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5th Plenary Meeting

EHHDN 2008
Lisboa

5th to 6th September

FIL Meeting Centre

Centro de Reuniões da FIL
**Thursday 4th September**

16.00–22.00 Registration

**Friday 5th September**

9.00–9.10 Welcome and introduction
G Bernhard Landwehrmeyer (Ulm, Germany)
Joaquim Ferreira (Lisbon, Portugal)
Bea De Schepper (Moerbeke-Waas, Belgium)

**Plenary session I: Hot Topics**
9.10–9.30 HD pathology in non-CNS tissue
Maria Björkqvist (Lund, Sweden)
Gillian Bates (London, UK)

9.30–9.50 Tracking progression of HD—does imaging help?
Jan Kassubeck (Ulm, Germany)
Edward Wild (London, UK)

9.50–10.10 Cell replacement therapy
Anne Rosser (Cardiff, UK)
Stephen Dunnett (Cardiff, UK)

10.10–10.30 Coping strategies
Katherine Moser (New York, USA)
G Bernhard Landwehrmeyer (Ulm, Germany)

10.30–11.00 Tea/coffee break

**Plenary session II: Working Group Summaries**
11.00–12.30 Presentation from each working group to entice participants to visit the working group “booths” (5 min each)

12.30–13.30 Buffet-style lunch

**Session I: Working Group Sessions**
12.30–16.00 Concurrent working group sessions in the form of convention centre-style booths (with seating)

16.00–16.30 Tea/coffee break

**Plenary session III: Keynote Presentation**
16.30–17.30 Molecular approaches to dissecting the pathogenesis of Huntington’s disease
Paul Muchowski (San Francisco, USA)

**Session II: Poster viewing (optional)**
18.00–24.00 Poster viewing
19.00–20.00 Buffet-style dinner
18.00–24.00 Bar

**Saturday 6th September**

**Plenary session IV: Presentations of Endorsed Projects**
9.00–9.20 Overview of submission and review process—summary of endorsed projects
Anne Rosser (Cardiff, UK)

10.30–11.50 Presentations of EHDN endorsed projects

11.15–11.45 Tea/coffee break

**Plenary session V: Business Meeting**
Raymund A C Roos (Leiden, The Netherlands)
- Network
- Workshops and working groups
- Registry
- Biosamples
- What is new on the web pages?
- Activities planned for 2009

12.30–13.00 Results of the election of new members of the Executive Committee

13.00–14.00 Poster viewing

13.00–14.00 Buffet-style lunch

**Plenary session VI: Scientific Presentations**

**Pathogenic mechanisms**
14.00–14.15 Increased activity of the hypothalamic-adrenal-axis in early-stage Huntington’s disease patients
Ahmad Aziz (Leiden, The Netherlands)

14.15–14.30 Disentangling molecular interaction networks for chorea Huntington
Matthias Futschik (Berlin, Germany)

**Experimental therapeutics (preclinical)**
14.30–14.45 Genetic knock-down of HDAC4 improves motor impairment in the R6/2 mouse model of Huntington’s disease
Gillian Bates (London, UK)

**Genetic aspects and testing**
14.45–15.00 Intermediate alleles for Huntington disease: patient understanding and current genetic counselling practices
Alicia Semaka (Vancouver, Canada)

15.00–15.15 Huntington’s Disease and Huntington-like phenotype: 10 years of local molecular diagnostic experience
Claudia Santos (Porto, Portugal)

**Clinical care and management**
15.15–15.30 Impact of Huntington’s disease on quality of life: a qualitative study
Mevhibe Hocaoglu (Reading, UK)

**Clinical characteristics and biomarkers**
15.30–15.45 Pain in Huntington’s disease
Marina de Tommaso (Bari, Italy)

15.45–16.00 Disturbed “motor resonance” at the basis of the emotion recognition deficit in Huntington’s disease? An EMG investigation
Iris Trinkler (Paris, France)

16.00–16.30 Tea/coffee break

**Plenary session VII: Keynote Presentation**
16.30–17.15 Keynote speaker: Update on CHDI Huntington’s disease therapeutics programme
Robert Pacifici (CHDI, Los Angeles, USA)

17.15–17.30 Poster awards and closing remarks
G Bernhard Landwehrmeyer (Ulm, Germany)

**EHDN plenary dinner**
Convento Do Beato, Lisbon

**Sunday 7th September**

**Social activities**
11.00 Colinas tour. Start at: Praça do Comércio
11.00 Olissippo tour. Start at: Praça do Comércio
A Pathogenic mechanisms

A.1 DISENTANGLING MOLECULAR INTERACTION NETWORKS FOR CHOREA HUNTINGTON

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Background: Although chorea Huntington is a classic Mendelian disease following dominant inheritance pattern, strong interindividual variability in the disease progression suggests the existence of biological modifiers that could provide novel therapeutic targets.

Aims: Our approach is directed towards the detection of novel disease modifiers and consolidation of the numerous seemingly unrelated molecular changes observed during chorea Huntington progression.

Methods: A htt-focused protein interaction network was constructed to capture the molecular context of Huntington. For the identification of modifiers, a novel multi-level prioritisation strategy based on complementary information was developed.

Results: Using this network approach, we were able to identify a set of potential modifiers. One of the identified modifiers was subsequently experimentally validated as an important factor for aggregation, neurotoxicity and disease progression in Huntington’s disease models.

Conclusions: Our study demonstrates that network approaches can greatly facilitate the elucidation of the molecular mechanisms underlying chorea Huntington.

A.2 LOSS OF HUNTINGTIN INTERACTING PROTEIN HIP14 IN VIVO RECAPITULATES FEATURES OF HUNTINGTON’S DISEASE

RR Singaraja, A Milnerwood, K Huang, AL Huisse, L Raymon, M Hayden.
The Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, Canada; Department of Psychiatry and Brain Research Centre, University of British Columbia, Vancouver, Canada

HIP14 (ZDHHC17) is a mammalian palmitoyl transferase that interacts less robustly with mutant polyglutamine expanded htt compared with wild type (wt). As a result, the palmitoylation of mutant htt is significantly reduced. If altered palmitoylation of mutant htt by HIP14 is crucial in the pathogenesis of Huntington’s disease (HD), HIP14+/− mice might be expected to display a phenotype similar to HD. Indeed, HIP14+/− mice displayed many similar features to the HD phenotype in YAC128 htt transgenic mice. These included a significant and specific decrease in striatal volume (wt: 13.5 ± 0.7, HIP14+/--; 11.2 ± 0.8 mm³, n = 7, p = 0.001), decreases in striatal neuronal counts (wt: 17.6 ± 1.2 × 10⁶, HIP 14+/--; 16.2 ± 1.4 × 10⁶, n = 7, p = 0.08) and size. In addition, HIP14+/− mice were defective in tests of motor coordination such as fixed and accelerating rotarod and swim speed. The mice also showed reduced sensorimotor gating as assessed by prepulse inhibition, all defects observed in the YAC128 HD mice. In addition, HIP14+/− mice displayed reduced corticostriatal transmission and significantly decreased presynaptic probability of release.

In contrast to YAC mice, an earlier, more severe phenotype was observed in the HIP14+/− mice, with specific striatal volume loss at 1 month rather than at 8 months in the YAC128 mice. In addition to htt, HIP14 palmitoylates several other proteins involved in synaptic function. One possibility for the enhanced phenotype is altered palmitoylation of other neuronal proteins identified as substrates of HIP14. Indeed, palmitoylation of post-synaptic proteins PSD95 and GluR1 and the presynaptic protein SNAP25 are reduced in HIP14+/− brains and localisation of both PSD95 and GluR1 are altered in striatal neurons isolated from HIP14+/− mice.

Palmitoylation of proteins is essential for their trafficking to and turnover at specific plasma membrane sites. Altered localisation and turnover of glutamate receptors caused by aberrant palmitoylation may thus underlie the striatal loss in HIP14+/− mice. The similarity in phenotype between HIP14+/− and HD mice indicates that palmitoylation may play an essential role in the excitotoxic cell death pathway in HD.

A.3 PROTEIN–PROTEIN INTERACTIONS IN POLY-Q DISEASE MODEL

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Background: In disease models for Huntington’s disease, modified Huntington (Htt) exon 1 with extended poly-Q stretches may confer neuroprotection under certain conditions. This may be due to conformational changes in Htt, exposure of the proline-rich region and changed protein–protein interactions, but the mechanism of this interesting phenomenon is not understood.

Aims: The aim of this project is to map the molecular details of these changed protein–protein interactions. We will investigate the difference in conformation between wild-type (wt) Htt and mutant variants and interactions with other proteins and wt and mutant Htt, especially with two chaperone heat shock proteins, which recently were found to be efficient suppressors of Htt aggregation.

Methods: We will use purified recombinant proteins and a combination of chemical crosslinking and mass spectrometry, a method recently developed by us. Nuclear magnetic resonance, electron microscopy and x-ray crystallography will also be used.

Results: The approach with chemical crosslinking and mass spectrometric mapping of crosslinked peptides for protein–protein interaction studies has been developed using a model system. Protein–protein interactions have been analysed within an oligomeric heat shock protein, Hsp21, and between Hsp21 and various substrate proteins in need of being protected from aggregation. We have verified previously suggested interactions between the subunit–subunit interfaces within the Hsp21 oligomer as a proof-of-principle of our experimental approach. Moreover, our data show that the Hsp21 monomer subunit interfaces become substrate binding surfaces upon oligomer disassembly.

Conclusion: Our approach will be useful for gaining insight into protein–protein interactions between Htt and suppressors of Htt aggregation.

A.4 ACTIVATION OF CASPASE-6 IS AN EARLY EVENT IN ACUTE AND CHRONIC MODELS OF HUNTINGTON'S DISEASE

RK Graham, Y Deng, K Vaid, N Bassado, Z Murphy, L Wang, MR Hayden. Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, Child and Family Research Institute, University of British Columbia, 521 West 28th Avenue, Vancouver, BC V6Z 4H4, Canada

Background: The characterisation of YAC mice expressing caspase-6-resistant (C6R) mutant huntingtin highlights proteolysis of htt at the S966aa caspase-6 (C6) site as a key mechanism and implicates activation of C6 as an early event in the pathogenesis of Huntington’s disease (HD). The aim of this study was to determine...
We demonstrate a significant increase in C6 activity and cell death in primary striatal neurons expressing mhtt post-N-methyl-D-aspartate treatment compared with untreated neurons. Pretreatment with a C6 inhibitor before N-methyl-D-aspartate rescues the cell death observed. In order to determine the time course of C6 activation in vivo we performed a natural history characterisation of C6 in wild-type (wt), YAC128 and C6R brain. Immunohistochemical analysis of wt brain demonstrates that the activation of C6 occurs predominantly in striatal neurons commencing at 9 months with an increase at 18 months. In contrast, striatal neurons in YAC128 brain display activation of C6 by 3 months, with levels increasing with age. Low levels of activated C6 are observed at 3 months in C6R striatum; however, levels remain constant with age. Assessment of C6 activity levels, using fluorogenic activity assays, confirms the immunohistochemical findings and demonstrates increased C6 activity in YAC128 versus wt striatum at 3 months (**p<0.01). In contrast, whereas cortical C6 activity is not increased in YAC128 at 3 months, by 12 months C6 activity is increased in YAC128 cortex compared with control (p<0.05). In human brain tissue, increased levels of activated C6 are observed in presymptomatic and early grade HD striatum (**p<0.01) and grade 3-4 HD cortex (**p<0.01) compared with control brain.

Conclusion: These data further support the hypothesis that C6 is the protease responsible for the cleavage of htt at aa886 and demonstrate that activation of C6 is an early marker of neuronal dysfunction in the YAC128 model of HD.

A5 DECREASING MUTATED HUNTINGTIN AGGREGATION AND TOXICITY BY OVEREXPRESSING MOLecULAR CHAPERONES OF THE DNAJ AND HSPB FAMILIES

S Carra, ML Vos, J Hageman, HJ Kampinga. University Medical Center Groningen, A Deusinglaan 1, 9713 AV Groningen, The Netherlands

Background: Molecular chaperones (HspB, HspA and DNAJ families) together with degradation systems (proteasome and autophagy) allow cells to cope with misfolded and genetically mutated proteins. Some molecular chaperones have been shown to protect against protein aggregation and toxicity in polyglutamine (polyQ) diseases, but effectiveness in vivo has remained limited so far.

Aims: We screened the chaperone activity of the small Hsp (HspB) and Hsp70 (HspA)/Hsp40 (DNAJ) family members in order to identify the most potent suppressors of polyQ aggregation and toxicity. We next focused on similarities and diversities in their mechanism of action.

Methods/Techniques: Chaperone activity was tested in mammalian cell cultures using the filter trap assay technique and using in-vivo models of Huntington’s disease (Xenopus) or SCA3 disease (Drosophila melanogaster).

Results/Outcome: Among the HspB family, we identified three members able to reduce polyQ aggregation, namely HspB7, HspB8 and HspB9. HspB8 works in concert with the co-chaperone Bag3 and stimulates autophagy, thus facilitating mutated huntingtin degradation. HspB7 is highly efficient in decreasing the aggregation rate of both short (43Q and 74Q) and long-length huntingtin (119Q). However, the mechanism is still unknown. HspB9 is mainly active on short-length polyQ proteins, by targeting them to the proteasome. Among the DNAJ family, a subfamily of the DNAJ chaperones, in particular DNAJ6 and DNAJ8 show the strongest chaperone activity against both short and long-length polyQ proteins. These chaperones appear to be regulated by (de)acetylation and to prevent aggregation as oligomeric complexes for which interaction with HspA is not required. Subsequent proteasomal degradation of DnaJ6 or DnaJ8-associated polyQ proteins, however, does rely on interaction with HspA members.

Conclusions: We identified several molecular chaperones that decrease polyQ aggregation by different mechanisms. The combined stimulation of these chaperones may act synergistically in clearing disease-associated proteins.

A5 EFFECTS OF PARKIN DEFICIENCY ON MUTANT HUNTINGTIN IN MICE

1. J Rubio, JÁ Rodriguez, C Tomas, C Ruiz, NA Casaniga, J Perucio, A Gómez, I Rodol, JU Lucas, M Angeles Mena, J García de Vélez. 1 Servicio de Neurología, Hospital Ramón y Cajal, Ctra de Colmenar Viejo Km 9,1, 28034 Madrid, Spain; 2 Laboratorio de Neurofarmacología, Hospital Ramón y Cajal, Ctra de Colmenar Viejo Km 9,1, 28034 Madrid, Spain; 3 Centro de Biología Molecular Severo Ochoa, USICOM, 28049 Madrid, Spain.

Huntington’s disease (HD) is a neurodegenerative disorder caused by an increased expansion of polyglutamines in huntingtin, a protein that aggregates in the brain of patients with HD and in mice models of the disease. We investigated whether additional stress to the ubiquitin proteasomal system by partial suppression of the E6 ligase, parkin, changes disease severity. We crossed R6/1 mice with homozygous parkin null mice and produced four kinds of mice: HD+/−, HD+/-/PK+/-, wild type (wt) and PK+−/− and HD+−/−/PK+−/− mice. Both HD+−/−/PK+−/− mice had abnormal behaviour, worse in the double mutant actitrack, labyrinth and length of stride.

HD+−/− and HD+−/−/PK+−/− mice had decreased levels of monoamines and their metabolites in comparison with wt and PK+−/− mice. The levels of reduced glutathione were increased in HD+−/− and slightly more in the striatum of HD+−/−/PK+−/− mice. HD−/− and HD−/−/PK−/− mice had increased levels of apoptosis in the striatum, slightly greater in the double mutants. Huntington inclusions were present in HD+−/− and HD+−/−/PK+−/− mice, less abundant in the double mutants. No differences were present in other regions.

Our data suggest that the suppression of parkin increases the pathogenic effects of mutant huntingtin more in the striatum than in other brain areas. Malfunction of the ubiquitin proteasomal system by mutant huntingtin appears as an additional but not critical mechanism of its toxicity.

A7 THE USE OF QUANTITATIVE REAL-TIME PCR TO CHARACTERISE TRANSCRIPTIONAL DYSREGULATION IN MOUSE MODELS OF HUNTINGTON’S DISEASE

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Background: Transcriptional dysregulation is a central pathogenic mechanism in Huntington’s disease (HD) and mouse models recapitulate the transcriptional changes that occur in the human disease. Quantitative real-time PCR (QPCR) assays that measure the transcript levels of genes for which transcriptional dysregulation is well established in HD could be used as biomarkers of disease progression in preclinical efficacy trials.

Aims: To establish a robust and accurate QPCR procedure using suitable reference genes that may be used to identify changes in gene expression in the R6/2 HD mouse model. To establish a test set of genes that can be used for preclinical assessment.

Methods: Reverse transcriptase QPCR and 2−ΔΔCt analysis was used to determine a set of reference and target genes for the cerebellum, cortex and striatum that identify expression changes in the R6/2 model compared with wild-type controls over time.

Results: Suitable housekeeping genes were ascertained for each region using the GeNorm software. These were used as reference genes for the normalisation of genes of interest. For each of the three brain regions a set of genes was identified that showed...
transcriptional dysregulation. The gene expression was then characterised at 2, 4, 8, 12 and 15 weeks, showing that genes become increasingly dysregulated in the older R6/2 mice.

**Conclusions:** Reliable normalisation using appropriate housekeeping genes is essential for the detection of gene-specific variation using QPCR. Transcriptional profiles alter according to brain region over time and therefore have the potential to be used as biomarkers for the progression of HD.

**Funding:** This study received financial support from the Wellcome Trust, CHDI Foundation.

**A.8 A LARGE NUMBER OF PROTEIN EXPRESSION CHANGES IN A MOUSE MODEL OF HUNTINGTON’S DISEASE EARLY IN LIFE PRECEDE OVERT DISEASE SYMPTOMS**

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2 Max-Delbrueck Center for Molecular Medicine, Molecular Cardiovascular Research, Berlin, Germany; 
3 Fred Hutchinson Cancer Research Center, Division of Clinical Research, Seattle, Washington, USA; 
4 Ecole Polytechnique Fédérale de Lausanne, Laboratory of Functional Neurogenomics, Lausanne, Switzerland

**Background:** Huntington’s disease (HD) is fatal in humans within 15 to 20 years of symptomatic disease. Although late-stage HD has been studied extensively, data on protein expression early and during disease progression are scarce. In this study, we used a large 2-D gel/mass spectrometry-based proteomics approach to investigate HD-induced protein expression alterations and their kinetics at early ages and during the course of the disease.

**Aims:** Early protein changes and their progression in HD were studied.

**Results and Outcome:** The murine HD model R6/2 was investigated at 2, 4, 6, 8 and 12 weeks of age, corresponding to absent, early, intermediate and late-stage HD. Unexpectedly, there were mostly HD stage-specific protein changes (71%–91%) and a drastic alteration (6% of the proteome) in protein expression as early as 2 weeks of age. Early changes included mainly upregulation of glycolysis/glucogenesis and downregulation of actin-skeleton. This suggests a period of highly variable protein expression that precedes the visible HD phenotype. Whereas an upregulation of glycolysis/glucogenesis-related protein alterations remained dominant during HD progression, late-stage alterations at 12 weeks showed an upregulation of proteins having proteasomal function. The early changes coincide with a peak in protein alteration during normal mouse development at 2 weeks of age. Co-regulation between altered messenger RNA and protein expression is always below 30%, although 88% of the altered proteins were represented by mRNA.

**Conclusions:** Our observations suggest that HD is characterised by a highly dynamic disease pathology not represented by linear protein concentration alterations over the course of the disease.

**A.9 NRF2-RELATED OXIDATIVE STRESS RESPONSE AND IMPAIRED DOPAMINE BIOSYNTHESIS IN A PC12 CELL MODEL OF HUNTINGTON’S DISEASE**

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**Background:** Huntington’s disease (HD) is a devastating disease for which currently no therapy is available. It is a progressive autosomal dominant neurodegenerative disorder that is caused by a CAG repeat expansion in the HD gene, resulting in an expansion of polyglutamines at the N-terminal end of the encoded protein, designated huntingtin, and the accumulation of cytoplasmic and nuclear aggregates. Not only is there a loss of normal huntingtin function, upon expansion of the CAG repeat there is also a gain of toxic function of the huntingtin protein and this affects a wide range of cellular processes.

**Aims:** To identify groups of genes that could play a role in the pathology of HD.

**Methods:** Messenger RNA changes were studied in an inducible PC12 model of HD before and after aggregates became visible.

**Conclusions:** This is the first study to show the involvement of Nrf2-responsive genes in the oxidative stress response in HD. Oxidative stress-related transcripts were altered in expression suggesting a protective response in cells expressing mutant huntingtin at an early stage of cellular pathology. Furthermore, there was a downregulation of catecholamine biosynthesis resulting in lower dopamine levels in culture. Our results further demonstrate an early impairment of transcription, the cytoskeleton, ion channels and receptors. Given the pathogenic impact of oxidative stress and neuroinflammation, the Nrf2-ARE signalling pathway is an attractive therapeutic target for neurodegenerative diseases.

**A.10 IDENTIFICATION AND CHARACTERISATION OF MICROGLIA-SPECIFIC SUPPRESSORS OF MUTANT HUNTINGTIN TOXICITY**

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2 Department of Neurology, University of Washington, Seattle, Washington, USA; 
3 Gladstone Institute of Neurological Diseases, San Francisco, California, USA; 
4 Departments of Biochemistry and Biophysics and Neurology, University of California San Francisco, San Francisco, California, USA

A number of studies have suggested a role for microglia in the onset and progression of Huntington’s disease (HD). We have characterised the enzyme kynurenine-3-monooxygenase (KMO), which is expressed predominantly in microglia in the central nervous system, as a candidate therapeutic target for HD by genetic approaches in yeast and pharmacologically in mammalian cells and in the R6/2 mouse model of HD. These studies suggest a role for microglia in the pathology of HD and also imply that cell autonomous effects of mutant huntingtin (htt) expression in microglia may contribute to HD pathology. Excitingly, recent studies in humans have shown a correlation between microglial activation and HD progression. We are therefore working to identify further microglia-specific therapeutic targets.

We are currently using a yeast model of mutant htt toxicity to screen complementary DNA libraries from unactivated, activated, and primary microglia to identify cDNA capable of suppressing mutant htt toxicity when overexpressed in yeast. We have identified 31 unique mouse cDNA capable of suppressing the toxicity associated with the expression of mutant htt in yeast. Many of these suppressors are associated with processes known to be affected in HD, including autophagy, protein folding, iron metabolism, actin cytoskeleton organisation and energy metabolism. The overexpression of a number of the suppressors has also previously been shown to be beneficial in a number of neurodegenerative disease models. Promising hits are being validated in a microglia–neuron co-culture system. We are also examining the expression patterns of these genes in microglia and other central nervous system cell types. Using these approaches we hope to gain insights into the microglia-specific cellular pathways that contribute to the pathology of HD. The screen may also aid in the identification of processes and specific proteins for therapeutic targeting in microglia and other cell types.
A NOVEL PATHOGENIC PATHWAY OF IMMUNE ACTIVATION DETECTABLE BEFORE CLINICAL ONSET IN HUNTINGTON’S DISEASE

1EU Wild, 2M Björkqvist, 3J Theile, 4A Silvestrini, 5R Andre, 6N Lahiri, 7E Rabion, 8RV Lee, 9CL Benn, 10D Soulet, 11A Magnusson, 12B Woodman, 13D Landl. 1Department of Neurodegenerative Diseases, Institute of Neurology, Queen Square, London, UK; 2Neuronal Survival Unit, Department of Experimental Medical Science, Wallenberg Neuroscience Center, Lund University, Lund, Sweden; 3Department of Medical Genetics and Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, University of British Columbia, Vancouver, Canada; 4Department of Neurology, School of Medicine, University of Washington, Seattle, Washington, USA; 5Department of Medical and Molecular Genetics, Kings College London School of Medicine, Guys Hospital, London, London, UK; 6Department of Haematology, Royal Free and University College Hospital (Hamstead Campus), London, UK.

Background: Huntington’s disease (HD) can cause several abnormalities outside the central nervous system. We previously demonstrated evidence of immune activation in peripheral plasma in manifest HD using proteomic profiling, but the nature of the immune activation in HD remains incompletely explored.

Aims and Methods: To investigate inflammatory activation in HD, we used multiplex ELISA to quantify levels of key inflammatory and immunomodulatory molecules in human plasma and serum from three different mouse models of HD. We used quantitative real-time PCR to examine huntingtin expression in HD monocytes and cytokines in HD striatum and performed functional studies of HD monocytes, macrophages and microglia.

Results: We found widespread evidence of innate immune activation detectable in plasma throughout the course of HD. IL-6 levels were increased in HD gene carriers with a mean of 16 years before the predicted onset of clinical manifestations. To our knowledge, this is the earliest plasma abnormality identified in HD. Monocytes from HD patients expressed mutant huntingtin and were pathologically hyperactive in response to stimulation, suggesting that the mutant protein triggers a cell-autonomous immune activation. A similar pattern was seen in macrophages and microglia from HD mouse models and the cerebrospinal fluid and striatum of HD patients exhibited abnormal immune activation, suggesting that immune dysfunction plays a role in brain pathology.

Conclusions: Together our data suggest parallel central nervous system and peripheral pathogenic pathways of immune activation in HD.

A MAPPING MOLECULAR CHANGES IN HUNTINGTON’S DISEASE BRAIN

N Stoy, Royal Hospital for Neurodiability, West Hill, Putney, London SW15 3SW, UK

With personal interests in systems biology and immunology, I shall attempt with this poster to map the various network connections/signalling pathways of at least some of the bioactive molecules that contribute either to neurodegeneration (nerve cell death) or to neuroprotection (nerve cell survival) in Huntington’s disease (HD). In addition, HD appears to be a useful paradigm, or blueprint, for understanding the complex processes involved in other neurodegenerative conditions, such as Alzheimer’s disease and Parkinson’s disease. All three of these conditions exhibit neuroinflammation, a term that describes the effects on nerve cells of changes in the activation status of immune system cells present in the brain, notably microglia. Neuroinflammation is set off by definite trigger factors and this raises the question as to whether “classic” immune responses are generated in the brain in HD, as is clearly the case in multiple sclerosis. Some advantages of trying to build network models of HD are: (1) that it has a known single abnormal gene starting point; (2) there are good animal models of the disease; (3) at any one time, the “system” (illness), although very complicated, is essentially in a (pseudo)steady state and (4) it might provide one way of exploring the question: “What are the immunological consequences of HD—and do they matter?”

HUNTINGTON’S DISEASE-RELATED MITOCHONDRIAL TOXINS AFFECT THE IMMUNOLOGICAL PROFILE OF MICROGLIAL CELLS

A Witting, University of Ulm, Helmholtzstrasse 8/1, 89081 Ulm, Germany

Background: Mitochondrial dysfunction and microglia activation are both integral parts of Huntington’s disease (HD). Mitochondrial toxins such as 3-nitropropionic acid (3-NP) and malonate induce HD-like degeneration in animals. These toxins are as well as mutant huntingtin affect not only neurons but also microglia. Metabolic regulation and inflammatory responses are highly integrated and interdependent. The specific hypothesis is that mitochondrial alterations induced by toxins or mutant huntingtin in microglial cells change their immunological profile with detrimental consequences for the diseased brain.

Aim: We will investigate the effect of mitochondrial toxins on the immunological profile of microglial cells.

Methods: We incubated primary mouse microglia with the mitochondrial toxins 3-NP and malonate and investigated the effect of the mitochondrial toxins on cell viability (LDH assay) and mitochondrial respiratory chain activity (WST-1). To investigate the effect of mitochondrial toxins on the classic activation of microglial cells we stimulated microglial cells together with the toxins with 1 µg/ml lipopolysaccharide and/or 100 U IFN-γ. The amount of TNF-α, IL-1β, IL-6 and glutamate was quantified in the supernatant and/or in the cells after overnight incubation with adequate assays, as described in the manuals. An alternative activation was induced by stimulation with 10 ng/ml IL-4 for 24 h. The amount of cytokines was quantified as described.

Results: Mitochondrial toxins induce a time and dose-dependent decrease in mitochondrial respiratory chain activity, subsequent cell death. The mitochondrial toxins changed the amount of classic and alternative induced release of cytokines and glutamate.

Conclusion: Our results show that changes in the mitochondrial respiratory chain activity can influence the immunological profile of microglial cells.

DISTRIBUTION OF POLYGLUTAMINE INCLUSIONS IN NON-CENTRAL NERVOUS SYSTEM TISSUE IN THE HDHQ150 KNOCK-IN MOUSE MODEL OF HUNTINGTON’S DISEASE

1H Muffitt, 2C Hobbs, 3B Woodman, 4G Bates. King’s College, London School of Medicine, Guy’s Hospital, London SE1 9RT, UK; 5Centre for Age-Related Disease, King’s College London, Guy’s Hospital, London SE1 1UL, UK.

Background: We have previously conducted a phenotypic comparison of the R6/2 and HdhQ150 knock-in Huntington’s disease (HD) mouse models. We found that when CAG repeat size, strain background and stage of disease are comparable both models develop similar widespread phenotypes. The distribution of polyglutamine aggregates throughout the central nervous system (CNS) was ubiquitous in both models.

Aim: To determine whether the polyglutamine aggregates are present in non-CNS tissues of the HdhQ150 mice and if so to compare the distribution in peripheral tissues with that previously established for R6/2 mice.

Methods: 22-month-old HdhQ150 homozygous knock-in and wild-type control mice were perfused with 4% paraformaldehyde. Organs and tissue samples were removed and processed for immunohistochemistry. Wax sections were immunoperoxidase stained with huntingtin antibody S830, counterstained with the nuclear stain methyl green and examined under the light microscope for the presence of huntingtin inclusions.

Distribution of polyglutamine inclusions in non-CNS tissues of the HdhQ150 knock-in mouse model of Huntington’s disease.
Inclusions have been identified in the following peripheral organs in HdG150 knock-in mice: skeletal muscle, adrenal glands, liver, pancreas, kidney, the myenteric plexus and Messner's plexus. This is similar to the pattern of aggregate distribution that we previously described in R6/2 mice.

Conclusions: The presence of inclusions in non-CNS tissues of R6/2 mice has not occurred because these mice express an N-terminal fragment of huntingtin as they are also present in the HdhG150 knock-in model. It is not known whether a similar pathology occurs in the human disease but it would be expected to be a feature of childhood onset HD caused by large CAG expansions.

Funding: This study was supported by the Wellcome Trust and Medical Research Council.

A.15 EXPRESSION OF WILD-TYPE HUNTINGTIN IN PORCINE TESTICULAR GERM CELLS

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Background: Huntington's disease (HD) is a fatal dominantly inherited neurodegenerative disease caused by expansion of the polyCAG stretch in the gene coding ubiquitous huntingtin protein (htt). Despite the ubiquitous presence of the HD gene in a variety of organs/tissues, the HD-associated pathology is predominantly expressed in specific brain regions. In addition, more recent data indicate that the mutated htt can be linked directly with a progressive degeneration of germinal epithelium in the testes. DAZL (deleted in azoospermia-like) is an autosomal gene from the DAZ gene family that plays an important role in germ cell development. The absence of DAZL is manifested by a lack of germ cells with similar pattern to the testicular degeneration observed in HD.

Aims: The aim of this study was to characterise the expression of wild-type htt in the porcine testicular tissue and to develop a readily accessible in-vivo assay (in addition to brain neuronal pathology), which would have a predictable value in defining the stages of HD progression.

Methods: Tissue expression of htt was measured by Western blotting and coupled with immunofluorescence staining of paraformaldehyde-fixed frozen sections prepared from porcine testes using anti-htt (mouse monoclonal (HDA3E10) to Huntingtin, Abcam) and anti-DAZL (rabbit polyclonal to DAZL, Abcam) primary antibodies.

Results: Western blot analysis revealed htt expression in the testes. Immunofluorescence staining confirms a co-localisation of DAZL and wild-type huntingtin. In addition to the expression in the testes, the htt protein was measured in the cortex by Western blot.

Conclusions: Our preliminary data proved the physiological co-localisation of htt and DAZL in germinial epithelium. This indicates that the expression of mutated htt in DAZL+ in germinial epithelium can play a key role in the testicular degeneration seen in HD patients and can have prognostic value in characterising the stages of HD.

A.16 GENERATION AND EXPRESSION CHARACTERISATION OF BAC-HD TRANSGENIC RATS WITH FULL-LENGTH MUTANT HUNTINGTIN

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Our group has previously generated and characterised transgenic rats, which express a fragment of mutant huntingtin (htt), as a model of Huntington's disease (HD) in detail. This rat model mirrors many aspects of HD, but it lacks the full-length mutant htt protein and therefore some aspects of the human condition might be imperfectly replicated. In order to overcome this potential disadvantage, we aim to generate transgenic rats, which express full-length mutant human htt in the same developmental and tissue and cell-specific manner seen in patients with the disease. To achieve this, bacterial artificial chromosomes (BAC) containing human genomic DNA spanning the full-length gene including all regulatory elements are used, which have been successfully integrated in mice by Dr William Yang's laboratory.

We have established one rat line, in which full-length htt expression was detected in all the brain regions at a low level. The processing of the mutant htt and its aggregate formation are screened in this line. To obtain lines that express mutant htt at a higher level and in the brain areas affected in human HD patients, we generated 24 new founders, which show germline transmission by PCR. These founders are analysed for copy number of BAC insertion, integrity of the BAC insertion and quantity of CAG repeats. In F1 transgenic rats of each line the level of RNA and protein expression in their brains will be measured and the number of integration sites will be identified.

A.17 VALIDATION OF CANDIDATE THERAPEUTIC TARGETS FOR HUNTINGTON’S DISEASE IN DROSOPHILA

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We recently identified 28 gene deletions that suppress toxicity of a mutant huntingtin (htt) fragment in a yeast model of Huntington’s disease (HD). Here we describe work validating a subset of these loss-of-function suppressors that have human homologues using a drosophila model of HD. In our experiments, we are directing mutant htt exon 1 95Q transgene expression both temporally and spatially via three promoters: (1) elav—which directs expression in most neurons; (2) gmr—which drives expression in all cells of the eye, including neurons and supporting cells and (3) tim—which is expressed in circadian clock neurons. The suppressors are being tested either via known loss-of-function alleles or using RNAi transgenic fly lines from the Vienna Drosophila RNAi Center. One of these suppressors being tested encodes the fly homologue of the mammalian enzyme kynurenine 3-monooxygenase (KMO). We have validated our initial yeast work pharmacologically in both mammalian cells and in the R6/2 mouse model of HD, making KMO a promising candidate therapeutic target for this disease. Here we report that a loss-of-function allele of the drosophila Kmo homologue, cinnamon (cn5), significantly enhances the number of rhabdomeres (eye photoreceptors) in Htt93Q cn5 individuals compared with Htt93Q expressing control flies, which suffer extensive eye degeneration. This work provides the first genetic evidence that inhibition of KMO function is neuroprotective in an animal model of HD and supports the notion of validating yeast candidate therapeutic targets in drosophila.

In addition to previously used metrics, we are studying behavioural phenotypes in HD model flies, such as circadian locomotor rhythms and visual tracking. We have examined circadian behaviour of the HD model flies that have been aged for several days, in light–dark cycles and constant darkness. We have observed that pan-neuronal expression of htt using the elav promoter led to reduced levels of locomotor behaviour in the flies and an impaired ability to synchronise to light–dark cycles. These behavioural characteristics represent sensitive and novel metrics for assaying the suppression of mutant htt-dependent toxicity. We are also measuring visual tracking using the fly’s optomotor responses, a simple measure of the fly’s ability to maintain its orientation to a moving visual field. Our initial results suggest that this approach will reinforce and extend that from the anatomical analyses. In
summary, we have found novel behavioural phenotypes in HD model flies that will serve as sensitive metrics for validating genetic modifiers of mutant htt toxicity identified in yeast.

A.18 THE PATHOGENIC MECHANISM OF HUNTINGTON’S DISEASE-LIKE 2 MAY INVOLVE HAPLOINSUFFICIENCY OF JUNCTOPHILIN-3

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Background: Huntington’s disease-like 2 (HDL2) is a progressive, late-onset autosomal dominant neurodegenerative disease that is clinically and pathologically very similar to Huntington’s disease (HD). HDL2 is caused by a CTG/CAG expansion in junctophilin-3 (JPH3), a gene involved in the regulation of neuronal calcium flux. HDL2 patient brains show cortical and basal ganglia degeneration, with neuronal intranuclear protein inclusions resembling those detected in HD brain and intranuclear RNA foci containing the JPH3 transcript, similar to those observed in myotonic dystrophy. Overexpression of JPH3 exon 2A RNA with a long CUG repeat in cell culture leads to the formation of RNA inclusions and toxicity, further evidence that RNA toxicity may contribute to HDL2 pathogenesis. In addition, the sequestration of unprocessed JPH3 transcripts into foci suggests that perhaps less JPH3 transcript and/or protein are present in neurons, consistent with a loss-of-function model.

Aim: To determine if loss of JPH3 expression contributes to HDL2 pathogenesis.

Methods: We extracted RNA and protein from HDL2 postmortem brains and assessed JPH3 RNA and protein levels by real-time PCR and Western blot, respectively. We also examined the motor function of junctophilin-3 knockout mice.

Results: We detected a significant loss of JPH3 transcript and protein in the cortex of postmortem HDL2 brains, possibly because the unprocessed transcripts are sequestered into foci. Furthermore, analysis of the jph3 knockout mice revealed that the null model exhibits a progressive motor phenotype and the heterozygous model presents a milder phenotype.

Conclusions: The data reported here provide strong preliminary evidence that loss of JPH3 expression contributes to HDL2 pathogenesis. Taken together with our previous evidence that JPH3 with an expanded repeat results in the transcription of toxic RNA, we propose a model in which HDL2 pathogenesis is the result of both gain and loss-of-function mechanisms. This model provides insights into possible mechanisms that may be common among HD and HD-like disorders.

A.19 MOLECULAR APPROACHES TO DISSECTING THE PATHOGENESIS OF HUNTINGTON’S DISEASE

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Background: Huntington’s disease (HD) is a fatal neurodegenerative disorder that is caused by an expansion of a polyglutamine (polyQ) tract in the protein huntingtin (htt), which leads to its aggregation in nuclear and cytoplasmic inclusion bodies. The misfolding of polyQ in htt into a toxic structure(s) is thought to underlie pathogenesis in HD.

Aims: Our laboratory utilises a broad array of molecular approaches in our efforts to understand how misfolded htt mediates pathogenesis, including structural analyses of misfolded proteins and their assembly into aggregates using atomic force microscopy, yeast genetic and chemical-genetic screens to identify proteins and small molecules that modulate aggregation and toxicity of mutant htt, and molecular genetic and pharmacological approaches in cellular and animal models of HD.

Results: We have recently made major progress in three areas. First, we have found that molecular chaperones may prevent toxicity of abnormal htt conformations by reducing levels of potentially toxic aggregation intermediates. Second, using genome-wide screening approaches in yeast, we have discovered novel sets of genes that are crucial for mutant htt toxicity. Finally, we have found that a reduction in the brain levels of the toxic kynurenine pathway (KP) metabolites 3-hydroxykynurenine and quinolinic acid ameliorates pathophysiology in an in-vivo model of HD.

Conclusions: Our results provide additional evidence that genetic screens in model organisms can successfully identify disease-modifying pathways that are conserved in lower and higher eukaryotes. Furthermore, our findings strongly implicate microglia and KP-mediated excitotoxicity in HD. Finally, the novel KP inhibitors we have generated may facilitate testing of the clinical relevance of this excitotoxic pathway in HD patients.
B Experimental therapeutics: preclinical

B.1 MAGNETIC RESONANCE IMAGING: PRE-MANIFEST HUMAN HUNTINGTON’S DISEASE AND POTENTIAL FOR PRECLINICAL THERAPEUTIC TRIALS IN HUNTINGTON’S DISEASE MOUSE MODELS

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Background: Magnetic resonance imaging (MRI) measures may have potential as biomarkers for clinical trials in both premanifest and manifest Huntington’s disease (HD).

Methods and Results: Structural MRI imaging studies at Johns Hopkins in HD indicate that striatal volumes begin to atrophy at least 11–12 years before expected onset and then continue to shrink predictably with disease course—and may prove a marker with greater power than motor ratings to detect change. Data from the PREDICT-HD study are corroborating and extending these findings. We have also found changes in functional MRI and DTI measures, which may begin even before detectable volumetric changes. Validation as outcome measures for clinical trials will require a demonstration that they change with treatment. We have therefore begun detailed MRI studies in several HD mouse models in which we are conducting treatment trials. Using T2-weighted MRI scans combined with large deformation diffeomorphic mapping, significant brain atrophy was present as early as 4 weeks of age in R6/2 mice and then continued in parallel with motor behavioural deficits. Striatum and cortex changes correlate best with motor changes. These studies suggest that R6/2 mice develop brain atrophy and behavioural changes very early, so that it may be difficult to study alterations in disease onset in this model. Preliminary studies in N171-2Q mice indicate that there is little or no significant brain regional atrophy at 6 weeks, but progressive atrophy after that. Our data suggest that N171-2Q mice might make it possible to track both the onset and progression of disease by MRI. Therapeutic trials in both R6/2 and N171-2Q mice are in progress.

Conclusions: MRI measures may thus have potential as biomarkers for preclinical mouse and both premanifest and manifest human clinical trials for HD.

B.2 COQ10 ANALOGUES TARGETING MITOCOCHONDRIAL IMPAIRMENT IN HUNTINGTON’S DISEASE

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Background: Edison’s drug development programme in Huntington’s disease (HD) is focused on developing a CoQ10 analogue targeting the purported mitochondrial impairment in HD. The observations underpinning the logic for the programme include: (1) positive correlation of CAG-repeat length with impairment in mitochondrial oxidative phosphorylation; (2) the presence of systemic markers of oxidative stress 8-OH dG, guanosine; (3) reduction in central nervous system lactate, a biomarker of anaerobiosis, upon treatment with CoQ10, and subsequent return to baseline on withdrawal of therapy.

Aims: The development of a high-throughput assay reflective of the mitochondrial impairment component of HD. The development of analogues of CoQ10 with improved intrinsic efficacy and increased systemic and central nervous system bioavailability. The development of physiological, metabolic and biochemical indices to guide phase II endpoints.

Methods/Techniques: A primary HD cell line was developed modelling the energy defect observed in HD. Correlations were made with regard to Q-length, used to screen CoQ10 analogues. A library of more than 100 analogues of quinone-based CoQ10 analogues were designed, synthesised and characterised with regards to clogP, redox potential, and biological activity. The measurement of physiological, metabolic and biochemical energy parameters at rest and under gated workloads are underway in HD versus control subjects.

Results/Outcome: A patient-derived primary cell assay has been established that reflects the energy defect in HD and correlates with Q-length. This assay is being deployed to screen and optimise CoQ10 analogues. Over 100 CoQ10 analogues have been screened. EPI-808,583 and EPI-442,983 have been selected as leads with EC50 values of 6 nmol and 15 nmol, respectively. A redox silent CoQ10 analogue is absent in biological activity, demonstrating redox dependency on drug action. The mitochondrial stress test is underway.

Conclusions: EPI-808,583 and EPI-442,983 are being readied for clinical development. Phase II design is pending completion of the mitochondrial stress test, anticipated in Q1, 2009.

Acknowledgement: Edison would like to thank the CHDI Foundation for their support of this work.

B.3 TRANSPPLANTATION OF HUMAN OLFACTOR Y NEUROEPITHELIAL CELLS IN R6/2 MODEL OF HUNTINGTON’S DISEASE

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Background: The olfactory neuroepithelium contains neural stem cells that undergo continual neurogenesis and tissue regeneration. We investigated whether intrastriatal transplantation of human olfactory neuroepithelial cells (ONEC) can rescue the striatal pathology in a transgenic model of Huntington’s disease (HD).

Methods: Human ONEC were cultured from nasal endoscopic biopsy specimens of healthy volunteers and induced into neurosphere-forming cells. In R6/2 transgenic mice, ONEC (0.5 million cells, R6/2-ONEC) or saline (R6/2-control) were transplanted into each bilateral striatum at the age of 5 or 8 weeks. We measured Rotarod performance, body weights, and limb clasping score twice every week and checked the survivals of the mice. Striatal atrophy and ubiquitin-positive nuclear aggregates, as well as the differentiated transplants of transplanted ONEC were measured by stereological methods at the age of 12 weeks.

Results: ONEC transplantation improved Rotarod performance and attenuated the limb clasping phenomenon of R6/2 mice from 8 to 12 weeks of age. The R6/2-ONEC mice showed expanded survival lengths compared with R6/2-control mice. Striatal neuronal loss and ubiquitin-positive huntingtin aggregation were all decreased in the R6/2-ONEC mice. Transplantation of ONEC at the earlier age (5 weeks) showed no difference in efficacy compared with transplantation at 8 weeks. Transplanted cells expressed Nestin, Tuj-1, GABA and GAD, although they showed limited migratory patterns and low cell survival.

Conclusion: Our data suggest that ONEC is a feasible cell source for future cell transplantation therapy for HD patients.

B.4 CASPASES-2 AND 6 AS DRUG TARGETS IN HUNTINGTON’S DISEASE

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Background and Aim: Caspase cleavage of huntingtin (ht) is a crucial event in Huntington’s disease (HD). Mutant htt resistant to cleavage by caspase-6 (C6) does not cause HD in a mouse model (Graham et al., 2006). Other lines of evidence support the role of C6 and also a role for caspase-2 (C2) in HD (Hermel et al., 2004). C2 and C6 are therefore validated drug targets for HD, although no specific small molecule inhibitors currently exist. We have undertaken two different approaches to inhibit caspases relevant to HD.

Methods and Results: First, we have utilised antisense oligonucleotides to reduce C2 and C6 levels in vitro and in vivo. Antisense
oligonucleotides (ASO) provide specificity for individual caspases due to their sequence targeting. In primary neurons ASO reduce C2 (64% reduction, one-way analysis of variance (ANOVA) \( p = 0.0012 \)) and C6 (56% reduction, one-way ANOVA \( p = 0.0166 \)) messenger RNA levels. In vivo caspase ASO are effective centrally when delivered intracerebroventricularly with osmotic pumps. After 4 weeks of intracerebroventricular delivery (25 \( \mu \)g/day), C2 mRNA was reduced 52% (one-way ANOVA \( p = 0.0018 \)) and C6 mRNA was reduced 43% (one-way ANOVA \( p = 0.0007 \)) in the cortex. This knockdown is stable or improved after 4 weeks of drug washout. The knockdown is specific, allowing us to examine the role played by individual caspases in HD pathology both in vitro and in vivo. C2 and C6 ASO are currently being tested in the YAC128 model of HD to determine their efficacy in reducing or eliminating previously validated signs and symptoms of HD.

In parallel we have developed a method suitable for screening for caspase-6 inhibitors. The assay relies on a luminescent signal generated by luciferase after caspase-6 cleavage, which is highly specific for caspase-6, with minimal cleavage by caspase-3 (6%). The method exhibits excellent linearity, signal-to-noise ratios (\( > 300 \)) and Z’ values (\( > 0.7 \)) for a wide range of caspase concentrations in a 384-well format and will be used for high-throughput screening of compound libraries.

**B.5 GENETIC KNOCK-DOWN OF HDAC 4 IMPROVES MOTOR IMPAIRMENT IN THE R6/2 MOUSE MODEL OF HUNTINGTON’S DISEASE**

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**Background:** Transcriptional dysregulation is a central mechanism underlying Huntington’s disease (HD) pathogenesis. We have previously shown that administration of the histone deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA) improves the motor performance of R6/2 mice. However, SAHA is a pan HDAC inhibitor that can inhibit 11 HDAC enzymes, namely: HDAC 1, 2, 3 and 8 (class I), HDAC 4, 5, 7 and 9 (class 2a), HDAC 6 and 10 (class 2b) and HDAC 11 (class IV). The SAHA target important for therapeutic development for HD requires delineation.

**Aims:** To identify the HDAC inhibitor target(s) relevant to HD therapeutic intervention.

**Methods:** We are in the process of conducting a series of genetic crosses to determine whether the genetic knock-down of specific HDAC improves HD-related phenotypes in the R6/2 mouse.

**Results:** We examined the effect of individually knocking down the expression level of HDAC 4, HDAC 5, HDAC 7 and HDAC 9 on the phenotype of the R6/2 mouse. Genetic knock-down of HDAC 5, HDAC 7 and HDAC 9 had no effect on a range of behavioural and molecular outcome measures. In contrast, reduction in HDAC 4 levels led to a pronounced improvement in R6/2 motor impairment as assessed by RotaRod performance. These beneficial effects occurred in the absence of the profound weight loss that occurred upon chronic SAHA administration. Identification of the molecular correlates of the phenotypic improvements is in progress.

**Conclusions:** Genetic reduction of HDAC 4 improves motor performance in the absence of detrimental effects, indicating that it is possible to dissociate the beneficial and toxic effects of SAHA administration.

**Funding:** The Wellcome Trust, CHDI Foundation, Medical Research Foundation.
C Clinical characteristics

C.1 HUNTINGTON’S DISEASE TOOLKIT: META-ANALYSIS PROVIDES BENCHMARKS FOR IDENTIFYING PROMISING INDICATORS OF PROGRESSION IN PREDIAGNOSIS AND EARLY HUNTINGTON’S DISEASE

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Background: Identification of tasks that reliably mark the approaching onset and progression of Huntington’s disease (HD) or the slowing of progression in response to treatment intervention can facilitate the discovery of useful treatment interventions.

Aims: The HD Toolkit meta-analysis provides benchmark effect sizes from well studied tests of neurocognitive function. We use these benchmarks to evaluate effect sizes for tracing and movement to target tasks.

Methods: We compared the effect sizes from published reports of tracing and movement to target tasks to benchmark effect sizes from published reports of four tasks: Stroop, Symbol Digit Modalities Test, Verbal Fluency, and Speeded Tapping. We computed cross-sectional effect sizes as the mean difference in performance between an HD group and controls, divided by the pooled standard deviation. Effect sizes were corrected for small sample sizes and were coded so that negative numbers indicated worse performance in the HD group compared with controls.

Results: In early HD (<7 years since onset), cross-sectional effect sizes in tracing and movement to target tasks were up to double the effect sizes of the most sensitive of the benchmark tasks (eg, Lemay et al, 2005, Circle Tracing Hedges g = 3.43 versus Symbol Digit Modalities Test g = 1.69). In prediagnosis HD, the cross-sectional effect size in a movement to target task was triple that of the effect size of the most sensitive of the benchmark tasks (Smith et al, 2000, g = 1.65 versus Speeded Tapping g = 0.50).

Task variants that revealed movement progress on a remote monitor or in a mirrored fashion and measures that monitored ability to correct a deviation from the intended course of movement seemed particularly sensitive.

Conclusions: Although available evidence is minimal, tracing and movement to target tasks warrant longitudinal study to assess sensitivity as markers of disease progression and treatment effectiveness. The HD Toolkit provides a means to set benchmarks for identifying additional promising tasks.

C.2 COGNITIVE FUNCTION IN PRESYMPTOMATIC HUNTINGTON’S DISEASE: A DOUBLE-BLIND COMPARISON BETWEEN CARRIERS AND NON-CARRIERS IN NORWEGIAN INDIVIDUALS

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Background: The onset of symptoms in Huntington’s disease (HD) shows great variability, making accurate determination of the start of clinical HD difficult. Less characteristic symptoms may appear earlier than motor symptoms. Healthy gene carriers provide the opportunity to examine the earliest signs of HD. Insight into subclinical signs will be critical for the development of clinical trials. Previous studies have given conflicting results.

Aim: The aim of the study is to compare cognitive performances between carriers and non-carriers in a Norwegian cohort. In addition, the influence of CAG repeat sizes and proximity to disease onset on cognitive decline was investigated.

Methods: A neuropsychological test battery covering the various cognitive domains was administered and population characteristics were recorded. Statistical analyses of characteristics were completed with analysis of variance and the χ² test. Group comparisons were executed with multivariate analyses of variance and co-variance. In addition, the relationships between CAG repeat size and proximity to the onset on cognitive performances were investigated by calculating correlations.

Results: No differences between carriers and non-carriers were revealed. However, a tendency towards lower performance on one neuropsychological variable and lower numeric mean performances were found. Group comparisons for CAG repeat sizes showed no significant differences and only two weak associations. Carriers closer and further from onset tended to differ only on dexterity of the non-dominant hand. Furthermore, some weak and some strong associations with cognition and proximity to onset were revealed.

Conclusions: Although not significant, carriers tend to perform less well than non-carriers. This is potentially caused by subtle cognitive decline that is insufficiently detectable by conventional cognitive assessments. Furthermore, there appears to be no or only a slight influence from CAG repeat size on cognition, whereas proximity to onset clearly has stronger influence.

C.3 EXECUTIVE FUNCTIONS IN HUNTINGTON’S DISEASE

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Huntington’s disease (HD) is a hereditary and progressive disease of the central nervous system and neuropsychological deficits are a main feature of HD. The executive functions include high-level mental activities such as motor control and programming, mental control, personality and emotion, fluency, creativity and planning. Planning is defined as the ability to organise cognitive behaviour in time and space. Deficits in these functions have been categorised as disorders of the executive system.

52 genetically confirmed patients (30 men, 22 women, age 46.9 ± 11.5, CAG repeats 45.9 ± 4.4) were tested with two different test batteries (Tower of London TL-D and Behavioural Assessment of Dysexecutive Syndrome (BADS)). The patients were divided into clinical stages 1–4 (Shoulson, 1979) and the results were compared separately.

The German version of the well-known test Tower of London TL-D measures planning abilities and the speed and accuracy of thinking. For this test, the patient is instructed to move three different coloured balls to match a target configuration by using a minimum number of moves. The BADS is a comprehensive neuropsychological assessment battery designed for “ecological validity” and other measures of frontal executive functions. The BADS is a test battery of six different element tests to investigate deficits in planning ability and “everyday” difficulties. The results are presented at the congress.

C.4 SYNTACTIC CHANGES IN HUNTINGTON’S DISEASE

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Introduction: Although general descriptions of Huntington’s disease (HD) have traditionally stated that this disease is not associated with language changes, an increasing number of studies have identified language deficits in patients with HD, even when they are in the early stages of the disease. The purpose of this study was to investigate language functions in HD compared with
healthy controls and to prove the debated role of the basal ganglia in language functions.

**Method and Materials:** 20 patients (12 men, eight women) with HD participated in the study. The control group comprised 20 age, sex and education-matched healthy subjects. A specific language screening was constructed that served to assess a wide range of language functions. Syntactic knowledge was tested in production and comprehension. The productive task of the syntactic screening consisted of arranging parts of a sentence in a grammatically correct way and generating a correct sentence out of three given parts. The second part of the screening was designed to probe divergent syntactic comprehension mechanisms with a sentence–picture matching task.

**Results:** Syntactic abilities are severely affected in patients with HD compared with healthy controls. Results suggest that HD patients experience difficulty on more demanding syntactic tasks, such as for example with semantically reversible sentences.

**Conclusion:** A correlation of these data with disease progression and degeneration measures of the basal ganglia is needed to disclose language functions of the basal ganglia. Additional correlations with age, sex and education scores will follow.

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**C.6 WORD LEARNING ABILITIES IN HUNTINGTON’S DISEASE**

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**Background:** Recent reports have documented that Huntington’s disease (HD) patients show difficulties in some aspects of language requiring rule processing (ie, syntax, morphology), whereas lexical abilities seem to be relatively spared. 1, 2 Although these results have been interpreted as a minor involvement of the striatum in lexical processing, this view assumes that words are simple associations between forms and meaning. However, throughout our lifespan we keep on encountering new words in our language and extracting the commonalities of the different contexts in which this new word appears, requiring similar abilities as rule processing.

**Aims:** Our aim was to study whether HD patients would be impaired in this type of word learning from context.

**Methods/Techniques:** 12 patients and 18 controls were confronted with a self-paced reading task adapted from Mestres-Missé et al 3 including three sentences in each trial having an unknown word at the end of the sentence. After reading the three sentences participants had to guess the meaning of the new word. In the experimental condition the three sentences led to the same meaning (M+), in the control condition the three sentences led to different meanings (M−). In addition, a third condition in which participants had only to give a semantically related word to a real word was included in order to control for the integrity of the semantic system.

**Results/Outcome:** Although showing comparable performances in semantic abilities to controls, HD patients showed poorer performances in the M+ condition. A significant decrease in reading times was observed in the controls from the first to the third sentence in this condition, whereas the M− condition did not vary. In contrast, HD patients did not show a decrease in reading times through sentences in the M+ condition, always comparable with the M− condition.


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**C.7 SENTENCE COMPREHENSION IMPAIRMENT IN HUNTINGTON’S DISEASE**

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The nature of language impairment in Huntington’s disease (HD) is still unclear. Some authors explain it by a co-occurring deficit in non-linguistic functions such as working memory (WM), whereas others propose a disorder of linguistic rule processing. In our study, we disentangled the respective roles of WM and of rule application in sentence comprehension deficits in HD patients, by using two syntactic rules that allow disentangling these two components. We tested WM by manipulating surface distance between the name and its determinant in sentences governed by gender agreement, while syntactic operation is held constant (the girl watches the dog that is green and the girl that watches the dog is green). On the other hand, to test rule application we varied conditions of co-
reference between a noun and a pronoun while holding WM constant: we contrasted sentences in which a linguistic principle (principle C) blocks co-reference (He smiled when Paul entered) and sentences that are ambiguous for co-reference (When he smiled, Paul entered). Fifteen HD patients at stage I of the disease and 15 healthy controls were tested. Results show that, like patients, likewise controls, have a preference for co-reference in ambiguous sentences; conversely, unlike controls, they accept co-reference even when it is blocked by principle C. An increase of WM in gender agreement sentences has no impact either on controls' or on patients' performance. We show that WM does not affect patients' ability to process syntax, suggesting that sentence comprehension impairments in HD are more likely to rely on linguistic rule deficits than on WM impairment.

C.8 UNDERSTANDING LANGUAGE COMPREHENSION DEFICITS AND SUPPORTING COMMUNICATION IN INDIVIDUALS WITH HUNTINGTON’S DISEASE

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Background: Individuals with Huntington’s disease (HD) are faced with increasing speech as well as cognitive/linguistic communication problems. The overall aim of this ongoing project is to describe the communication disorder and to develop and evaluate different types of strategies to support communication.

Aims: Two studies will be reported and their specific aims were to explore auditory language comprehension in relation to disease progression and evaluate the use of Talking Mats to support communication.

Study 1

Methods: Eighteen individuals in different stages of HD were compared with a control group on general and more complex language tasks. Also, a relative or close friend answered a questionnaire regarding perceived communicative changes.

Results: The results showed significant differences on the general measure of auditory language comprehension, including individuals in early stages compared with their controls, but also significant differences in the ability to understand metaphors, ambiguities and make inferences.

Conclusion: Auditory language comprehension shows great variability within the group of individuals with HD and can be severely affected early on.

Study 2

Methods: Five individuals all in later stages of HD took part in the second study. Three types of interview techniques were compared: unstructured conversation, structured conversation and conversation using Talking Mats (www.talkingmats.com). The interviews were video recorded and evaluated using the protocol Effectiveness Framework of Functional Communication (EFFC).

Results: Talking Mats increased the effectiveness of communication for all five participants.

Conclusion: Talking Mats supports conversation and might also be suitable for individuals with less apparent communicative problems.

C.9 ALTERED AUDITORY SENSORY PROCESSING IN PREMANIFEST HUNTINGTON’S DISEASE: ARE THERE DIFFERENT PHASES IN PREMANIFEST HUNTINGTON’S DISEASE?

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Introduction: There are only a few data about the role of striatal-thalamic areas as an analyser in central somatosensory control in Huntington’s disease (HD). The aim of this study was to assess auditory sensory processing mechanisms by functional magnetic resonance imaging (fMRI) in patients with premanifest HD.

Methods: 18 premanifest HD and corresponding controls were included. The group was divided into two subgroups close premanifest HD, less than 10 (respectively 14.9) years and far premanifest HD (>10 years), according to their estimated age of disease onset (eAO) using Ranes’s and Langbehn’s formulae, respectively. Tone perception and processing were characterised by fT IMRI by employing repeated tone stimulation (three digitally generated pulses (5 Hz) 800-80 Hz sine tone blocks (A1–A3)). Statistical analysis was done by SPM2, 2 x 2 x 2 mm voxel size and 8 mm kernel. Second level analysis was done by using a t-test, p uncorrected < 0.001, minimum cluster size 10 voxels. In addition, individual activation intensities of corresponding areas were determined in defined regions of interest by defining a sphere with a radius of 4 mm around activation maxima.

Results: The close premanifest HD group presented predominantly downregulated processes compared with controls (left BA4 in A1 and right ACC, BA6 and insula in A3), whereas the far premanifest HD group presented with stronger bilateral activation of the right caudatum in A1 and the right globus pallidus, left ACC, BA7, BA46 and right cerebellum in A3. Compared with close premanifest HD activation intensities were significantly higher for the bilateral thalamus and right BA44 in the far premanifest HD group in A1.

Discussion: Our findings seem to reflect an altered activation pattern to auditory stimulation depending on the progression of neuronal dysfunction. They also stress the involvement of the basal ganglia-thalamic circuits in the processing of sensory auditory stimuli. In accordance with other studies using functional techniques we found upregulated processes in our far from eAO group and predominantly downregulated processes in our close premanifest HD group. We suggest that there are different phases of up and downregulation in premanifest HD, depending on the years to eAO.

C.10 INCREASED SUSCEPTIBILITY TO VISUAL ILLUSORY EFFECT IN HUNTINGTON’S DISEASE

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Background: An accumulating literature suggests that deficits in visual processing are among the earliest cognitive abnormalities to emerge in patients with Huntington’s disease (HD).

Aim: The present study examined the nature of altered visuospatial representations in HD, particularly the degree to which patients are susceptible to illusory effects.

Methods: Nine right-handed patients with HD and 11 right-handed age-matched healthy controls were tested on two self-paced computerised line bisection tasks. The stimuli consisted of plain horizontal lines and lines with bilateral fins whose direction (facing left/right/both) were manipulated to create the Judd illusion effect. In the perceptual bisection task, participants viewed pre-biased lines on screen and judged whether or not they thought these were accurately bisected. In the motor bisection task, participants used two large buttons to move the bisection mark left or right to their perceived midpoint.

Results: In both perceptual and motor bisection tasks, the HD and control groups made accurate bisection judgements in the baseline (no fins) condition. Both groups also demonstrated significant illusory effects in bisection tasks. However, the magnitude of both left and right-induced visuospatial biases in illusory conditions was significantly greater for HD patients compared with controls, indicating that patients were more susceptible to illusory effects of the flanking visual elements in both perceptual and motor line bisection tasks.

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Conclusions: The results of this preliminary study suggest that HD patients are more prone to visual distractability compared with controls when performing line bisection under illusory conditions.

C.11 PSEUDO-NEGLECT IN HUNTINGTON’S DISEASE: A RETROSPECTIVE ANALYSIS

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Early disorders in visuospatial perception in patients with Huntington’s disease (HD) may correspond to a specific phenotype of the disease. Both pseudoneglect and neglect have been described in patients with HD, in a group study and in a single case study, respectively (Ho et al, 2003, 2004). Such hemi-attentional troubles in the right visual field are consistent with the time course of the neural degeneration of the disease, damaging first the left striatum evidenced by recent neuroimaging studies. Here, we aimed to confirm the existence of this pseudoneglect profile with a simple visuospatial paper–pencil task (Zazzo’s cancellation task) in 20 consecutive unelected patients with 16 controls matched for age and education level. Participants were instructed to cross out one, two or three small aligned signs covering a full page with a time constraint of 90 s for each page. We analysed their performance by separating the page into two equal parts. We rated the percentage of omissions on both sides (number of omissions/number of targets to cancel). We conducted a two-way analysis of variance with “target numbers” (one, two and three signs to cancel) and side (left, right) as within factors. Patients produced more omissions and the task elicited more omissions for the three than two targets condition and even more for the one target than the two targets condition. There was no effect of side but there was an interaction between side and group. The percentage of omissions was more important in the right part in patients only, suggesting a pseudoneglect profile on this rapid and simple paper–pencil task. Further studies are needed to determine what is the relevance of the pseudoneglect disorder as a marker of disease evolution and what is its prognosis value, if any.

C.12 THE POWER OF POSITIVES: EVIDENCE FOR AN OVERALL EMOTIONAL RECOGNITION DEFICIT IN HUNTINGTON’S DISEASE

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The recognition of emotions of disgust, anger and fear have been shown to be significantly impaired in Huntington’s disease (e.g. Sprengelmeyer et al, 1997, 2006; Gray et al, 1997, Malders et al, 2003, Montagne et al, 2006; Johnson et al, 2007; De Gelder et al, 2008). The relative impairment of these emotions might have implied a recognition impairment specific to negative emotions. Could the asymmetric recognition deficits be due not to the complexity of the emotion but rather reflect the complexity of the task? In the current study, 15 Huntington’s patients and 16 control subjects were presented with negative and positive non-speech emotional vocalisations that were to be identified as anger, fear, sadness, disgust, achievement, pleasure and amusement in a forced-choice paradigm. This experiment more accurately matched the negative emotions with positive emotions in a homogeneous modality. The resulting dually impaired ability of Huntington’s patients to identify negative and positive non-speech emotional vocalisations correctly provides evidence for an overall emotional recognition deficit in the disease. These results indicate that previous findings of a specificity in emotional recognition deficits might instead be due to the limitations of the visual modality. Previous experiments may have found an effect of emotional specificity due to the presence of a single positive emotion, happiness, in the midst of multiple negative emotions. In contrast with the previous literature, the study presented here points to a global deficit in the recognition of emotional sounds.

C.13 DISTURBED MOTOR RESONANCE AT THE BASIS OF THE EMOTION RECOGNITION DEFICIT IN HUNTINGTON’S DISEASE? AN EMG INVESTIGATION

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Background: Patients with Huntington’s disease (HD) have a deficit recognising emotional expressions. Recently, it has become clear that this deficit extends to other modalities and is not specific to disgust (Snowden et al, 2006; Johnson et al, 2007; Henley et al, 2008). In a recent study we established that this recognition deficit comes along with a production and that recognition and production are a highly correlated deficit (Trinkler and Bachoud-Lévi, 2008). This points to a potential role of “motor resonance” in emotional recognition, ie, a mechanism for recognising emotional expression in somebody else through an internal motor simulation thereof, which might be impaired in HD.

Aims: We aimed to compare motor resonance and the production of emotional expressions between Huntington’s patients and healthy controls using electromyography.

Methods/Techniques: 14 early HD and 14 matched healthy subjects were tested on three conditions of motor production of emotional expressions using electromyography: (1) spontaneous micro-mimickry of emotional expressions as is observed in healthy subjects (Dimberg, 1982); (2) overt imitation of facial expressions; (3) production of facial expressions from emotional words (“anger”, “disgust”, “joy”). Measurements were taken repeatedly from three facial regions: zygomatic (active in smiling), corrugator (active in frowning) and nasalis (active in wrinkling the nose in disgust).

Results: HD patients show less and less specific activation of the muscle active in the corresponding emotion in all three conditions. They thus lack automatic facial mimicry and show significantly less imitation and less ability to mime an emotional expression overtly compared with healthy subjects.

Conclusions: The absence of motor resonance for emotional facial expressions in HD might account for their difficulty in recognising emotions in others and may potentially be at the core of an empathy deficit.

C.14 A STUDY OF EMOTIONAL COGNITION IN HUNTINGTON’S DISEASE USING THEORY OF MIND TASKS

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Background: Huntington’s disease (HD) is a degenerative disorder with predominant involvement of the frontostriatal system. This condition gives rise to altered social and breakdown in interpersonal relationships, although the factors underlying these changes remain poorly defined.

Aims: This study used cognitive and affective theory of mind tasks, respectively, to explore the ability of patients with HD to interpret social situations and their ability to ascribe mental states to others.

Methods: Ten HD patients and 10 healthy volunteers matched by age and educational level were given a non-verbal cognitive theory of mind task assessing the attribution of intentions to others (Premack et al, 2005) and a revised version of the “Reading the Mind in the Eyes” Test (Baron-Cohen et al, 2001), which is an affective theory of mind task assessing the understanding of other people’s mental states from their eyes.

Results: The two measures of theory of mind were indicative of a significant impairment in HD patients.
Conclusions: Our results are consistent with the idea that both cognitive and affective aspects of theory of mind are impaired in HD patients, indicating that cortico-subcortical circuits participate in the mediation of higher social functions. Nevertheless, it would be important to determine precisely the specific role of the striatum in theory of mind performances and the contribution of theory of mind deficits to disorganised behaviour and breakdown in interpersonal relationships in daily life in HD patients, as has been suggested by Snowden et al (2003).

C.15 NEUROPSYCHIATRIC ASPECTS OF HUNTINGTON’S DISEASE: COMPARING SELF-REPORT AND CAREGIVER ASSESSMENT OF BEHAVIOURAL CHANGES

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Introduction: Huntington’s disease (HD) is a hereditary neurodegenerative disorder characterised by a triad of symptoms, namely motor symptoms, cognitive deterioration and psychiatric alterations. Neuropsychiatric abnormalities, such as depression, aggression, anxiety, apathy or sleeping disorders particularly place an enormous emotional burden on patients and their caregivers in their daily life. However, the awareness of these disturbances seems to be impaired in HD patients. The purpose of the current study was to evaluate the difference between patients’ and caregivers’ perceptions of neuropsychiatric symptoms.

Methods: Thirty patients with HD attending the Department of Psychiatry at the Medical University of Graz and their caregivers participated in the study. The caregivers were administered the Neuropsychiatric Inventory (NPI), a clinical instrument with established validity and reliability. The patients’ rating of the neuropsychiatric disturbances perceived was assessed with an adapted version of the NPI (NPIad), which did not evaluate hallucinations and delusions, because of the inability of the affected to perceive them as a pathological change. In addition to that the duration and stage of the disease as well as the Unified Huntington’s Disease Rating Scale (UHDRS) scores were documented.

Results: No correlation was found between the caregivers’ and the patients’ assessment of the neuropsychiatric disturbances and the distress resulting from these. Furthermore, caregivers described a higher frequency and severity of symptoms. The total score of the NPI was significantly correlated with the stage of the disease, the UHDRS cognitive, function and behaviour score and the distress score. Moreover, no correlation was found for the NPIad and the other parameters evaluated.

Conclusions: Patients with HD have a significantly different awareness of neuropsychiatric symptoms in comparison with their caregivers. Disturbances are reported more frequently and severely by the caregivers than by the patients themselves. Impaired perception does not seem to be related to the progression of the disease. Future studies examining larger samples may underline these findings.

C.16 PSYCHIATRY IN HUNTINGTON’S DISEASE

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At the present time the treatment of Huntington’s disease (HD) focuses on the neurological symptoms of the disease such as movement disorders and cognitive impairment. However, in clinical practice, the psychiatric disturbances are just as relevant as the neurological ones, because they often more subjectively impede the daily life of patients. In some cases, psychiatric symptoms such as depression and aggression appear years before the onset of neurological symptoms, so behavioural change may be an early indicator of disease onset. There are no clear results between the correlation of the number of CAG repeats and the age of onset of psychiatric symptoms. We present a systematic review of the major original psychiatric studies in HD, in order of their clinical importance: depression and suicide with a prevalence of 50%, irritability and aggression occur in 60% and 40%, apathy in 57%, psychotic symptoms in up to 12%, anxiety disorders in approximately 28% in the course of disease, obsessive and compulsive symptoms in 20% and mania in approximately 5%.

C.17 HUNTINGTON’S DISEASE RESEMBLING SCHIZOPHRENIA: A CASE REPORT

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We describe the case of a 23-year-old man who was admitted to the Department of Psychiatry of the Graz Medical University. At admission to the clinic he had reportedly suffered from social withdrawal, poor concentration and dysphoria for years. His avolition had caused him to drop out of high school, leaving him without training qualifications and unable to sustain himself socially or to provide minimum self-care. Furthermore, he presented with massive symptoms of thought disorder, mainly disorganised speech and derailment, illogicity and a general poverty of speech. The patient’s family history of Huntington’s disease (HD) led us to consider an early manifestation of HD as the cause.

The genetic testing revealed 41 repeats of the trinucleotide CAG marking a predisposition for HD. However, a result of 41 CAG repeats makes the onset of HD at this early age highly unlikely as there appears to be a strong negative correlation between the number of CAG repeats and the age at onset of the disease. Moreover, the patient showed no motor symptoms nor pathological eye movements in extensive testing, as used for patients in the early stages of HD.

The treatment with quetiapine and sertraline led to a distinct improvement of the patient’s psychiatric symptoms. He became increasingly communicative, organised in thinking and was able to restructure his life. Therefore, we think that the psychiatric symptoms of the patient are most likely unrelated to the patient’s predisposition for HD and are probably caused by schizophrenia simplex.

C.18 PAIN IN HUNTINGTON’S DISEASE

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Aims: In the past few years, some research has focused on the effects of motor cortex activation on pain perception and elaboration. Pain is a frequent symptom in early Parkinson’s disease, whereas little is known about pain processing in Huntington’s disease (HD). The aim of the present study was to examine pain features and nociceptive laser evoked potentials (LEP) in a cohort of HD patients, at an early stage of the disease.

Methods: Twenty HD patients were selected, on the basis of a Mini-Mental State Examination score of 25 or greater, and a clinical onset of 5 years or less. Forty control subjects, age and sex matched, were also examined. The LEP were obtained by five scalp electrodes, positioned at the Fz, Cz, Pz, referred to the nasion. A 0–100 visual analogue scale was employed to rate the stimuli. All subjects were also submitted to the brief pain inventory scale. The dorsum of the right and left hands was stimulated.

Results: Only one patient reported pain of a neuropathic type. All the LEP components appeared bilaterally reduced in amplitude in HD, in respect to controls. The P2 wave amplitude was inversely correlated with the functional capacities score.

Discussion: A pain pathways dysfunction emerged in early HD. The reduced amplitude of all the LEP waves may suggest a
C.19  OBJECTIVE MOTOR PHENOTYPE ASSESSMENT OF GAIT AND POSTURE IN HUNTINGTON’S DISEASE: A STUDY IN PROGRESS

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Background: Patients with Huntington’s disease (HD) develop an impairment of balance and gait (Rumpf et al., 2007). An objective assessment of gait and balance may serve as a surrogate marker for motor phenotype dysfunction.

Aims: To investigate the sensitivity of different tools, GAITRite mat, force plate, ActiWatches and B&L stride analyser to detect deterioration in motor skills before clinical manifestation, and to assess the correlation of objective parameters to the severity of HD as assessed by the Unified Huntington’s Disease Rating Scale—Total Motor Score (UHDRS—TMS), total functioning capacity and functional assessment scale.

Methods: Presymptomatic and symptomatic HD gene carriers and controls are placed on a force plate (Satel, France) and instructed to stand still with eyes open and closed for 25 s. The stability of centre of mass location is assessed by variables “SURFACE” and “DISTANCE” reflecting the centre of mass mobility. Subjects are equipped with ActiWatches around both ankles and stride analyser insoles in their socks and instructed to walk down the GAITRite mat in five consecutive conditions: “normal walking”, “fast walking”, “dual task walking”, “tandem forward/backwards walking”, and “walking on metronome”. The parameters assessed are velocity, cadence, gait cycle, and quantity of kinetic in counts per 2 s. All subjects are assessed clinically using the UHDRS—TMS, total functioning capacity and functional assessment scale.

Results: Preliminary analysis suggests that all techniques can be applied successfully in assessing motor dysfunction in HD. Differences between symptomatic patients and controls are observed. Statistical analysis comparing presymptomatic gene carriers and controls is currently pending, as are comparisons between the different assessment modalities, but will be available at the time of poster presentation.

Conclusion: The current study will elucidate the feasibility of the use of motor assessment devices, GAITRite mat, force plate, ActiWatches and B&L stride analyser, to provide objective and quantitative readouts of motor phenotype dysfunction in HD.

Funding: RR was supported by a grant from the EHDN.

C.20  GAIT ANALYSIS IN SUBJECTS WITH HUNTINGTON’S DISEASE: IS THERE AN INCREASE IN STRIDE-TO-STRIDE VARIABILITY?

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Introduction: It is currently difficult to specify the passage from the presymptomatic to the early symptomatic stage in patients with Huntington’s disease (HD). We hypothesised that a high stride-to-stride variability could be an early clinical marker of the disease. The objective of this study was to compare stride time variability in patients with HD (early and presymptomatic stage) with healthy controls subjects.

Method: Stride time variability in eight patients with HD, five early-stage (40 ± 3.5 years, 60% women) and three with the presymptomatic form (28.7 ± 6.7 years, 100% women) and 10 healthy controls (36.1 ± 7.6 years; 70% women) was measured while walking at normal walking speed using the SMTEC footswitch system.

Results: Stride time variability was 2.4 ± 0.6% in early-stage HD patients, 1.8 ± 0.4% in presymptomatic subjects and 1.5 ± 0.6% in healthy control subjects. There was a trend towards an increase in stride time variability across the three groups (p = 0.071). In addition, an asymmetry of stride time variability between the right and left step was shown in the early symptomatic stage of HD compared with the presymptomatic stage (4.6 ± 3.9 versus 2.0 ± 1.7; p = 0.571).

Conclusion: The results show that stride time variability is higher in subjects with HD compared with healthy controls, with a gradient between the early and presymptomatic stage of HD.

C.21  RELATIONSHIP BETWEEN IMPAIRMENT OF VOLUNTARY MOVEMENTS AND SHORT-TERM MEMORY IN HUNTINGTON’S DISEASE

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Background: Impairment of voluntary movements and memory precedes the dyskinetic syndrome in Huntington’s disease (HD). Working memory and free recall from short-term memory are the most impaired components of memory in HD. These functions strongly depend on attention and executive functions.

Aims: The aim of the study was to find a relationship between impairment of voluntary and involuntary movements and memory deficit in HD.

Methods: Forty patients with genetically confirmed HD in various stages were investigated. The rate of motor involvement was quantified by means of the Unified Huntington’s Disease Rating Scale (UHDRS). Voluntary (oculomotor and bradykinesia/fine motor) and involuntary components of UHDRS (rigidity, dystonia and chorea) were evaluated separately. For assessment of memory the auditory verbal learning test and verbal paired associates were used. For estimation of short-term and long-term memory and voluntary components of UHDRS factor scores with Bartlett’s factor coefficients were employed. The generalised least squares estimator was used for the corresponding factor analysis.

Results: Voluntary components (bradykinesia/fine motor) were found to be significantly correlated with short-term memory disturbances (r = −0.412, p<0.008), but not with long-term memory in the auditory verbal learning test and verbal paired associates (r = −0.286, p<0.07). Involuntary components did not correlate significantly with any part of memory performance.

Conclusions: Correlation of short-term memory performance with voluntary movement impairment together with a lack of correlation of voluntary movement impairment with long-term memory performance indicate mainly decreased potential of the central processing system. Both voluntary movement and short-term memory require more attention and processing speed than the execution of already acquired abilities and recall from long-term memory. Involuntary movements do not load significantly processing capacity. It can be concluded that voluntary movement and short-term memory impairment appear to be more sensitive markers of disease progression than involuntary movements.

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C.22 A NOVEL METHOD OF STIMULUS PRESENTATION FOR
EVOKING SACCADES IN HUNTINGTON’S DISEASE PATIENTS
WITH CHOREA: PRELIMINARY REPORT

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Background: One of the functional biomarkers allowing the precise
monitoring of Huntington’s disease (HD) development is
the distribution of saccadic latency, the time taken to make a
saccade to a suddenly displaced visual target. In HD, impairment of
cortical, cognitive levels are reflected in characteristic changes in
the stochastic distribution of saccadic latency. There is a practical
limitation in using this methodology in HD patients because of
choreiform head movements.

Method: We use a standard saccadometer, modified so that the
stimulus display is attached to the head in close vicinity to the eye
(6 cm) and moves exactly with the head. This effectively cancels the
vestibulo-ocular reflex response, providing adequate eye stability even
when the head is making choreiform movements. The onset of the
target is adaptively controlled and tailored to the patient’s individual
capacity to respond, which facilitates sustaining attention on the
task. The horizontal target displacement was 10° randomly to the
right or left, with a randomised foreperiod of 1.0–2.0 s.

Results: Saccadic latency distributions of 100 trials recorded by five
subjects with proximal display were compared with 100 trials
obtained using a conventional saccadometer with a viewing
distance of 2.5 m. For four of the subjects, the distributions were
significantly different (Kolmogorov–Smirnov, p<0.001), as were the
medians (t-test on reciprocal medians, p<0.001); the remaining
subject showed no significant difference in either (p>0.05). Overall,
the mean latency was 158 ms for the conventional saccadometer and
158 ms for the new version.

Conclusion: This technique is potentially capable of providing
constant experimental conditions throughout the whole period of HD
progression, and the subjects tested reported viewing the proximal
stimuli as more comfortable. However, it must be borne in mind that
it cannot be used to make direct comparisons with latency
distributions measured with the conventional saccadometer.

C.23 THE TEN EURO NEUROTEST: A SIMPLE, QUANTITATIVE TEST
OF DEXTERITY THAT IS USEFUL IN THE FOLLOW-UP OF
PRESYMPTOMATIC GENETIC CARRIERS AND PATIENTS WITH
HUNTINGTON’S DISEASE

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Background and Aim: We recently introduced the Ten Euro Neurotest (TEN) as a simple, quantified “bedside” test for
dexterity.1 In the present study, we validated the TEN in a larger sample of Huntington’s disease (HD) patients. Furthermore, we
tested whether the TEN can be used as a marker for imminent HD in presymptomatic gene carriers.

Methods: The TEN is performed with 10 coins of one Euro aligned
on a straight line in the middle of an A4 paper. The subject is
instructed to turn the coins as fast as possible, starting with the
most distant coin, and to replace them on the line starting from
the top of the paper working downwards. The time is clocked and the
accuracy with which the coins are replaced on the line is measured
using a ruler. Ninety-two healthy control subjects, 56 patients with
manifest HD and 12 presymptomatic gene carriers participated in
this study.

Results: Test–retest reliability of the TEN was excellent for “time”
(scores intraclass correlation coefficient (ICC) for dominant/non-
dominant hand in controls 0.91/0.93, in HD patients 0.88/0.94) and
good for the “accuracy” score (ICC in controls 0.63/0.72, in HD
patients 0.71/0.90). Patients performed the TEN slower and less
accurately than controls. Dexterity decreased significantly with
increasing disease severity (Unified Huntington’s Disease Rating
Scale motor score, total functional capacity) and genetic disease
load (calculated as CAG repeat length ? 35.5 * age)2. Moreover, the
presymptomatic gene carriers already performed worse than the
controls.

Conclusions: The TEN is a simple, reliable quantitative tool to
measure impaired dexterity in HD. TEN performance is already
impaired in presymptomatic gene carriers, suggesting that the TEN
can detect imminent HD. TEN scores worsen with increasing
disease severity and genetic disease load. These qualities advocate
using the TEN in the follow-up of presymptomatic gene carriers
and HD patients.

reliable and valid test of dexterity in patients with Huntington’s disease.
Award winning poster at the World Congress on Huntington’s Disease. Dresden,
2007.
2. Penney JB Jr, Vonsattel JP, MacDonald ME, et al. CAG repeat number governs
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C.24 CAN GAIT INITIATION PARAMETERS BE USEFUL AS EARLY
MARKERS OF HUNTINGTON’S DISEASE IN PRESYMPTOMATIC
MUTATION CARRIERS?

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Objective: To quantify gait initiation disturbances in presympto-
matic Huntington’s disease (HD) patients.

Background: Gait initiation combines preparation and execution
of the first step. Interaction between motor and cognitive aspects of
preparation and execution of movement can be studied using a
paradigm of gait initiation with and without external cuing.

Methods: 10 presymptomatic mutation carriers (PMC), 10
symptomatic HD subjects and 10 age-matched controls
were recorded. They had to initiate gait with and without an external
beep.

Results: PMC demonstrated decreased first step speed (p<0.05)
duration (p<0.05) compared with controls in both conditions.
PMC presented a shorter amplitude of the postural adjustments in
PMC compared with controls. These impairments were more
pronounced in HD subjects.

Conclusions: Preparation and execution of first step are impaired in
PMC in both self-triggered and externally cued conditions.
Temporal parameters of step execution (step duration), but also
spatial parameters of postural adjustments preceding first step
(backward shift of the centre of pressure) could be considered as
early markers of the disease.

C.25 IMPAIRMENTS OF POSTURAL CONTROL IN PATIENTS’ WITH
HUNTINGTON’S DISEASE WHILE SITTING: A NEW MOTOR
PHENOTYPE BIOMARKER?

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Background: Patients with Huntington’s disease (HD) develop a
progressive impairment of stability of stance and walking (Rumpf et
al, 2007), frequently resulting in falls and injuries. Objective
To investigate whether patients with HD exhibit impairments in the control of postural stability while sitting with or without the availability of visual feedback and to assess whether these measures correlate with the severity of disease as assessed clinically by the Unified Huntington’s Disease Rating Scale—Total Motor Score (UHDRS—TMS).

**Method:** HD patients (n = 15) and controls (n = 15) were seated on a force plate (Satel, France) with eyes open and closed for 25 s. Subjects were instructed to sit still. Stability of centre of mass (COM) location was assessed by the variables SURFACE and DISTANCE reflecting COM mobility. Data were stored and analysed using a data acquisition system. All subjects were assessed clinically using the UHDRS—TMS. Non-parametric statistics were performed to compare patients and controls (Mann–Whitney test) and to assess dependent variables (Wilcoxon test) using SPSS 15.0.

**Correlation analysis was performed using non-parametric Spearman correlations.**

**Results:** Both measures SURFACE and DISTANCE were significantly increased in HD compared with controls (p<0.001 for all conditions except DISTANCE for eyes closed with p = 0.002). In HD SURFACE (r = 0.74, p = 0.004 eyes open; r = 0.64, p = 0.018 eyes closed) and DISTANCE (r = 0.78, p = 0.001 eyes open; r = 0.65, p = 0.019 eyes closed) were correlated with the severity of the disease as assessed in the UHDRS—TMS.

**Conclusion:** Assessment of stability of sitting using a force plate provides objective and quantitative readouts of motor phenotype dysfunction in HD. The measures SURFACE and DISTANCE of COM dyslocation were correlated with the severity of motor phenotype (UHDRS—TMS). A possible use of these measures as surrogate markers for trials in HD warrants further exploration.

**Objective:** To determine which clinical tests of postural instability (PI) in patients with Huntington’s disease (HD) are most sensitive and which symptoms are associated with PI.

**Background:** Balance disorder is one of the common symptoms of HD and can occur in early stages of the disease. PI causes falls and resulting injuries and has a large impact on patient independence.

**Methods:** We examined 20 HD patients (11 women, nine men) with a mean age of 50.4 years (SD 12.1), a mean disease duration of 6.2 years (SD 2.5), and a mean number of CAG triplets of 45.5 (SD 11.3). Patients were evaluated using the Unified Huntington’s Disease Rating Scale (UHDRS), Mini-Mental State Examination (MMSE) and six clinical tests of PI (pull test, push and release test, stance with feet close together, one limb stance, tandem stance and tandem gait). Results of the six PI tests were used in computing a factor score representing the level of instability in each patient. The above tests were compared with a questionnaire we developed regarding PI disorders and falls that was given caregivers and patients independently.

**Results:** PI was found in 16 out of 20 patients. The clinicians examined the patients more with the caregivers’ response to the questionnaire (r = 0.78) than with the patients’ response (r = 0.51). In addition, there is a high correlation between the validity of patients’ response with MMSE score (r = −0.87). Factor analysis showed that the stance with feet close together and tandem gait best correlated with the factor of instability. PI was found to be correlated with MMSE, the subscore of independence scale and of the functional assessment of UHDRS; in particular there was a high correlation with the Luria test. In addition, the push and release test was not able to be completed in six patients because of lack of cooperation due to cognitive impairment.

**Conclusions:** The tests of stance with feet close together and tandem gait were best able to predict falls. The push and release test is not a suitable test for HD patients because of the high prevalence of cognitive difficulties. The strong correlations of PI with MMSE score and the Luria test suggest that PI in patients with HD is related to cognitive impairment.

**Aim:** To determine which clinical tests of postural instability (PI) in patients with Huntington’s disease (HD) are most sensitive and which symptoms are associated with PI.

**Background:** The Royal Hospital for Neurodisability provides assessment, rehabilitation, treatment and long-term placements for people with HD. The HD service is provided over three different geographical areas, each suited to the differing stages of the disease from the middle to the late stage.

**Method:** The multidisciplinary group has reviewed retrospectively the incidence of falls reported over the past 2 years. The dataset was composed of the name of the patient, date and time of accident, severity of the falls and a brief description of the accident.

**Results:** 101 falls were reported over the 2 years. Ninety per cent of the falls were experienced by mobile patients, ie, middle stage of the disease and falls were marginal in the later stage of the disease (only 10%). 97% of the falls resulted in either no injury or just a bruise, two falls resulted in a cut and only one required A&E admission. The head was the main site of impact. Falls mainly occurred when patients where attempting to mobilise. The average number of falls per patient was five (with a range of 0–22). The distribution of falls per time of the day showed two peaks: one around 10:00 hours and one around 16:30 hours.

**Conclusions:** Falls are a real risk for patients with HD who are mobile. However, with a good risk assessment system, an adapted environment and the appropriate standards of care the outcome of falls can be minimised and the impact on patient independence limited. It is a difficult balance to strike between supporting the independence of the patient and preventing falls over the trajectory of the illness.

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Method: We included 37 patients with HD (17 women and 20 men, age 41.98 ± 7.99 years) in our study. The following urodynamic parameters were examined: maximum flow rate, voided volume, flow time, stranguary volume, bladder capacity, number of detrusor contractions, intensity of detrusor contractions, frequency of micturition, fill rate, peristaltic function, intravesical pressure, compliance and detrusor pressure. Normal distribution was checked by the Kolmogorov–Smirnov test. Group differences were checked with the t-test or Mann–Whitney U-test for significance.

Results: Patients treated with neuroleptics show a significantly lower intravesical pressure (25.14 cm H_2O; p = 0.026) compared with the neuroleptic-free group (47.61 cm H_2O). Other urodynamic parameters are not influenced by neuroleptics. We did not find any significant effect for antidepressants and benzodiazepines on function of the bladder. Disease progression was included as a covariate in our analysis.

Discussion: The aim of our study was to investigate the influence of neuroleptics, antidepressants and benzodiazepines, often used in the symptomatic treatment of HD, on bladder function. Antidepressants and benzodiazepines do not show any effect on examined urodynamic parameters. Only patients with neuroleptics show, compared with the non-neuroleptics group, a significant reduction of intravesical pressure. Although the decrease is rather strong, there seems to be no clinical effect. The lowering of intravesical pressure could be explained by the α-antagonising side effect of low potency neuroleptics reducing bladder resistance. Summing up bladder function in patients with HD is not influenced by psychopharmacological medication according to our data.

C.30 WEIGHT LOSS IN HUNTINGTON’S DISEASE IS RELATED TO THE NUMBER OF CAG REPEATS

Aims: In order to elucidate the underlying mechanisms of weight loss in HD, we studied its relation to other disease characteristics including motor, cognitive and behavioural disturbances and CAG repeat number.

Methods: In 517 early-stage HD patients, we applied mixed-effects model analyses to correlate weight changes over 3 years to CAG repeat number and various components of the Unified Huntington’s Disease Rating Scale (UHDRS). We also assessed the relation between CAG repeat number and body weight and caloric intake in the R6/2 mouse model of HD.

Results: In HD patients mean body mass index decreased by −0.15 units per year (p < 0.001). However, no single UHDRS component, including motor, cognitive and behavioural scores, was independently associated with the rate of weight loss. Conversely, each unit increase in CAG repeat length was associated with a faster rate of weight loss in HD patients. In R6/2 mice, larger CAG repeat lengths were also accompanied by a lower body weight, whereas caloric intake was higher in mice with larger repeat lengths.

Conclusions: Weight loss in HD is directly linked to CAG repeat length and is likely to result from a hypermetabolic state. Other signs and symptoms of HD are unlikely to contribute to weight loss in early disease stages. Elucidation of the responsible mechanisms could lead to effective energy-based therapeutics.

C.31 ASSESSMENT OF ADVANCED HUNTINGTON’S DISEASE PATIENTS WITH THE LATE-UHDRS: A PILOT STUDY

Background: The Unified Huntington’s Disease Rating Scale (UHDRS) has confirmed efficacy in Huntington’s disease (HD) assessment, and is used worldwide for clinical studies. However, it appeared substandard for late-stage changes in rating over time. The lack of efficient measures in advanced patients thus excludes them from potential therapeutic trials.

Aims: We have designed the Late-UHDRS scale, inspired by the regular UHDRS, in order to fill out specific clinical changes in advanced HD. It aims to overcome the limitations of examination due to the patient’s communication disorders.

Methods: It provides four scores in the motor, vegetative, cognitive and behavioural domains, contains 40 items and takes less than 30 minutes to complete. Patients were selected with a total functional capacity less than 5 and assessed in Crétteil and Leiden with both this scale and the regular UHDRS.

Results: 46 patients (25 in Crétteil, 21 in Leiden) were assessed, 13 cross-sectionally and 33 longitudinally with a mean 10.9 months interval (SD 4.8). We assessed the internal consistency and longitudinal changes, compared with the regular UHDRS and the interrater reliability.

Conclusions: Altogether, compared with the regular UHDRS, the Late-UHDRS seems more efficient for longitudinal assessment in advanced HD patients and is easier to assess independently from the presence of a caregiver at the examination.

C.32 THE BEHAVIOUR OBSERVATION SCALE HUNTINGTON’S DISEASE: LONGITUDINAL VALIDATION

Background: In nursing homes for patients with Huntington’s Disease there is a need for an observation instrument quickly and easily to assess the patient’s behavioural pattern. The Behaviour...
Observation Scale Huntington (BOSH) is a promising instrument for this purpose, but its structure and characteristics have been studied on a minimal (cross-sectional) sample and a limited number of administrations. The first analyses have yielded three components: deterioration of activities of daily living, social-cognitive deterioration and rigidity-aggression. More data are expected to reveal more and more precise components. Clinical observation has pointed to possible components, such as fractiousness, cognitive functioning, inflexibility and eating and drinking capacities.

**Aims:** To determine the component structure of the BOSH more precisely. To describe the course of disease in terms of the components and to discriminate groups of patients on behavioural patterns.

**Methods:** In the period between 2000 and 2008 the BOSH has been administered every 6 months for a total of more than 100 patients in the nursing home Overduin in Katwijk, The Netherlands.

**Statistical Methods:** Three-mode principal component analysis will be used for determining the principle components. Regression mixed modelling in SAS (PROC MIXED) will be used to determine the time course of the subscales. Discriminant analyses will be performed for determining possible subgroups.

**Results:** The first preliminary results on principle component structure and course of the disease will be presented.

**C.33 BENIGN HEREDITARY CHOREA: CLINICAL AND NEUROIMAGING DATA FROM A FAMILY WITH NEW MUTATION OF THE THYROID TRANSCRIPTION FACTOR GENE**

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**Objective:** To describe clinical and morph-functional changes in a pedigree with chorea due to a novel thyroid transcription factor 1 (TITF-1) mutation.

**Background:** TITF-1 mutations have recently been associated with benign hereditary chorea, an autosomal dominant disorder, characterised by chorea and possible hypothyroidism and respiratory alterations.

**Design/Methods:** A 23-year-old woman presented with involuntary choreiform movements, since she was 8 years old. Her father, a 54-year-old man, had slight, sporadic, hyperkinesias since childhood. The proband’s son had neonatal respiratory distress, pylectasis, congenital hypothyroidism, psychomotor developmental delay and recently developed slight, sporadic limb hyperkinesias. We studied the patients extensively, we sequenced the entire TITF-1 gene and performed TITF-1 functional analysis.

**Results:** Subclinical hypothyroidism was found in the proband and in the father. Magnetic resonance imaging evidenced ventricular dilatation in both patients. Positron emission tomography was normal in the proband, but showed caudate and left temporo-parieto-occipital hypometabolism in the father. Neuropsychological evaluation showed long-term verbal memory deficit and mild intelligence test impairment in the proband, whereas mainly short-term memory deficit was shown in the father. In all the three affected members of the family, we found a heterozygous change in the TITF-1 gene, not previously described, from cytosine to adenine in the second base of the triplet encoding for the amino acid at position 145. The mutation is responsible for a change from serine to a stop codon (S145X). A functional analysis shows that the mutated TITF-1 is not binding DNA, nor activating the canonical thyroid target gene promoter or interfering with the ability of wild-type TITF-1 to activate the transcription and it is mostly in the cytoplasm.

**Conclusions/Relevance:** Up to now, 19 different mutations of TITF-1 have been found in several families affected by benign hereditary chorea. We report a novel mutation in the exon 2 of the TITF-1 gene in a family in which the phenotype is heterogeneous and more severe in new generations.
D Biomarkers

[0.1] TRACK–HD TRACKING PROGRESSION IN PREMANIFEST AND EARLY HUNTINGTON’S DISEASE

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TRACK–HD is a multicentre, multinational, prospective, observational biomarker study of premanifest and early Huntington’s disease (HD). The goal of the project is to contribute essential methodology that will provide unique insights into the neurobiology of premanifest and early HD and form the basis for neuroprotective trials in premanifest and early HD. TRACK–HD complements existing observational studies (Predict–HD, PHAROS, Registry and COHORT), sharing some features, but also having areas of unique emphasis, including extensive annual testing, implementation of multi-site 3T magnetic resonance imaging acquisition and novel assessment techniques. Premanifest subjects are stratified to focus on those close to motor onset. The use of a small number of sites allows flexibility for evaluating relatively complex and expensive techniques and dynamic modification of the study as promising new methodologies emerge. Here we give an update on recruitment and assessment to date. By the end of July all 350 subjects will have been enrolled and baseline assessments completed.

[0.2] INCREASED ACTIVITY OF THE HYPOTHALAMIC–ADRENAL AXIS IN EARLY-STAGE HUNTINGTON’S DISEASE PATIENTS

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Background: Huntington’s disease (HD) is a hereditary neurodegenerative disorder characterised by motor, cognitive, psychiatric and behavioural disturbances. Recently, progressive alterations of the hypothalamic–pituitary–adrenal (HPA) axis in the R6/2 mouse model of HD reminiscent of a Cushing-like syndrome were reported. However, no data are available on the diurnal cortisol secretion patterns in HD patients.

Aims: To perform a detailed functional analysis of the HPA axis in HD patients in relation to symptoms and signs.

Methods: Twenty-four hour pulsatile cortisol secretion was studied in eight early-stage, medication-free HD patients compared with eight age, sex and body mass index-matched control subjects. Blood sampling for the determination of cortisol concentration was performed at 10-minute intervals. Multiparameter autodeconvolution analysis was applied to study cortisol half-life, the number of secretory bursts, secretory burst half-duration, mean mass secreted per burst and basal, pulsatile and total production rates. Cosinor analysis was applied to assess 24 h variations in cortisol concentration while the orderliness of the concentration time series was evaluated by approximate entropy. The Unified Huntington’s Disease Rating Scale (UHDRS) was used to assess clinical presentation in HD subjects. Statistical significance was set at p<0.05.

Results: The amplitude of the diurnal cortisol profile, the total number of cortisol secretory bursts as well as the pulsatile and total cortisol secretion rates were significantly higher in HD patients compared with controls (eg, total secretion in HD was 4781 versus 2658 (nmol/l per 24 h) in controls, p=0.016). There was also a trend towards a higher basal cortisol secretion rate. In HD patients, UHDRS functional assessment score and total functional capacity scores both correlated inversely with the basal and total cortisol secretion rate.

Conclusion: HPA axis hyperactivity is an early feature of HD and is likely to have a central origin as the number of secretory bursts was increased. Increased cortisol levels might account for a number of disease signs such as mood disturbances and cognitive impairment.

[0.3] DYSREGULATION OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN HUNTINGTON’S DISEASE

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Background: Neurodegeneration in Huntington’s disease (HD) is primarily found in the basal ganglia and cerebral cortex, but hypothalamic involvement in early disease stages has also been described. The hypothalamic dysfunction is a major component of the hypothalamic–pituitary–adrenal axis (HPA) and previous studies report a hyperactivation of this axis in HD.

Methods: Presymptomatic (n = 26) and symptomatic (n = 58) HD mutation carriers were recruited from outpatient clinics and a specialised nursing home. Disease stage was defined with the confidence level of the motor section of the Unified Huntington’s Disease Rating Scale. Validated non-mutation carriers (n = 28), who were at 50% risk for HD, were included as a comparison group. HPA axis functioning was measured in saliva with a cortisol awakening response (CAR), the area under the curve and the dexamethasone suppression test.

Results: The CAR and the area under the curve were significantly higher in presymptomatic mutation carriers compared with symptomatic mutation carriers. After adjusting for awakening time, sex and age, the differences remained intact for the CAR only. No significant differences were found between the three groups for the dexamethasone suppression test.

Conclusion: This study indicates a hyperactivation of the HPA axis in presymptomatic mutation carriers compared with symptomatic mutation carriers. This may reflect a decreased activation of the HPA axis after the onset of motor symptoms.

[0.4] GROWTH HORMONE RESPONSE TO ARGinine INFUSION: PRELIMINARY RESULTS OF A STUDY OF HYPOTHALAMIC DYSFUNCTIONS IN HUNTINGTON’S DISEASE

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Introduction: There is increasing evidence pointing towards an early involvement of the hypothalamus and the endocrine system in Huntington’s disease (HD). Investigating neuroendocrine changes in HD opens up the possibility of finding biomarkers for HD, as well as of identifying novel targets for therapeutic interventions. The aim of the study is to investigate hypothalamic dysfunctions in HD further through a detailed examination of the endocrinological changes in these patients. Here we present the preliminary results of the growth hormone (GH) response to arginine infusion in seven patients with a molecular diagnosis of HD. GH secretion from the pituitary gland is regulated by the hypothalamic peptides growth hormone-releasing hormone and somatostatin, which are modulated by various neuronal networks, especially the noradrenergic and cholinergic systems. Arginine,
through stimulation of hypothalamic alpha2-adrenoceptor, raises concentrations of GH in serum in healthy people.

**Materials and Methods:** Seven patients (five men, two women, mean age 45.14 ± 11.52 years and disease duration 7.40 ± 2.06 years) underwent the arginine test after a 12-h fast, between 08:00 and 08:30 hours. After subjects had rested in a supine position for at least 30 minutes, baseline samples (T0) were collected from a cannulated antecubital vein. Then 30 g arginine (arginine hydrochloride, 30% solution) was infused intravenously over 30 minutes and blood was sampled every 30 minutes for 1 hour (T30, T60, and T90). Serum GH was measured with a commercially available immunoradiometric kit. Disease severity was clinically evaluated with the United Huntington’s Disease Rating Scale motor section. No patient had a history of endocrinological illness or was taking drugs acting on the central nervous system.

**Results:** In four patients we observed an absence of response (T0: 0.29 ± 0.02 µg/l; T30: 0.80 ± 0.25 µg/l; T90: 0.85 ± 0.11 µg/l), in two patients the GH peak was delayed at T90 (T0: 1.01 ± 0.29 µg/l; T30: 4.50 ± 0.12 µg/l; T60: 8.18 ± 0.52 µg/l; T90: 14.03 ± 0.52 µg/l), in one patient the peak was at T30 (T0: 0.71 µg/l; T30: 11.80 µg/l; T60: 11.30 µg/l; T90: 4.50 µg/l).

**Discussion:** The GH response to arginine was altered in most of the patients who performed the test. This may be due to an impairment of cholinergic hypothalamic systems in HD, confirming in vivo an involvement of the hypothalamus in the disease. No correlation was found between GH response and disease severity and disease duration.

**0.5 NEUROENDOCRINE DISTURBANCES IN HUNTINGTON’S DISEASE: GROWTH HORMONE/INSULIN-LIKE GROWTH FACTOR 1 POSSIBLE BIOMARKERS**

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**Background:** Huntington’s disease (HD) is a severe inherited neurodegenerative disorder characterised, in addition to neurological impairment, by weight loss suggesting endocrine disturbances.

**Aims:** The aims of this study were to look for neuroendocrine disturbances in patients with HD and, should such disturbances be found, to determine whether they developed late, as a result of advanced neuron loss, or instead constituted an early effect of the mutant huntingtin protein.

**Methods:** We compared plasma levels of hormones from the five pituitary axes in 219 patients with genetically documented HD and in 71 sex and age-matched controls. Relationships between hormone levels and disease progression, including weight-loss severity, were evaluated.

**Results:** Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) were significantly higher in patients than in controls (0.25 (0.01–3.75) versus 0.15 (0.005–4.89) ng/ml, p = 0.005, respectively). Cortisol was higher (p = 0.002) in patients (397.3 ± 161.3 nmol/l versus 279.8 ± 130.1 nmol/l), whereas no differences were found for other hormone axes. In patients, elevations in GH and IGF-1 and decreases in thyroid-stimulating hormone, T3 and testosterone (in men) were associated with the severity of impairments (independence scale, functional score, total functional capacity, total motor score, behavioural score). Only GH was independently associated with body mass index (β = −0.26, p = 0.001).

**Conclusion:** Our data suggest that the thyrotropic and gonadotropic axes may undergo alterations over the course of HD. The somatotropic axis is overactive even in patients with early disease, and the GH increase may explain the weight loss seen in HD patients. Both GH and IGF-1 deserve further investigation as biomarkers for HD progression.

**0.6 COGNITION IN RELATION TO METABOLIC CHANGES IN THE BRAIN OF PRECLINICAL MUTATION CARRIERS OF HUNTINGTON’S DISEASE**

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**Background:** Mutation carriers of Huntington’s disease (HD) who do not yet suffer from motor symptoms are considered preclinical mutation carriers (PMC). HD not only leads to progressive loss of motor functions but also causes cognitive, behavioural and emotional changes, eventually leading to subcortical dementia. However, it is unclear which of these domains is most informative in marking an individual’s transition from healthy functioning to clinical HD. Alterations in the brain functioning of individuals with HD are thought to occur first and most severely in the striatum, but changes in other brain regions will also arise, resulting in widespread brain atrophy. It has not yet been clarified which specific pathological processes in the brain may be responsible for the diversity in cognitive dysfunction of PMC.

**Aims:** To explore the relationship between cognitive performance and biochemical alterations in the brain of PMC. This study is part of an ongoing follow-up project on the development of a reliable biomarker of neuronal dysfunction in preclinical HD.

**Methods/Techniques:** 22 PMC and 14 controls underwent neuropsychological assessment, neurological examination, 18F-fluorodeoxyglucose and 11C-raclopride positron emission tomography and magnetic resonance imaging scanning. All measures were repeated after 2 years.

**Results/Outcomes:** Our first results indicate normal cognitive functioning of all PMC at baseline, although biochemical abnormalities appeared in a considerable part of them, especially on 11C-raclopride positron emission tomography. However, relatively more PMC scored in the lower range of normal cognitive functioning compared with the control group. The imaging data are now being analysed and patterns of regional metabolic covariance will then be related to cognitive functioning measures.

**0.7 CHANGES IN STRIATAL DOPAMINE D2 RECEPTOR BINDING IN PRECLINICAL HUNTINGTON’S DISEASE**

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**Objective:** Carriers of the Huntington’s disease (HD) mutation develop a progressive neurodegenerative disorder before a preclinical phase. The objective of this study is to examine the value of 11C-raclopride (RAC) positron emission tomography scans as a biomarker for HD pathophysiology before the onset of clinical motor HD.

**Methods:** We conducted a prospective cohort study with clinical and neuropsychological assessment and collected complete RAC data in 18 of 27 preclinical mutation carriers (PMC) and 11 of 14 controls. Follow-up was longer than 2 years in all subjects. We calculated RAC binding potential to measure dopamine D2 receptor availability in the putamen and caudate.
Results: No PMC had overt neuropsychological dysfunction. RAC binding potential was abnormal in up to 44% of PMC with the putamen more sensitive to changes than caudate. The rate of decline of RAC binding potential was 2.6% per year, which is not significantly higher than in controls (1.8% per year). Follow-up putaminal binding potential correlated weakly with predicted distance to onset of clinical HD (p = 0.034 for linear fit), but the rate of decline did not. Three PMC developed motor abnormalities suspect for HD during the study. They showed no increased rate of decline of putaminal RAC binding potential, but two had low RAC binding potential at baseline.

Conclusions: Many PMC have striatal abnormalities but we found no clearly increased rate of D2 receptor changes around the onset of clinical HD. In order to estimate a more reliable risk of clinical conversion from striatal D2 binding data, a longer follow-up of the present study cohort will be necessary.

D.08 MONITORING NEUROPROTECTIVE EFFECTS OF RILUZOLE IN HUNTINGTON’S DISEASE BY BRAIN AND PERIPHERAL BIOMARKERS

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Riluzole interferes with glutamatergic neurotransmission thereby reducing excitotoxicity, enhancing damaged neurite formation in motoneurons and increasing serum concentrations of brain-derived neurotrophic factor, involved in striatal degeneration in patients with Huntington’s disease (HD). We set up a longitudinal prospective study to analyse the magnitude of volumetric and metabolic brain changes in riluzole-treated and untreated patients (100 mg/day versus placebo). All patients performed well in cognitive tasks, had a Mini-Mental State score above 25 and were matched for gender, HD duration, age of neurological onset, progression rate and mutation size. None of them had taken neuroleptic or antidepressant medications. Twenty-two patients were enrolled and underwent magnetic resonance imaging (MRI) and [18F]-fluoro-2-deoxy-D-glucose positron emission tomoscopy scanning, according to our fully automated protocols. Two MRI and positron emission tomography scans were obtained for each patient and a mean interval of 17 months elapsed between scanning sessions. Of 22 patients, 11 received blinded treatment with the neuroprotective agent. Follow-up MRI scans differed remarkably in the two groups. The repeated scan obtained in untreated HD subjects showed the considerably greater loss of functional grey matter volumes in patients who did not receive riluzole than in those who did. Coherently with structural MRI data, metabolic changes in all brain areas were greater in untreated patients than in riluzole-treated patients. Finally, mean serum brain-derived neurotrophic factor concentrations were higher in treated than in untreated subjects (Mann–Whitney U, p = 0.012).

Riluzole therefore safely contributed to preserve HD patients’ brains from progressive degeneration and dysfunction, thus confirming its potential beneficial neuroprotective effect in early or even presymptomatic HD.

D.09 CORRELATION BETWEEN BRAIN PARENCHYMA SONOGRAPHY FINDINGS AND CLINICAL STATUS IN PATIENTS WITH HUNTINGTON’S DISEASE

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Background: Brain parenchyma sonography (BPS) has become a new diagnostic tool in the evaluation of extrapyramidal disorders. Furthermore, recent studies report alterations of mesencephalic raphe structures in unipolar depression and in depressed Parkinson patients. The aim of this study was to evaluate BPS findings in patients with Huntington’s disease (HD) in correlation with their neuropsychological and psychiatric status.

Methods: Twenty-five patients with genetically confirmed HD were included (mean age 48.6 years, 16 women) following approval by the ethics committee. Neurological and psychiatric statuses including standardised scales were assessed by independent physicians. Echogenicities of basal ganglia including mesencephalic raphe structures were investigated according to previously described examination protocol for extrapyramidal disorders using a Siemens Sonoline Elegra system. The sonography examiner was blinded for clinical data.

Results: Six patients (24%) showed hyperechogenicity of the substantia nigra, two patients (8%) of the caudate nucleus and one patient (4%) of the lentiform nucleus. No correlation between these findings and the neurological status was seen. Twelve patients (48%) showed symptoms of depression at the time of evaluation, and of those, nine (75%) had hypoechogenic raphe structures. Nineteen patients (76%) had a history of depressive episodes, 13 (68.4%) of them with a hypoechogenic raphe region. All six patients without any history of depressive episodes showed normal echogenicity of raphe structures.

Conclusion: As a novel finding, a relationship between mesencephalic raphe echogenicity and depressive state could be identified in HD. An alteration of the serotonergic brainstem raphe might be involved in the pathogenesis of depression in HD.

D.10 7T MAGNETIC RESONANCE SPECTROSCOPY IN HUNTINGTON’S DISEASE

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Background: Gaining further understanding of the pathophysiology of brain changes in Huntington’s Disease (HD) is crucial in the light of developing new interventions to be tested in clinical trials. To date, imaging techniques have shown structural and functional abnormalities in various brain structures in manifest gene carriers of HD and to a lesser extent in premanifest gene carriers. Magnetic resonance spectroscopy (MRS) provides a non-invasive in-vivo technique to measure alterations in brain metabolite concentrations as a reflection of functional changes. Low field MRS has shown generalised changes in the relatively large brain structures of premanifest gene carriers and manifest gene carriers. Ultra high field (7T) MRS has the potential to perform measurements in subregions, with greatly increased signal-to-noise ratio and spectral resolution. We expect to gain further insight into the underlying disease processes, even before structural changes can be demonstrated, essential in the search for a clear biomarker.

D.11 MAINLY AFFECTED CORTICAL BRODMANN AREAS AND CONSPICUOUS POWER CHANGES IN DIFFERENT STAGES OF HUNTINGTON’S DISEASE: A STUDY USING LOW RESOLUTION BRAIN ELECTROMAGNETIC TOMOGRAPHY

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Background: The EEG in Huntington’s disease (HD) has been reported to be abnormal in several previous studies. By using EEG tomography such as three-dimensional low-resolution electromagnetic tomography (LORETA) we could already identify cortical
brain areas predominantly involved in our patients. The aims of the present study were to identify particularly affected Brodmann areas (BA) in daytime brain function in HD patients and to focus on power differences correlated with stages of disease.

**Methods:** In 71 patients and 71 healthy controls a 3-minute vigilance-controlled EEG was recorded during midmorning hours. Thereafter, EEG results were compared with controls within the whole group and within different subgroups by using LORETA for imaging of the regional brain electrical activity.

**Results:** Delta LORETA power was significantly increased, mainly over right frontal cortices with a maximum in the BA 11 of the inferior frontal gyrus. A decrease of theta, alpha and beta power, accentuated over the left frontotemporal brain areas with most often the maximal difference in the BA 20 of the inferior temporal gyrus, was found. The increase in delta power was not significant in the early stages of disease. Furthermore, with increasing disease severity the significant decrease of beta power became less. HD is not thought to be a lateralised disease; however, clear differences in the results between the right and the left hemisphere were found.

**Conclusion:** BA 11 belongs to the orbitofrontal cortex and is involved in planning, reasoning and decision making. BA 20 plays a part in high-level visual processing and recognition memory. Both areas are strongly connected to the basal ganglia. The caudate and thalamic activation of the orbitofrontal cortex may be relatively preserved in early HD, allowing this circuit to act in a compensatory fashion for the loss of dorsolateral prefrontal cortex function. The impaired recognition memory of patients with HD may be a result of damage to the ventrocaudal striatum, but the possibility of cortical atrophy, which might produce a similar deficit, can still not definitively be excluded. Contrary to our expectations with increasing disease severity, the decrease of beta power became less. Moreover, further analysis revealed an increase of frontal beta LORETA power with progressive worsening of the disease. These changes were also found in normal aging, so these results might be discussed as faster aging processes in HD patients.

**D.12 PPARGC1A, ENCODING PGC-1A, IS A POTENTIAL MODIFIER GENE OF HUNTINGTON’S DISEASE**

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Huntington’s disease (HD) is one of the most common autosomal dominant inherited neurodegenerative disorders. HD is caused by an unstable CAG repeat expansion in the HD gene (HTT), localised on chromosome 4p16.3. The number of CAG repeats is the main predictor of disease onset, but the remaining variation is strongly heritable. Recent studies implicated PGC-1α (encoded by PPARGC1A) in the pathogenesis of HD. We therefore ascertained possible associations of PPARGC1A polymorphisms with disease onset in European HD patients. Initial studies in Italian patients suggested associations between PPARGC1A haplotypes located in the transcribed region and disease onset (p = 0.0161), whereas no such associations were observed with haplotypes located in the promoter region. Based on these studies, we identified associations of rs7665116, located in a conserved region of intron 2, with CAG adjusted age at onset in 449 Italian HD patients (p = 0.0016). If confirmed in other populations, these findings may have implications for the identification of therapeutic targets in HD and other neurodegenerative disorders.
E Genetic aspects/testing

E.1 INTERMEDIATE ALLELES FOR HUNTINGTON’S DISEASE: PATIENT UNDERSTANDING AND CURRENT GENETIC COUNSELLING PRACTICES
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Background: Predictive testing (PT) for Huntington’s disease (HD) has the ability to “predict” whether an individual will ever develop HD and thus have the ability to pass the disease onto their children. Some individuals who undergo PT receive an unusual test result called an “intermediate allele” (IA). Individual with an IA will never develop HD yet there remains a risk for their children to develop HD.

Aims: Numerous studies have examined the PT experience and psychosocial consequences of receiving a positive or negative test result. Despite the characterisation of IA over 15 years ago, no studies have provided insight into the clinical, psychological and social experience of individuals who receive an IA result. The purpose of this study is to explore IA carriers’ understanding of the result implications and the current genetic counselling practices regarding IA.

Methods: Using grounded theory qualitative methodology, 18 IA carriers and five medical genetics professionals from three Canadian sites participated in open-ended interviews. Interviews were transcribed and analysed using the constant comparative method and the coding procedures of grounded theory.

Results: 55% of participants were unaware that their children remained at risk of developing HD, despite being counselled about this clinical consequence. Those IA carriers who were aware of the risk to their children experienced psychological distress, uncertainty and guilt. Medical genetics professionals described inconsistent counselling practices regarding the type of information on IA exchanged during PT. Family history appears to influence both patient understanding and professional counselling practices.

Conclusions: This study represents the first empirical study on the PT experience of IA carriers. The results of this study will contribute to the development of PT guidelines specific to IA that will provide guidance to clinicians on how to provide appropriate education, counselling and support to this unique subset of patients.

E.2 PREDICT-HD: A COMPANION STUDY EXPLORING ATTITUDES OF PARTNERS TO PREDICTIVE TESTING AND PARTICIPATION IN RESEARCH
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Background: Huntington’s disease (HD) has a major impact on the family system. A limited amount of qualitative research has explored the effects from the perspectives of partners. PREDICT-HD is an international collaborative study investigating symptom onset markers in presymptomatic individuals. Partners of gene carrier individuals are also invited to attend.

Aims: The aim of this qualitative study was to investigate the effects of predictive testing and participation in PREDICT-HD from the partners’ perspectives.

Method: 12 partners of carrier individuals attending PREDICT follow-up appointments in Manchester were interviewed about their experiences of HD and predictive testing, coping with the knowledge that their spouse would one day develop HD and attitudes to involvement in research. Interviews were transcribed in full and analysed using the constant comparison method.

Results/Outcome: Participants all reported feeling pleased that their spouse had had the predictive test; even those partners who initially reported misgivings or who had subsequently experienced difficulties in their relationship. The main benefit of testing was seen as preparation for the future and rehearsal for their role as carer. Participants used their experience with their spouses’ families or previous experience as carer to act as a template for how they viewed their role as support person. This focused on two key areas—communication within the family and anticipated extent of involvement in physical care. The option to participate in research was welcomed by all partners, primarily as a means of providing hope, if not for their own family for future generations. The PREDICT appointment did, however, have the potential to raise difficult issues for couples and heightened awareness to the possibility of early symptoms.

Conclusions: Participants recommended that partners continue to be involved in research and that psychological support should be included as an integral part of research studies.

E.3 ATTACHMENT AND EMOTION REGULATION IN PREDICTIVE TESTING FOR HUNTINGTON’S DISEASE
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Background: Based on early experiences with caregivers, individuals develop mental working models of self and others in close relationships. These working models of attachment may be secure or insecure, depending on the degree to which they are characterised by anxiety or the avoidance of others. In a previous study, we found more insecure attachment in individuals with a Huntington’s disease (HD) family background. Working models of attachment are activated in threatening situations, in which they influence the use of emotion regulation strategies. Insecure attachment (high anxiety and/or high avoidance) is associated with emotional instability. As predictive DNA testing for HD can be perceived as a threatening situation, attachment style may predict emotion regulation and psychological outcomes of testing, in both testees and partners.

Aims: To investigate relationships between attachment style, emotion regulation and psychological reactions to testing for HD.

Methods: Before testing, attachment style, cognitive emotion regulation, social interactions and psychological wellbeing are assessed in testees and partners. One week and 6 months after receiving test results, the psychological wellbeing of participants is assessed. Comparisons are made with testees for other neurodegenerative disorders and for hereditary breast and ovarian cancer.

Results: Inclusion of participants is ongoing. An outline of the study will be presented. We hypothesise that individuals with secure working models of attachment have more adaptive emotion regulation strategies and higher levels of psychological wellbeing. Because of different family dynamics, attachment is expected to be more insecure in individuals with an HD family background.

Conclusions: Knowledge about attachment, working models and emotion regulation may enhance understanding of individual reactions to testing for HD. It can be useful for adequate psychosocial counselling.

E.4 NEGOTIATING A SPACE BETWEEN HEALTH AND ILLNESS: EXPERIENCES OF THOSE TESTING POSITIVE FOR HUNTINGTON’S DISEASE AND THOSE WHO PARENT WITH THEM
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Background: Technological advances in molecular genetics mean that those who know from their family history that they are at risk...
The aim of this presentation is to present perceptions of health and illness of mothers and fathers living with the current knowledge of their gene-positive status. Although not yet symptomatic, it is almost inevitable that they will develop HD in later life. It touches on how perceptions change for those who suspect they are beginning to become symptomatic and their partners.

Methods: Qualitative in-depth interviews were conducted with men and women testing positive and those who parent with them. Theoretical sampling involved recruiting men and women who had tested positive, parenting under a range of circumstances and with dependent children of different ages. Analysis was aided by a grounded theory model of responsibility generated from earlier research. This model encapsulated what families found important when making decisions about becoming parents.

Results: It will be argued that developments are generating new landscapes of health and illness. Examples will be given of how parents construct, negotiate and maintain this previously unknown space—described as “living in no man’s land”. They will show how spatial and temporal dimensions are used to create boundaries between the healthy, affected, at-risk, tested and future sufferers. Boundaries are tentative as uncertainty remains about when those tested positive will become symptomatic.

Conclusions: Entering this space fulfills an important moral purpose, ie, enabling parents to negotiate different positions of agency and responsibility before becoming symptomatic.

E5 DIAGNOSIS AND RESEARCH OF HUNTINGTON’S DISEASE: SPANISH EXPERIENCE IN A GENETIC SERVICE

Introduction: The genetic service of the FJD hospital has been working on diagnosis of Huntington’s disease (HD) since 1994, following the quality standards established by the European Molecular Genetics Quality Network since 2000. We work in a multidisciplinary team together with the representative of the Spanish Huntington’s Disease Association. Our experience in 1500 families includes predictive and diagnostic tests, prenatal and preimplantation genetic diagnosis (PGD) and research studies. The last innovations incorporated are the analysis of fetal DNA circulating in maternal plasma and PGD studies.

Materials and Methods: Six pregnancies among 30 prenatal diagnoses were selected for fetal DNA circulating studies in maternal plasma. In all of them the father was the gene carrier. 10 informative couples were requested for PGD; it had already been done in two of them. DNA was extracted from peripheral blood, maternal plasma, chorion villi and abortion remains. Direct and indirect studies with fluorescent primers were performed and analysed by capillary electrophoresis.

Results: In four out of six cases, by analysis from maternal plasma, the fetus could be correctly diagnosed. In two cases this diagnosis was not possible due to the length of the expansion. Both were from the same family and the fetuses showed a considerable number of CAG repeats, 78 and 114, respectively. Differences in the number of repeats were not observed in different tissues from abortion remains of the fetus with 114 repeats. In PGD results, no clinical pregnancy was obtained from the first family. Results for the second family are not yet available.

Conclusions: A combination of research and diagnostic studies could provide additional information to be considered for appropriate genetic counselling.

E6 HUNTINGTON’S DISEASE: THE SAGA TO GET THE CORRECT DIAGNOSIS OF A NEURODEGENERATIVE DISEASE IN A POPULATION WITH SCARCE RESOURCES AND TECHNOLOGY IN NORTHEASTERN BRAZIL

Feira Grande (FG) is a small city (with approximately 23 000 inhabitants, predominantly young) of Alagoas, northeastern Brazil. In the 1980s, while still a child, I did not understand why an elderly couple of married cousins from the neighbourhood displayed a progressive imbalance of movements. I saw others in the municipality with worse symptoms, and adult people used to describe this to me as a hereditary terminal disease called “nervous”. Over time, I consulted local physicians, who referred to it as Parkinson’s disease, prescribing dopamine-type drugs to patients. When I attended the disciplines of genetics and biochemistry (Federal University of Alagoas, UFAL), during my graduation in dentistry in the capital, I constructed a simple pedigree with data collected from the relatives of live or dead patients in FG. But the local physicians had no interest in it and after concluding my first degree and returning to FG, I joined the Program for Family Health. So I found other family groups with neurodegenerative symptoms. From 2001 to 2003, I built a more complex pedigree and found a genetic correlation of symptoms in six generations; this did not corroborate the diagnosis of Parkinson’s disease. With the support of my former Professor of Biochemistry, who also managed to add to this cause the backing of three clinical geneticists of UFAL, I founded a group to define the markers that would be screened to identify the neurodegenerative disease in FG. After referring patients to clinical, neurological, biochemical and genetic evaluation (2005), the true diagnosis was finally obtained—Huntington’s disease (HD). This was announced to the Brazilian Society of Huntington (2006), which, perplexed with the record on coverage of HD cases, sent its representatives to FG (2007) to advise family and HD patients (treatment, genetic counselling and rights). There is now a commitment from the government for the installation of a multidisciplinary centre to support relatives and carriers of HD.

E7 HUNTINGTON’S DISEASE AND HUNTINGTON-LIKE PHENOTYPE: 10 YEARS OF LOCAL MOLECULAR DIAGNOSTIC EXPERIENCE

CGF/IBMC is the reference laboratory for Huntington’s disease (HD) in Portugal. We performed more than 1000 HD tests over the past 10 years, including diagnosis, predictive and prenatal tests.

Only 58% of all diagnostic requests were confirmed; from those excluded, we selected 200 patients and studied them for HD-like genes: an extra eight octapeptide repeats in the FRPN gene (HDL1); a CAG/CAG repeat in the junctophilin (JPH5) gene (HDL2); a CAG expansion in two SCA genes—ATN1 (DRPLA) and TBP (HDL4/SCA17); as well as others included in the differential diagnosis of HD: neuroferritinopathy (FTL gene) and benign hereditary chorea (TITF-1 mutations).
Expansion of CAG repeats in ATN1 and the insertion on PRNP were excluded in all cases. One family (mother and son with chorea since childhood, myoclonus, falls and dysarthria) carried a nonsense mutation in TITF-1. An FTL mutation was detected in one gypsy family (mother asymptomatic and son with mild non-progressive mental retardation and gait disturbances by the age of 13 years; both had pallidal involvement on magnetic resonance imaging). We also found a CAG expansion in TBP (a patient with behavioural disturbances, epilepsy, aphasia, imbalance and gait ataxia). Finally, we found a 47 CTG/CAG expansion in the JPH3 gene in a Brazilian white patient with a familiar history of disease (onset at age 44 years of bradipsychism, mutism, dysarthria, cognitive deterioration and chorea, as well as ataxic gait; he had cortical atrophy).

This work stresses the importance of also performing the exclusion of HD-like disorders whenever the HD mutation has been excluded and it is clinically indicated.
**F Clinical care and management**

**F.1 ORAL CARE IN HUNTINGTON’S DISEASE**


**Background:** The Mun-H-Centre is a Swedish national orofacial resource centre for rare disorders and a national resource centre for orofacial aids and assistive devices. Since 1999 the authors have been members of the Huntington’s disease (HD) team at Sahlgrenska University Hospital/Ostra in Göteborg and because of that have had the unique opportunity of treating a number of patients with the diagnosis of HD.

**Aim:** To collect, document and develop information relating to rare diagnoses and to circulate this knowledge as a contribution to ensure that patients with rare disorders receive better treatment and can have an improved quality of life.

**Methods/Techniques:** Dentists and dental hygienists at Mun-H-Centre have followed 20 patients with HD and observed oral problems over time. At Mun-H-Centre there is a multiprofessional team for trying out orofacial assistive devices to patients with disabilities. The team members represent occupational therapy, physiotherapy, speech–language pathology and dentistry.

**Result/Outcome:** Our experiences are documented and illustrated as follows: orofacial symptoms, risk factors for deterioration of oral health, preventive dentistry and cooperation with the patient’s personal assistants, treatment in the dental chair, examples of orofacial aids and assistive devices for oral care, eating and drinking.

**Conclusions:** It is important for a person with HD to see a dental team regularly in order to maintain a good quality of life through a healthy mouth, for the purpose of speaking and communicating as well as eating and enjoying meals. Preventive dentistry from an early stage of the disease and orofacial assistive devices that can compensate for lack of function are recommended.

**F.2 NEW TOPICS FOR HUNTINGTON’S DISEASE IN EUROPE?**

Project team for the network around Huntington’s disease in the region of Västra Götaland, Sweden. Klinisk Genetik, Medicinaregatan 1 D, SU/Sahlgrenska, 413 45 Göteborg, Sweden

**Background:** During our project we have found that there are topics concerning the care of persons with Huntington’s disease (HD) that are necessary to agree at an international level. One of these topics is to find a good model for taking care of and informing children in families with HD about the disease. Some other important issues are orofacial care and speech as well as cognitive/linguistic communication problems.

**Aims:** To search for models and to create new models in order to facilitate life for persons with HD and for their families.

**Methods:** Cooperation with professionals, caregivers and associations in Europe. We will plan workshops together and we will arrange meetings over the internet. We will participate in the working group Standard of Care and Quality of Life.

**Result:** To create good models and a networking team in these fields.

**Presentation:** We will present these ideas in a poster presentation.

**F.3 IMPACT OF HUNTINGTON’S DISEASE ON QUALITY OF LIFE: A QUALITATIVE STUDY**

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**Background:** Even though Huntington’s disease (HD) is an autosomal dominant neurodegenerative disease characterised by motor, cognitive and and behavioural disturbances, there has been little research reflecting the first-hand experience of the health-related quality of life of people living with HD.

**Aims:** This qualitative study examines patients’ personal experience of the impact of HD as a part of a larger EHDN project to develop a disease-specific patient-centred health-related quality of life instrument for HD. The development of such an instrument would benefit from examining patients’ direct experience and how they themselves perceive the impact of HD on their health-related quality of life.

**Methods:** Thirty-nine semistructured interviews were conducted primarily with people living with different stages of HD, with some input from their companions, carers and health professionals familiar with HD. The computer-assisted qualitative data analysis software package NVivo 7 was used for sequential analysis of the data using grounded theory.

**Results:** Six dimensions of quality of life emerged: (1) physical and functional dimension; (2) cognitive dimension; (3) emotional dimension; (4) social dimension; (5) legal and financial dimension and (6) self dimension.

**Conclusions:** A model of quality of life for people living with HD is conceptualised to capture the interaction of these dimensions in mediating the subjective construct of health-related quality of life of people living with HD.

**F.4 IMPROVING CARE AT END OF LIFE: HOW DOCUMENTING WISHES CAN ENABLE INFORMED DECISION-MAKING**

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End-of-life care for individuals with Huntington’s disease is an important but difficult area for both patients and clinicians. One of the key components of support at late-stage disease is knowledge about what the preferences and wishes of the affected person are in relation to feeding and medical treatment.

These informed decisions ought to be made and recorded when a patient is known to be able to make such choices. For this to be demonstrated, individuals should undergo regular neuropsychological assessment. Patients should be encouraged to appoint someone who can manage their financial and personal affairs when they can no longer do so, and these contact details should be recorded in the medical notes. This information must be easily accessible to clinicians so that they can act appropriately, following the patient’s wishes, if for example, the patient has an emergency hospital admission. This should then prevent any additional distress to the patient and their families or carers. This poster describes a document in which the clinician can record affected individuals’ wishes and their recommendations for end-of-life care, which we feel should be part of a recognised standard of care in Huntington’s disease.

**F.5 WHO CARES ABOUT MY FEELINGS? CHILDREN’S SITUATION IN FAMILIES WITH HUNTINGTON’S DISEASE**

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**Background:** Living with a parent with Huntington’s disease (HD) can be difficult when the parent’s personality is gradually changing. It can be hard for a child to understand what is going on. Children can show signs of anxiety, grief and being burdened with a sense of guilt. Another pressure for the children is that they themselves are at risk.

**Aims:** The primary aim is to answer the questions: How should we inform children about HD? When? Who should do it? In what way should we talk to children? A secondary aim is to develop a model of management for Sweden and we searched for models in other countries.
Methods: Questionnaires were sent out to 29 international Huntington associations in 22 different countries and the number of answers was 15. Three interviews with children were performed and three visits, two of them in Sweden and one in Scotland.

Results: The results showed that there is a definite need to give attention to the children at an early stage. In our study, 33% of the associations answered that they do not have any particular strategy for coping with the children’s situation. The other associations answered that they attend to the children’s needs in different ways. The best model was found in Scotland. Conclusion: There is an obvious and urgent need for guidelines in this area and also specifically formulated, well structured, good information for children in families with HD. A majority of associations were eager to collaborate and the EURO-HD might be a very suitable forum to create a unified model to improve and facilitate the children’s situation.

F.6 CURRENT PHARMACOLOGICAL MANAGEMENT IN JUVENILE HUNTINGTON’S DISEASE

Background: Huntington’s disease (HD) is a progressive neurodegenerative disorder. Onset under 20 years is termed “juvenile Huntington’s disease” (JHD). The clinical presentation of JHD can be strikingly different from adult-onset HD. The management of JHD is aimed at symptom relief; there is little published evidence to guide this.

Aim: To survey the current pharmacological management of JHD in the United Kingdom.

Methods: Patients were identified through the Huntington’s Disease Association and hospital practitioners. A questionnaire was sent to each family. Information gathered included symptoms, medications, side effects and perceived effectiveness.

Results: Seven families responded. The mean time since diagnosis was 7 years. Common symptoms included speech difficulties (7), swallowing difficulty (6), stiffness (6), sleeping difficulty (5), pain (4) and behavioural problems (4). The mean number of medications was six (range two to 15). The most commonly prescribed agents were atypical antipsychotics (4). The indications for these medications included: antimuscarinics (2), levodopa with dopa-decarboxylase inhibitors (2), baclofen (2) and tizanidine (1). The following medications were also prescribed: benzodiazepines (3) and opiate analgesia (5).

Conclusions: Identifying the current practice is a first step towards establishing an evidence base for possible intervention. We hope to extend this survey to Europe and the United States. We are still recruiting in the United Kingdom. In this survey of patients with JHD most were on an anti-parkinsonian medication and/or muscle relaxants and sedation/analgesia. Atypical antipsychotics were commonly prescribed for agitation and behavioural problems in this group of patients. Pain is a feature of JHD that must not be overlooked.

F.7 BEST CARE IN HUNTINGTON’S DISEASE: A FIRST CONSENSUS DOCUMENT IN ITALY

The Italian lay association for Huntington’s disease (HD) (AIICH-Roma Onlus and AIICH-Milano) provided the initial input in July 2007 asking our research group to create a multidisciplinary panel of experts with the main task of providing recommendations for the best care of HD patients.

The consensus document the panel has produced (the first in our country) answers some key questions, such as the real characteristics of patients involved, the alternative strategies for management, the clinical problems, and outcomes and offers suggestions about the best approach to patients and families.

The document is now in press (10,000 copies) and will then be disseminated to the relevant audience (neurologists, geriatrists, medical professionals involved with movement disorders). The lay association will also be active in distributing the handbook to family doctors involved with HD patients.

As levels of clinical expertise in HD vary considerably among different regions, this consensus document is aimed at promoting a common and better approach to the care of these patients. It can also constitute an important tool of continuous medical education and of appraisal of practice standards.
competence centre, which offers information, counselling and courses on a selected range of rare disorders. The centre has responsibility for over 50 rare diagnoses and focuses on both medical and psychological problems. The Centre’s service is aimed at the appropriate patients and their families and at professionals working with rare disorders.

**Aims:** Huntington’s disease (HD) is an inheritable, chronic disease. It is therefore necessary to provide ongoing information regarding the individual patient over a period of several years, both to professionals, family members and those genetically at risk so they can plan for today but also for the future. The presentation will illustrate the variety of courses we offer to those affected by HD, both for patients, their families and professionals.

**Methods:** We arrange three types of course: for professionals; for patients and their families; for family members genetically at risk.

**Results:** We arrange: information meetings for professionals in the patient’s local environment; regional courses when there are several patients in the same district, with up to 60 participants; regular courses for professionals, held in each county; courses for the newly diagnosed and their families; courses for persons at risk. This year we have held a course for professionals from seven counties at Rikshospitalet.

**Conclusions:** Our courses provide comprehensive information on HD to professionals, patients, their families and persons at risk. They meet others who are in the same situation and are encouraged to establish a network.
G Experimental therapeutics: clinical

G.1 THE ROAD TO DELIVERY OF HUMAN EMBRYO STEM CELL-BASED THERAPIES

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Realising the therapeutic promise of human embryo stem cells (hESC) necessitates overcoming diverse challenges. This begins with meeting the legal and ethical challenges of procuring embryos. Next, the efficiency of in-vitro culture systems supporting cells must be improved using reagents whose specification complies with regulatory standards. This is followed by qualification of resulting cells and assessment of their biosafety both in relation to the prospective transplant recipient and the community at large. Complicating the address of these challenges are constantly evolving and internationally variant regulatory standards that have the capacity to negate the utility of cells for emerging therapies before clinical trials are even begun.

To address these challenges Roslin Cells Ltd was established in 2006 as a not-for-profit company owned by the University of Edinburgh, the Scottish National Blood Transfusion Service and the Roslin Institute. It is core funded by Scottish Enterprise, which recognised the market failure caused by a lack of industrial investment in a promising yet unproved technology and limited research council support for translational research. Similarly to other UK centres attempting to derive hESC, Roslin Cells Ltd is licensed by the Human Fertilisation and Embryology Authority. In addition it is the first centre to be licensed by the Human Tissue Authority for the processing, testing, storage, distribution and export/import of embryos and stem cells intended for human application. To date Roslin Cells Ltd has isolated five new research grade hESC, including one from a clinically failed egg created in the course of assisted conception that otherwise would have been discarded. Roslin Cells Ltd has now begun to isolate clinical grade hESC under increasingly defined culture conditions that will safeguard against contamination with known or unknown pathogens. Clinical evaluation of the resulting cells will still require development of methods to differentiate cells with specialised function required to treat different types of disease, as well as the characterisation of such cells in animal models for their biosafety. Although this will still require further investment of time and resources before clinical benefits can be had, the first important step of creating a resource of clinically suitable cells is underway.

G.2 NEURAL TRANSPLANTATION IN HUNTINGTON’S DISEASE: FOLLOW-UP ASSESSMENT IN NINE PATIENTS

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Background and Aims: At the University of Florence, during the past 4 years, we have performed human fetal striatum transplantsations (HFST) in nine patients affected by Huntington’s disease (HD), according to the accepted protocol. We present the main biological and clinical results.

Methods: Standard procedure (Bachoud-Lévy, 2000) was applied to the first six interventions, the remaining grafts were performed by a double approach refinement. Patients were assessed with the Unified Huntington’s Disease Rating Scale, neuropsychological and psychiatric battery: twice in the year before the graft and yearly after the graft. Furthermore, patients underwent regular magnetic resonance imaging/18F-fluorodeoxyglucose positron emission tomography/iodobenzamide single-photon emission computed tomography examinations.

Results: Nine patients underwent HFST: two patients reached 2 years of follow-up, four patients one year, two patients 6 months and one patient 3 weeks. The gender ratio of the patients was three women/five men, mean age was 47 years (±8, 86 SD), the age at disease onset was 34.25 years (±10, 18 SD), mean duration of illness was 13 years (±6, 93 SD), mean CAG repeats 49.25 (±5, 97 SD). Three patients showed a conspicuous growth of the graft on one side (without signs or symptoms of neurological deterioration), within a period of 7-9 months after grafts, followed by a stabilisation of growth. Our clinical findings are very similar to those presented by Bachoud-Lévy; in particular, we noticed an improvement in the cognitive domain, whereas we did not find a striking improvement in motor symptomatology. In the three patients who showed graft growth, we did not observe, so far, any positive correlations in the clinical outcome.

Conclusions: The evaluation of HFST as a useful therapeutic tool is still under debate, as well as our knowledge of the capacity of fetal tissue to create new connections with an adult neurological structure affected by degenerative disorders.

G.3 BILATERAL STIMULATION OF THE GLOBUS PALLIDUS INTERNUS TO TREAT CHOREA AND AXIAL DYSTONIA IN HUNTINGTON’S DISEASE: A CASE REPORT

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Background: Huntington’s disease (HD) produces motor abnormalities that are poorly responsive to medical therapy. Deep brain stimulation (DBS) may offer a treatment option for afflicted patients but its role in the management of HD remains unclear.

Case History: A 42-year-old man with a diagnosis of HD for the past 4 years, with predominant axial dystonia in the neck, severe chorea in the upper extremities and with severe impairment of gait was enrolled for surgery. The surgical procedure was similar to that performed in patients with dystonia. The surgery was carried out under local anaesthesia. The globus pallidus target was determined by magnetic resonance imaging, computed tomography and unit cell recordings. The pallidal target was 3 mm anterior to the midcommissural plane, 20 mm lateral to the midline and 4 mm below the intercommissural line. The optic tract determined the lower boundary of the globus pallidus. It was identified by phosphenes seen by the patient during stimulation. The implanted electrode was a DBS model 3387 (Medtronic, Minneapolis, Minnesota, USA). DBS parameters were: 2.8 V, 120 ms, 180 Hz, monopolar.

Conclusions: Bilateral pallidal stimulation produced a dramatic reduction in choreathetoid and dystonic movements and an overall improvement in gait. The cognitive profile showed no deterioration. The patient reported better quality of life. The immediate post-surgical results were promising but too early to draw conclusions.
A CASE OF ARIPIPRAZOLE-INDUCED CHOREA

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Background: Aripiprazole is a second-generation antipsychotic with the property of a dopamine-2 receptor partial agonist, often used as a second-line agent, raising the question of an optimised therapeutic switch after prolonged treatment with typical/atypical neuroleptics.

Case report: A 66-year-old woman had a 20-year history of psychiatric disease treated with various antipsychotics (haloperidol, risperidone). In 2003, after shifting from haloperidol to aripiprazole, she presented with facial dyskinesias. Afterwards dyskinesias diffused to all the body regions and after a few months she had generalised chorea. In 2006, aripiprazole was discontinued and olanzapine was introduced, with a dramatic increase of choreic dyskinesias. At that point the patient was referred to our hospital. The neurological examination revealed: orolingual dyskinesias, generalised chorea, gait unsteadiness, motor impersistence, no apparent cognitive dysfunction. She had no family history of movement disorders. Neuroimaging, laboratory tests and genetic testing revealed no other possible pathogenetic causes of chorea. Olanzapine was discontinued and tetrabenazine was titrated up to 75 mg a day, with a gradual improvement of chorea.

Conclusions: The dyskinesias started after the exposure to aripiprazole. Only a few cases of aripiprazole-induced movement disorders have been reported so far; in one case aripiprazole was reported to improve tardive dyskinesias. Tetrabenazine was effective in treating chorea. Previous exposure of this patient to neuroleptics would increase the basal ganglia responsiveness and favour the agonist profile of aripiprazole. We hypothesise that chronic administration of neuroleptics may lead to dopamine-2 receptor hypersensitivity in the nigrostriatal pathway. This would promote the activation of dopamine-2 receptors by aripiprazole, explaining the emergence of dyskinesias. Tetrabenazine was confirmed to be effective in treating chorea.

BUPROPION: FIRST EXPERIENCE IN HUNTINGTON’S DISEASE

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Background: Depression and especially apathy are central clinical features in Huntington’s disease (HD). Apart from the dopaminergic antidepressant effect, the biochemical structure of bupropion resembles amphetamine structures, resulting in an improvement of apathy.

Methods: Seven patients with depression and apathy with genetically confirmed HD (three men, four women; mean age 51.4 ± 13.2 years) were treated with bupropione 150–300 mg/day. The extent of depression was assessed by the Hamilton Depression Rating Scale (HDRS). Neurological status was documented by the Unified Huntington’s Disease Rating Scales (UHDRS; subscales motor score (MS), independence scale (IS), total functional capacity (TFC)). Ratings were performed initially and in a follow-up investigation 6 months later or at the time of discontinuation of medication.

Results: The mean age of motor onset was 44.4 ± 12.6 years; psychiatric onset was 42.8 ± 14.7 years (n = 6). Initial mean scores for UHDRS were: MS 40.1 ± 24.5; IS 60.0 ± 8.2; TFC 7.1 ± 2.2; HDRS was 19.1 ± 10.7. Due to side effects or the absence of therapeutic effects four of seven patients terminated treatment before maturity. Three patients stopped treatment after several days because of increased irritability (one 300 mg/day and two 150 mg/day). One patient on 150 mg/day stopped treatment after 3 months due to non-response. Of three remaining patients (two 150 mg/day, one 300 mg/day) MS was 54.7 ± 24.5, chorea, IS and TFC were unchanged, whereas HDRS improved to 8.3 ± 4.9. As the initial HDRS for these patients had been 15.3 ± 10.1, the improvement definitely depends on the one patient at 300 mg/day who ameliorated from 26 to 6 with less apathy.

Conclusions: In single HD patients bupropion may be an effective antidepressant. However, we had many non-responders. This effect seems to be dose dependent. In addition, we observed increased irritability in some patients. As this is only an initial case series we emphasise that further research needs to be done on this compound in HD.
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