Brain function changes in Huntington's disease are associated with monoaminergic neurotransmission

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Introduction

Huntington's disease is the most common hereditary neurodegenerative disease, caused by a CAG repeat expansion in the Huntingtin gene and characterized by cognitive, psychiatric, and motoric symptoms. During disease progress, an initial loss of striatal neurons culminates in brain wide atrophy. In parallel, neuronal function as measured with resting state fMRI (rs-fMRI) or FDG-PET is disturbed.

Recently, efforts were made to investigate patho-mechanisms that underly neurodegeneration induced functional alterations by analyzing their spatial correlations with mRNA gene expression maps (derived ex vivo[1]), or with PET/SPECT probability maps of certain receptors or transporters (derived in vivo[2]) in healthy subjects.

Besides sparse research on local neuronal dysfunction, the relationship of functional brain alterations in Huntington's disease with specific neurotransmitter systems remains largely unknown, although corresponding analyses were performed in studies regarding other neurodegenerative diseases.

The **aim** of this study was to elucidate neurotransmitter systems that are associated with local neuronal dysfunction induced by Huntington's disease. Further, we wanted to check whether this association is linked to the disease severity and whether these associations can be replicated in a second, independent cohort.

Methods

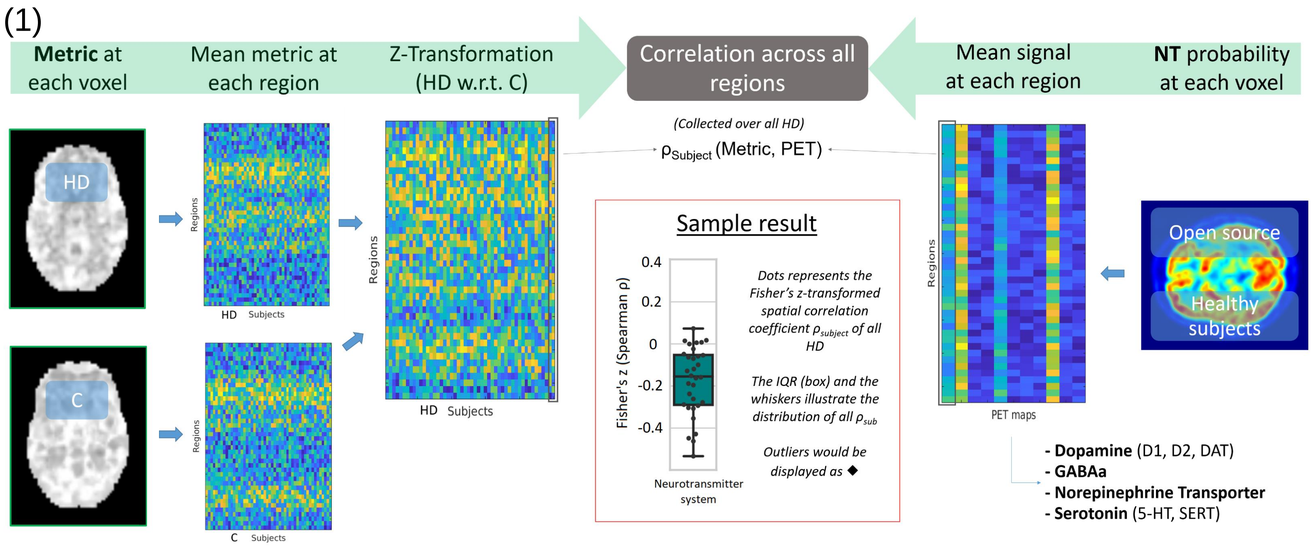
Data:

- Structural and functional (rs-)fMRI (6 min)
- PET/SPECT derived maps of neuro-transmitter systems in healthy populations, provided by *JuSpace*[2] toolbox
- Respective mRNA gene expression maps, provided by *Menga*[1] toolbox
- Two independent cohorts of manifest HD & age and sex matched healthy controls

Preprocessing of rs-fMRI:

1. SPM12[3]: Default preprocessing pipeline including inter alia spatial normalization and smoothing
2. CONN[4]: Two maps of functional connectivity metrics in GM voxel (size 3 mm^3)
   - Fractional amplitude of low frequency fluctuations (**fALFF**), a proxy of local spontaneous activity
   - Local correlation (**LCOR**), a proxy of local activity synchronization

(1)



Contrasts:

- T-contrasts using general linear modelling
  - Age & sex were regressed out

Spatial association (co-localization):

- Spatial correlation analyses of z-transformed maps of fALFF or LCOR of each HD proband (relative to mean fALFF and LCOR map of respective HC group) and
  - Neurotransmitter maps
  - Corresponding mRNA gene expression maps

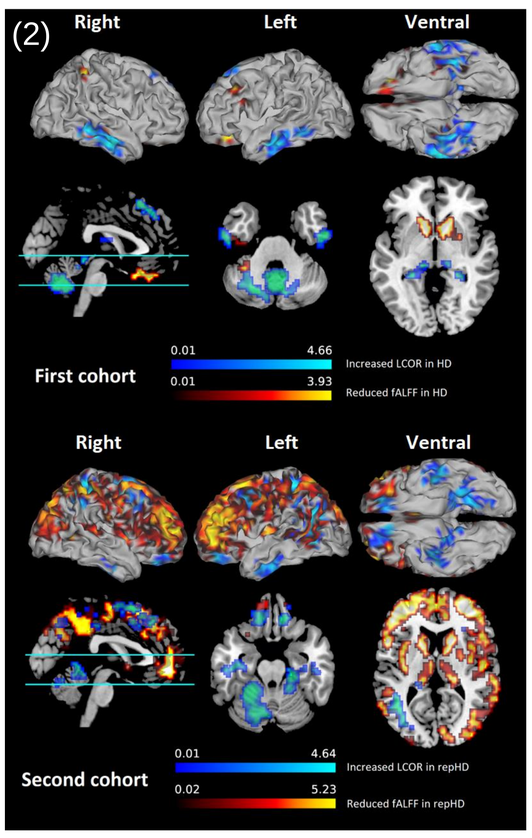
Link to severity:

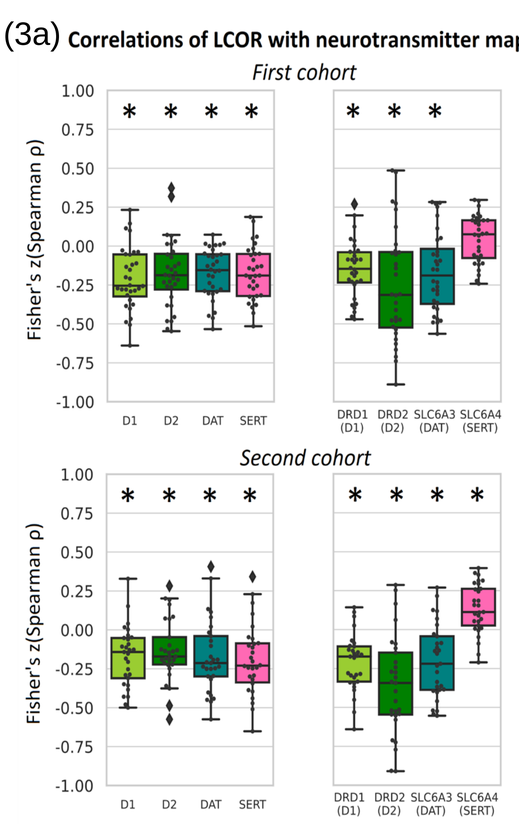
- Correlation analyses of spatial correlation coefficients and sub-scores of the Unified Huntington's Disease Rating Scale (UHDRS):
  - Total Motor Score
  - Function Score
  - Total Functional Capacity (TFC)

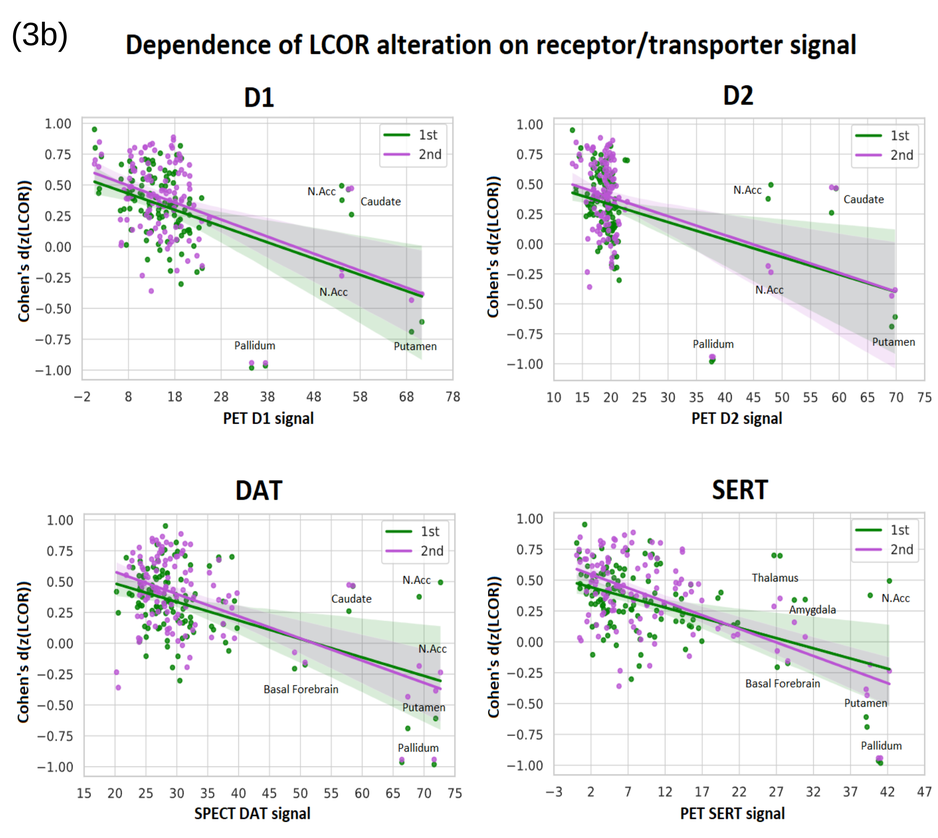
Impact of atrophy:

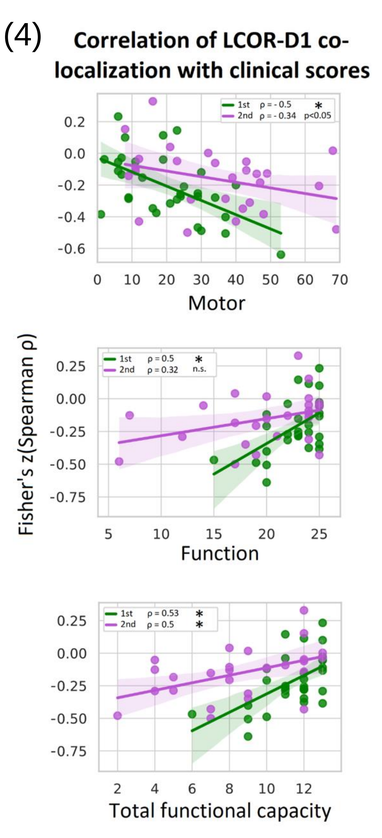
- Repetition of all analyses with previously atrophy-corrected fALFF and LCOR maps

Results









	First cohort		Second cohort	
Group	HD	C	repHD	repC
Number	32	30	29	39
Age in years (μ ± σ)	47.6 ± 9	46.6 ± 9.6	52.2 ± 9.9	50.3 ± 13.6
Sex (m | f | d)	23 | 10 | 0	9 | 14 | 0	17 | 12 | 0	18 | 21 | 0
UHDRS – Motor (μ ± σ)	20.1 ± 12.6	0.6 ± 0.9	34.1 ± 18	-
UHDRS – Function (μ ± σ)	22.9 ± 2.4	25 ± 0	19.8 ± 5.4	-
UHDRS – TFC (μ ± σ)	11.5 ± 1.6	13 ± 0	8.6 ± 3.2	-
TFC disease staging (1|…|5)	25|6|1|0|0	-	9|11|5|1|0	-

Contrasts (Fig. 2)

1st and 2nd cohort:

- fALFF reduction in cortex, basal ganglia, limbic system, cerebellum
- LCOR increase in cortex, thalamus, limbic system, cerebellum

2nd cohort:

- Much more wide-spread pattern of fALFF reduction

Neurotransmitter Systems (Fig. 3a,b):

1st and 2nd cohort:

- LCOR-alteration negatively co-localized with PET/SPECT maps of D1, D2, DAT, SERT and mRNA maps DRD1, DRD2, SLC6A3

2nd cohort:

- LCOR-alteration additionally positively co-localized with SLC6A4
- fALFF-alteration negatively co-localized with 5-HT1b, μ-opioid receptor, and HTR1b

Link to severity (Fig. 4):

- Strength of co-localization of D1 with LCOR-alteration correlated significantly with motor and functional symptom severity

Impact of atrophy:

- Results largely similar after atrophy correction

Interpretation

Contrasts

- Functional alterations located in key cortical and sub-cortical areas for motor behavior and cognition
- Pattern similar to literature[5,6]
- Discrepancy between 1st and 2nd cohort in terms of voxel-wise differences could be due to the more advanced stage of 2nd cohort
- Discrepancy possibly indicates progression of disease

Neurotransmitter systems

- Disturbed local synchronization co-localized with dopaminergic and serotonergic systems
- These systems might be particularly vulnerable to HD pathology
- Increased cortical synchronization may reflect uncoupling from subcortical (e. g. basal ganglia) input
- Decreased sub-cortical synchronization may be the result of a general loss of neuronal activity (neuronal death)
- Fits to previous studies that reported cortical and sub-cortical changes in respective neurotransmitter systems[7]
- Fits with the fact that these systems play a key role in motor behavior and cognition, both of which are impaired in HD

Conclusion

- Robustness of our findings underpinned by
  - Consistent results on mRNA level
  - Link to disease severity
  - Replication in second, independent cohort
- Co-localization effects may be biomarker of disease staging in HD

References

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