25:1715-21
25. Mesulam MM. From sensation to cognition. Brain 1998;121 (Pt 6):1013-52
26. Biswal BB, Mennes M, Zuo XN, et al. Toward discovery science of human brain function. Proc Natl Acad Sci U S A 2010;107:4734-39
27. Veer IM, Beckmann CF, van Tol MJ, et al. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. Front Syst Neurosci 2010; 4: 41
28. Zhang D, Raichle ME. Disease and the brain's dark energy. Nat Rev Neurol 2010;6(1):15-28
29. Damoiseaux JS, Beckmann CF, Arigita EJ, et al. Reduced resting-state brain activity in the "default network" in normal aging. Cereb Cortex 2008;18:1856-64
30. Hafkemeijer A, van der Grond J, Rombouts SA. Imaging the default mode network in aging and dementia. Biochim Biophys Acta 2012 Mar;1822(3):431-41
31. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801
32. Filippini N, MacIntosh BJ, Hough MG, et al. Distinct patterns of brain activity in young carriers of the APOE-4 allele. Proc Natl Acad Sci U S A 2009;106(17):7209-14
33. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3
34. Penney JB, Vonsattel JP, MacDonald ME, et al. CAG repeat number governs the development rate of pathology in Huntington's disease. Annals of Neurology 1997;41:689-92
35. Langbehn DR, Brinkman RR, Falush D, et al. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clin Genet 2004;65:267-77
36. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23 Suppl 1:S208-S219
37. Jenkinson M, Bannister P, Brady M, et al. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17:825-41
38. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143-55
39. Zuo XN, Kelly C, Adelstein JS, et al. Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. Neuroimage 2010;49:2163-77
40. Khalili-Mahani N, Zoethout RM, Beckmann CF, et al. Effects of morphine and alcohol on functional brain connectivity during "resting state":A placebo-controlled crossover study in healthy young men. Hum Brain Mapp 2012 May;33(5):1003-18
41. Beckmann CF, DeLuca M, Devlin JT, et al. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 2005;360:1001-13
42. Oakes TR, Fox AS, Johnstone T, et al. Integrating VBM into the General Linear Model with voxelwise anatomical covariates. Neuroimage 2007;34(2):500-08
43. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 2009;44(1):83-98
44. Seibert TM, Majid DS, Aron AR, et al. Stability of resting fMRI interregional correlations analyzed in subject-native space: A one-year longitudinal study in healthy adults and premanifest Huntington's disease. Neuroimage 2012;59:2452-63
45. Whitwell JL, Josephs KA, Avula R, et al. Altered functional connectivity in asymptomatic MAPT subjects: a comparison to bvFTD. Neurology 2011;77:866-74
46. Wolf RC, Vasic N, Schonfeldt-Lecuona C, et al. Dorsolateral prefrontal cortex dysfunction in presymptomatic Huntington's disease: evidence from event-related fMRI. Brain 2007;130:2845-57
47. Wolf RC, Sambataro F, Vasic N, et al. Aberrant connectivity of lateral prefrontal networks in presymptomatic Huntington's disease. Experimental Neurology 2008;213:137-44
48. Saft C, Schuttke A, Beste C, et al. fMRI reveals altered auditory processing in manifest and premanifest Huntington's disease. Neuropsychologia 2008;46:1279-89
49. Wolf RC, Gron G, Sambataro F, et al. Magnetic resonance perfusion imaging of resting-state cerebral blood flow in preclinical Huntington's disease. J Cereb Blood Flow Metab 2011;31:1908-18
50. Georgiou-Karistianis N, Sritharan A, Farrow M, et al. Increased cortical recruitment in Huntington's disease using a Simon task. Neuropsychologia 2007;45:1791-800