Tapping linked to function and structure in premanifest and symptomatic Huntington disease

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ABSTRACT

Objective: Motor signs are functionally disabling features of Huntington disease. Characteristic motor signs define disease manifestation. Their severity and onset are assessed by the Total Motor Score of the Unified Huntington's Disease Rating Scale, a categorical scale limited by interrater variability and insensitivity in premanifest subjects. More objective, reliable, and precise measures are needed which permit clinical trials in premanifest populations. We hypothesized that motor deficits can be objectively quantified by force-transducer-based tapping and correlate with disease burden and brain atrophy.

Methods: A total of 123 controls, 120 premanifest, and 123 early symptomatic gene carriers performed a speeded and a metronome tapping task in the multicenter study TRACK-HD. Total Motor Score, CAG repeat length, and MRIs were obtained. The premanifest group was subdivided into A and B, based on the proximity to estimated disease onset, the manifest group into stages 1 and 2, according to their Total Functional Capacity scores. Analyses were performed centrally and blinded.

Results: Tapping variability distinguished between all groups and subgroups in both tasks and correlated with 1) disease burden, 2) clinical motor phenotype, 3) gray and white matter atrophy, and 4) cortical thinning. Speeded tapping was more sensitive to the detection of early changes.

Conclusion: Tapping deficits are evident throughout manifest and premanifest stages. Deficits are more pronounced in later stages and correlate with clinical scores as well as regional brain atrophy, which implies a link between structure and function. The ability to track motor phenotype progression with force-transducer-based tapping measures will be tested prospectively in the TRACK-HD study. ***Neurology*® 2010;75:2150–2160**

GLOSSARY

CoV = coefficient of variation; **DBS** = disease burden score; **Freq** = frequency; **HD** = Huntington disease; **ICV** = intracranial volume; **IOI** = interonset interval; **ΔIOI** = deviation from interonset interval; **IPI** = interpeak interval; **ΔIPI** = deviation from interpeak interval; **ITI** = intertap interval; **log** = logarithmic; **MT** = metronome tapping; **ΔMTI** = deviation from midtap interval; **preHD** = premanifest Huntington disease; **RT** = reaction time; **ST** = speeded tapping; **TD** = tap duration; **TF** = tapping force; **TFC** = Total Functional Capacity; **UHDRS** = Unified Huntington's Disease Rating Scale; **UHDRS-TMS** = Unified Huntington's Disease Rating Scale–Total Motor Score; **VBM** = voxel-based morphometry.

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder. Motor deficits, such as chorea, bradykinesia, and dystonia, are ascribed to basal ganglia dysfunction.[1] Nevertheless, widespread cortical[2] and white matter[3,4] loss develop, contributing to the complex clinical phenotype and functional decline observed in HD.[5]

Initial changes in HD gene carriers are detected years before diagnosis[6,7] favoring an early introduction of disease-modifying therapies. Motor signs are amenable to quantita-

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tive assessment and may provide objective measures for disease onset and progression. Several quantitative motor tasks, including force-transducer-based assessments, detect deficits in premanifest gene carriers.[7-9] In tapping tests, they were related to predicted time to diagnosis.[6] Correlations with the Unified Huntington's Disease Rating Scale–Total Motor Score (UHDRS-TMS) and its arm subscore were observed; performance deteriorated during a 3-year follow-up in manifest HD.[10]

These results support further exploration of quantitative tapping assessments in HD. We used precalibrated sensors to assess isometric tapping forces standardized across 4 centers. Recording forces permits 1) accurate evaluation of tap initiation (avoiding delays caused by vertical movements in button-pressing devices and the omission of taps through incomplete depression) and 2) definition of new variables of tapping performance derived from force evolution or peaks. Automated evaluation routines provide a standardized readout. We hypothesized that deficits in a speeded and a metronome tapping task are detectable in premanifest and early symptomatic HD, and correlate with 1) disease burden, 2) clinical motor signs of HD, 3) regional gray and white matter atrophy, and 4) cortical thinning.

METHODS

Subjects. A total of 123 patients with early HD (HD), 120 premanifest gene carriers (preHD), and 123 control subjects were recruited in 4 centers (Leiden, London, Paris, Vancouver) as part of the biomarker study TRACK-HD.[7] Selection criteria for preHD included a Disease Burden Score (DBS = [CAG repeat − 35.5] × age)[11] >250 and a UHDRS-TMS ≤5 at the screening visit. All gene carriers required a CAG expansion of ≥40 repeats. PreHD was further split at the median of years until predicted disease manifestation, i.e., 10.8 years, into preHD-A and preHD-B,[12] early manifest participants into stages 1 (HD1) and 2 (HD2) according to their Total Functional Capacity (TFC) scores.[13] Control subjects were age- and gender-matched to the combined gene-positive group and required negative genetic testing if at risk for HD. Gene-positive participants were assessed clinically using the UHDRS-TMS. Handedness was determined according to the Edinburgh Inventory[14]; ambidextrous subjects were considered right-handed. See table e-1 on the *Neurology*® Web site at www.neurology.org for demographics; more detailed information can be found elsewhere.[7]

Standard protocol approvals and patient consents. The study was approved by all local ethical standards committees on human experimentation; written informed consent was obtained from all subjects.

Tapping. The tapping apparatus was equipped with precalibrated and temperature-controlled force sensors (Mini-40, ATI) covered with sandpaper. Normal forces were recorded at 0.025 N resolution and 400 Hz sampling frequency. WINSC/WINZOOM software (University of Umeå, Sweden) was used for recording and data analysis. A high-pitched tone of 0.25 s duration served as cue. Subjects placed their nondominant hands on a rest, the index finger above the force-transducer (figure 1A). Recording started after practice periods.

Speeded tapping required maximal possible velocity between 2 cues. In metronome tapping, subjects were presented with 10 auditory pacing tones at 1.8 Hz (0.55 s intercue interval) and instructed to harmonize their fingertaps with the pacing tones. A self-paced phase of 10 seconds followed and ended with another auditory cue. Subjects performed five 10-second trials in both conditions (figure 1, D and E).

Quality control and analyses were performed centrally and blinded to subject groupings. Automated routines were created for data evaluation in WINZOOM and Visual Basics for Applications in Excel®. Statistical analyses were performed by an independent, centralized team of statisticians.

The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. Metronome tapping analysis was solely based on the self-paced period of the trial.

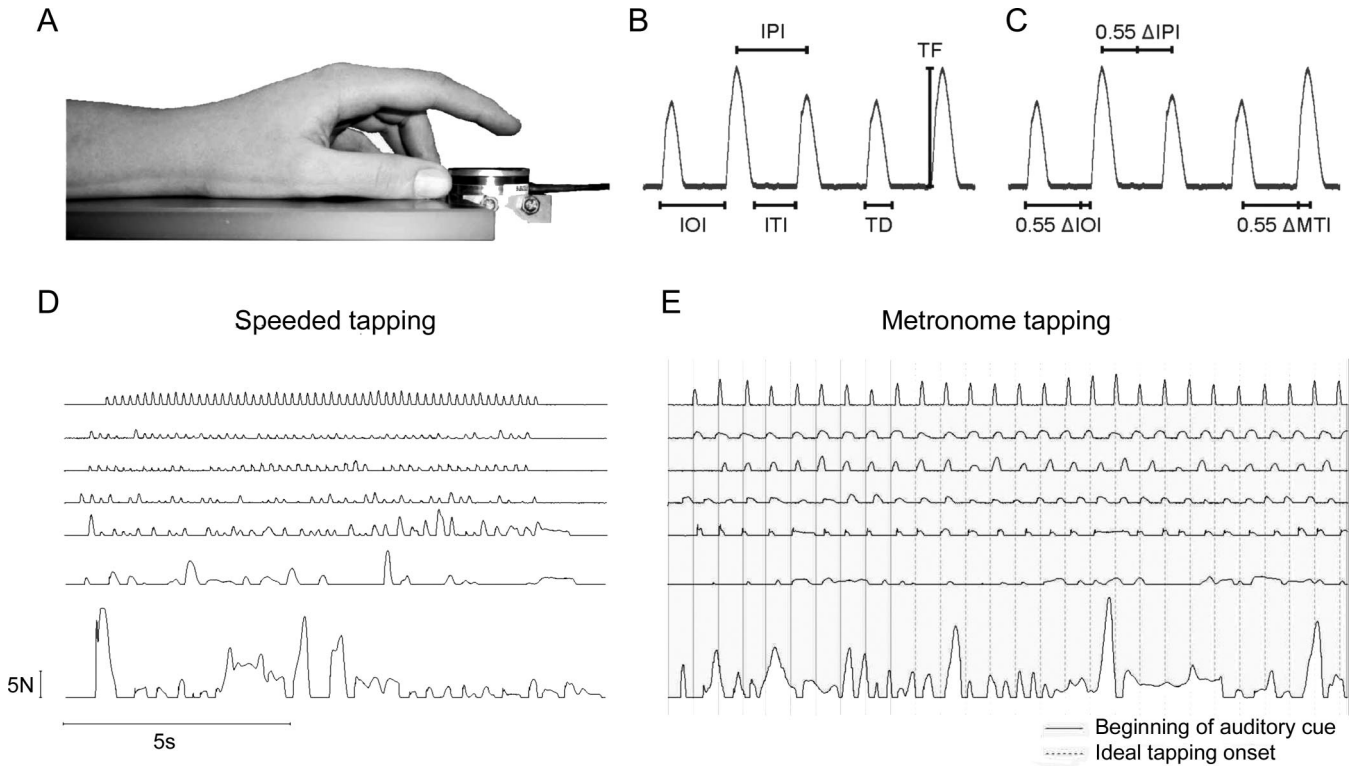
The variability of tap durations (TD), interonset intervals (IOI), interpeak intervals (IPI), and intertap intervals (ITI) were the primary outcome measures for speeded tapping (figure 1B). In addition, variability of peak tapping forces (TF) was calculated as coefficient of variation, and the tapping frequency (Freq), i.e., the number of taps between the onsets of the first and the last tap divided by the time in between, were determined.

For the metronome task, TD, ITI, and TF were analogously defined (figure 1C). Furthermore, the intercue interval was subtracted from the IPIs (ΔIPI), the interval between the midpoints (ΔMTI, i.e., the tapping measure published in Tabrizi et al.[7]), and the onsets (ΔIOI) of 2 consecutive taps. The reaction time (RT) until the onset of the first tap was calculated.

MRI. All participants underwent 3-T MRI scans with standardized protocols for Siemens and Phillips scanners. Volumetric brain measures included striatal and total intracranial volume (ICV), voxel-based morphometry (VBM), and cortical thickness (assessed by Freesurfer). Details can be found elsewhere.[7] Only explicitly right-handed subjects were included in imaging analyses as a lack of symmetry in left- and right-handed subjects has been suggested.[15] Freesurfer methods are optimized for Siemens scanners, therefore cortical thickness correlations only included the scans of 2 sites.

Statistics. In this cross-sectional analysis, the 5 subgroups (control, preHD-A, preHD-B, HD1, and HD2) were the a priori predictor variables of interest for all speeded and metronome tapping measures. Potential confounders (i.e., age, gender, study site, and education level) were controlled for in all formal analyses. We estimated adjusted differences among groups and subgroups using linear models. Furthermore, in the case of outcomes originally measured as SDs of mean performance, we performed logarithmic and inversed transformations prior to analyses. These transformations greatly improved concordance with standard normality assumptions for linear model inference. Although inversed

Figure 1 Data acquisition, variables, and examples



(A) Setup of the tapping device and position of hand and index finger in relation to the force-transducer. (B) Definitions of measures for speeded tapping (IOI = interonset interval; IPI = interpeak interval; ITI = intertap interval; TD = tap duration; TF = tap force) and (C) additional measures in metronome tapping (ΔIOI = deviation from IOI = IOI − 0.55 s, ΔIPI = deviation from IPI = IPI − 0.55 s, ΔMTI = midtap interval = [interval time between the arithmetic middles of 2 consecutive taps] − 0.55). (D, E) Finger tapping shows deterioration in advanced stages of Huntington disease. A range of sample recordings from (top to bottom) good to poor performance are given for (D) speeded tapping and (E) metronome tapping—the solid gray lines represent the onset of auditory cues in metronome tapping, the continued dashed lines mark the ideal rate after cues stopped.

transforms have been used in previous similar analyses,[6,7] we focus on logarithmic transforms, since they constantly yielded better mathematical assumptions for model inference.

Associations between tapping measures, the UHDRS-TMS, TFC, and DBS were analyzed by Pearson correlation for the preHD, HD, and a combined gene-positive group. For premanifest participants, measures were correlated to probability of estimated disease onset within 5 years according to Langbehn et al.'s parametric model[12,16] and for all gene-positive participants to the ratio of striatal to intracranial volume (striatal/ICV) by a least squares regression model.

A hypothesis-free analysis was performed to identify correlation between regional atrophy assessed in VBM and tapping impairment in the combined gene-positive group. A multiple regression model was used with age, gender, ICV, and disease burden, accounting for disease severity, as covariates. An explicit mask generated using the optimal thresholding technique[17] was used to specify the location of statistical testing. Results are reported corrected for familywise error, at the $p < 0.05$ level.

Similarly, the amount of cortical thickness decrease was correlated with selected tapping measures in a subgroup consisting of all gene-positive subjects scanned by Siemens MRI machines. A surface-based regression analysis was used, with age, gender, and disease burden as covariates. Each score was modeled independently, using a model of the thickness for each subtest [offset + (slope × motor score) + (slope × age) + an error term]. The offset and slope are subject-independent regression coefficients estimated separately for each vertex using a general linear model. t Statistics at each vertex were used to test the hypothesis that the slope coefficient was equal to zero. Results are reported corrected for a false discovery rate at the $p < 0.01$ level.

RESULTS

Between-group and -subgroup comparisons. All speeded tapping intervals (IPI, IOI, ITI, and TD) distinguished at $p < 0.0001$ throughout groups and delineated all subgroups with one exception: ITI in HD2 vs HD1 was not significant (table 1, table e-2, and figure 2A). Speeded tapping intervals best distinguished the preHD-A group from controls with the highest effect size for IOI. Best subgroup differentiation was observed for HD1 vs preHD-B. Peak TF distinguished between groups, although with lower effect sizes, but not between all subgroups. The tapping frequency also did not differentiate all subgroups, but exhibited the strongest effect size at the threshold between HD1 and preHD-B (figure 2A).

All metronome tapping intervals (ΔIPI, ΔMTI, ΔIOI, ITI, and TD) differentiated all groups ($p < 0.0001$). Each subgroup distinction was made at $p < 0.0001$, however, by different variables. ΔMTI and ITI in preHD-A vs controls and TD in preHD-B vs

Table 1 Between-group comparisons[a]

	PreHD vs controls	HD vs controls	HD vs preHD	PreHD-A vs controls	PreHD-B vs preHD-A	HD1 vs preHD-B	HD2 vs HD1
Speeded tapping							
Intervals							
IPI	1	2.36	1.52	0.85	0.42	1.13	0.43
log SD	<0.0001	<0.0001	<0.0001	<0.0001	0.0317	<0.0001	0.0416
IOI	1.03	2.37	1.53	0.9	0.41	1.15	0.41
log SD	<0.0001	<0.0001	<0.0001	<0.0001	0.0356	<0.0001	0.0426
ITI	0.98	2.31	1.42	0.84	0.38	1.09	0.27
log SD	<0.0001	<0.0001	<0.0001	<0.0001	0.0446	<0.0001	0.3432
TD	0.89	2.14	1.53	0.71	0.5	1.14	0.52
log SD	<0.0001	<0.0001	<0.0001	0.0047	0.0281	<0.0001	0.0011
Additional variables							
TF	0.55	1.21	0.71	0.48	0.26	0.53	0.28
CoV	0.0002	<0.0001	<0.0001	0.0204	0.2005	0.0061	0.1111
Freq	−0.34	−1.96	−1.73	−0.21	−0.27	−1.46	−0.32
	0.0357	<0.0001	<0.0001	0.3661	0.1456	<0.0001	0.0654
Metronome tapping							
Intervals							
ΔIPI	0.63	1.83	1.42	0.37	0.59	1.06	0.75
log SD	<0.0001	<0.0001	<0.0001	0.0445	0.016	<0.0001	<0.0001
ΔMTI	0.61	2.07	1.62	0.28	0.79	1.14	0.75
log SD	<0.0001	<0.0001	<0.0001	0.0704	<0.0001	<0.0001	<0.0001
ΔIOI	0.65	2.06	1.59	0.32	0.8	1.16	0.73
log SD	<0.0001	<0.0001	<0.0001	0.041	<0.0001	<0.0001	0.0002
ITI	0.59	1.99	1.6	0.23	0.89	1.14	0.55
log SD	<0.0001	<0.0001	<0.0001	0.0924	<0.0001	<0.0001	0.004
TD	0.76	1.77	1.15	0.65	0.29	0.83	0.73
log SD	<0.0001	<0.0001	<0.0001	<0.0001	0.0728	<0.0001	0.0001
Additional variables							
TF	0.61	1.71	1.15	0.56	0.05	1.18	0.63
CoV	0.0001	<0.0001	<0.0001	0.0031	0.6518	<0.0001	<0.0001
RT	0.28	0.48	0.14	0.33	−0.06	0.14	0.09
	0.0365	0.0006	0.2059	0.0577	0.7658	0.324	0.7302

Abbreviations: CoV = coefficient of variation; Freq = frequency; HD = Huntington disease; IOI = interonset interval; ΔIOI = deviation from interonset interval; IPI = interpeak interval; ΔIPI = deviation from interpeak interval; ITI = intertap interval; log = logarithmic; ΔMTI = deviation from midtap interval; preHD = premanifest Huntington disease; RT = reaction time; TD = tap duration; TF = tapping force.

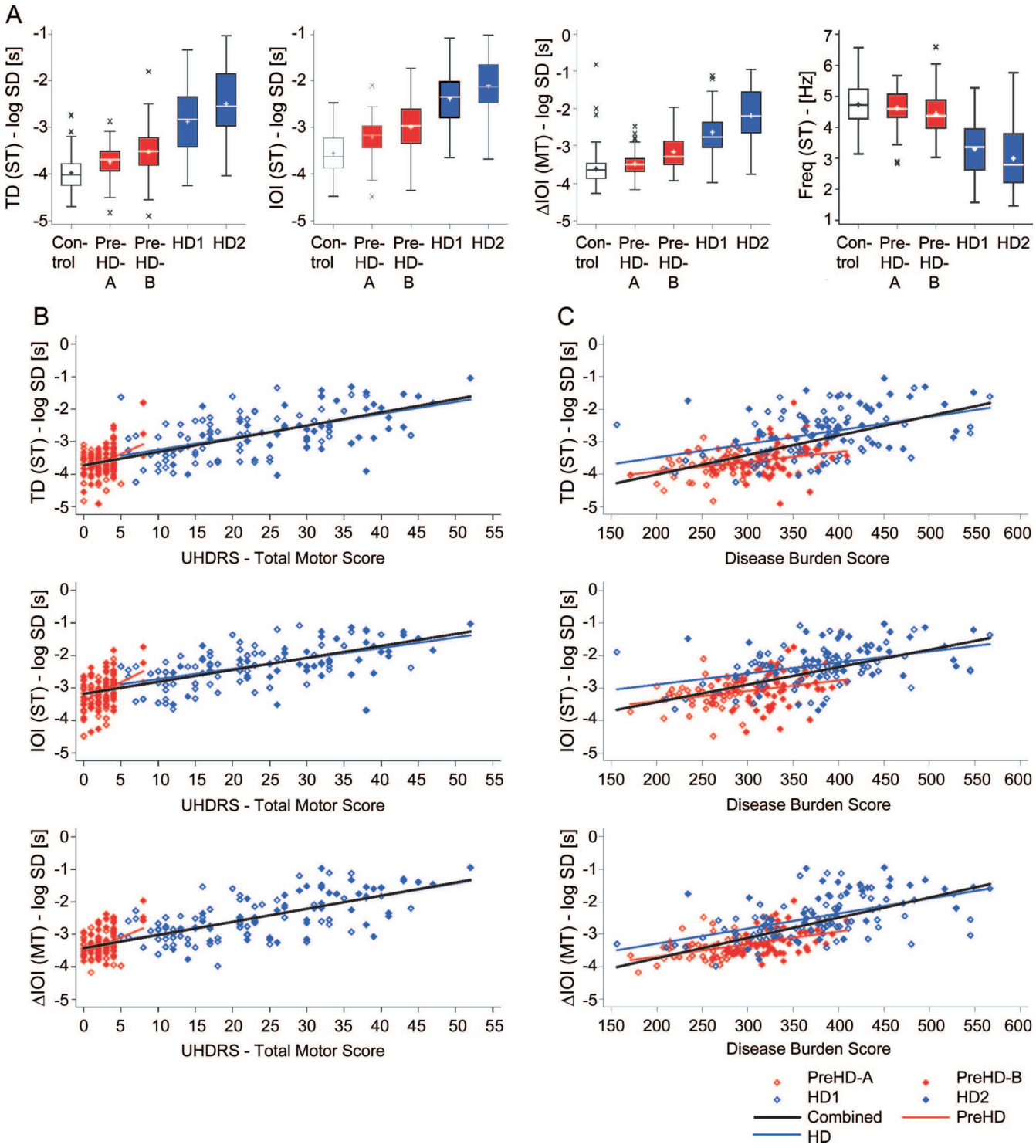
[a] Values are adjusted effect sizes and specific estimates (*p* values).

preHD-A did not reach significance. ΔIOI performed well throughout all group and subgroup comparisons. Metronome tapping intervals better distinguished preHD-B vs preHD-A and HD2 vs HD1 compared to speeded tapping. Again, best subgroup differentiation was observed for HD1 vs preHD-B. TF reached significance for all group and subgroup comparisons except preHD-B vs preHD-A. The reaction time did not distinguish HD vs preHD or any subgroups.

We did not observe interactions between study site and subgroup for any of the variables.

DBS and UHDRS-TMS correlations. The variability of all speeded tapping intervals correlated with the DBS and UHDRS-TMS in all groups. The correlations to the fingertap subscore were significant for the combined gene-positive (HD + preHD) and the HD group but mostly failed significance for preHD. The combined group presented higher *r* values than

Figure 2 Box plots and correlation analysis of selected tapping items by subgroups



(A) Unadjusted results of the nondominant hand of tap duration (TD) (speeded tapping [ST]), interonset interval (IOI) (ST), deviation from interonset interval (ΔIOI) (metronome tapping [MT]), and frequency (Freq – ST). Correlations between tapping variables and (B) Unified Huntington's Disease Rating Scale–Total Motor Score and (C) Disease Burden Score (DBS = [CAG repeat – 35.5] × age).[11] Correlations are displayed for TD (ST), IOI (ST), and ΔIOI (MT). For *r* values, please see table 2. HD = Huntington disease.

the HD or preHD group. Correlations to the UHDRS-TMS were slightly higher than to the DBS or UHDRS-TMS fingertap subscore. TD showed strongest correlations to nearly all scores. Correlations of TF variability (CoV) to UHDRS-TMS and DBS were weaker than those of the interval variables, the preHD results did not correlate to the DBS, and only the combined group showed correlations to the

Table 2 Pearson correlations of the tapping variables with disease burden, UHDRS-TMS, and its fingertap subitem[a]

	DBS			UHDRS-TMS			UHDRS-fingertaps		
Variable	Combined	HD	PreHD	Combined	HD	PreHD	Combined	HD	PreHD
Speeded tapping									
Intervals									
IPI	0.58	0.4	0.31	0.7	0.56	0.38	0.58	0.42	0.18
log SD	<0.0001	<0.0001	0.0007	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0513
IOI	0.58	0.41	0.31	0.7	0.56	0.38	0.59	0.42	0.2
log SD	<0.0001	<0.0001	0.0008	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0337
ITI	0.52	0.32	0.27	0.62	0.44	0.29	0.48	0.31	0.06
log SD	<0.0001	0.0004	0.0029	<0.0001	<0.0001	0.0013	<0.0001	0.0008	0.5299
TD	0.6	0.43	0.32	0.72	0.55	0.38	0.63	0.45	0.29
log SD	<0.0001	<0.0001	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0015
Additional variables									
TF	0.32	0.2	0.15	0.39	0.3	0.2	0.27	0.17	0
CoV	<0.0001	0.0282	0.1021	<0.0001	0.0011	0.0291	<0.0001	0.0697	0.9722
Freq	−0.6	−0.44	−0.23	−0.72	−0.53	−0.17	−0.62	−0.45	−0.17
	<0.0001	<0.0001	0.0131	<0.0001	<0.0001	0.0596	<0.0001	<0.0001	0.0717
Metronome tapping									
Intervals									
ΔIPI	0.63	0.51	0.34	0.73	0.62	0.33	0.61	0.44	0.3
log SD	<0.0001	<0.0001	0.0002	<0.0001	<0.0001	0.0003	<0.0001	<0.0001	0.0008
ΔMTI	0.66	0.51	0.45	0.76	0.63	0.36	0.65	0.48	0.31
log SD	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0008
ΔIOI	0.67	0.51	0.46	0.76	0.64	0.38	0.65	0.49	0.31
log SD	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0006
ITI	0.66	0.47	0.51	0.73	0.56	0.42	0.62	0.4	0.35
log SD	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TD	0.58	0.49	0.27	0.7	0.65	0.22	0.54	0.43	0.12
log SD	<0.0001	<0.0001	0.0027	<0.0001	<0.0001	0.016	<0.0001	<0.0001	0.2008
Additional variables									
TF	0.44	0.29	0.08	0.64	0.54	0.22	0.51	0.39	0.08
CoV	<0.0001	0.0014	0.419	<0.0001	<0.0001	0.0184	<0.0001	<0.0001	0.4182
RT	0.03	0	−0.03	0.04	−0.05	0.15	0.08	0.03	0.08
	0.628	0.9622	0.7322	0.5314	0.5507	0.1137	0.2257	0.783	0.4175

Abbreviations: CoV = coefficient of variation; DBS = disease burden score; Freq = frequency; HD = Huntington disease; IOI = interonset interval; ΔIOI = deviation from interonset interval; IPI = interpeak interval; ΔIPI = deviation from interpeak interval; ITI = intertap interval; log = logarithmic; ΔMTI = deviation from midtap interval; preHD = premanifest Huntington disease; RT = reaction time; TD = tap duration; TF = tapping force; UHDRS = Unified Huntington's Disease Rating Scale; UHDRS-TMS = Unified Huntington's Disease Rating Scale–Total Motor Score.

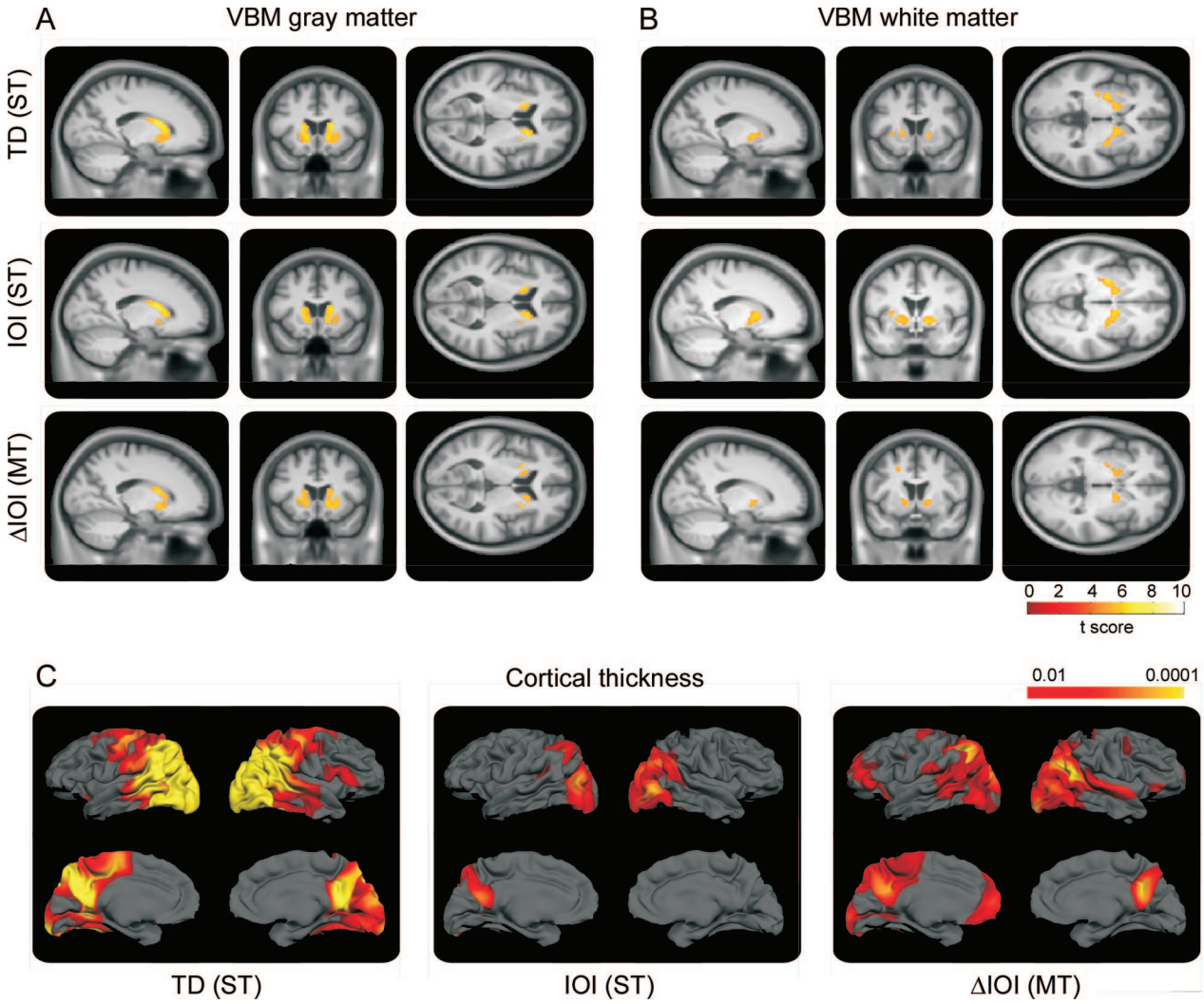
[a] Pearson correlation coefficients: Prob > r under H0: rho = 0.

UHDRS-fingertap subitem. The tapping frequency correlated well with the UHDRS scores and DBS in the HD and combined groups; preHD results were only correlated to the DBS.

Variability of metronome tapping intervals correlated with DBS, UHDRS-TMS (figure 2, B and C), and UHDRS-TMS fingertaps throughout groups with an exception in TD for the preHD group (table 2). Metronome tapping correlations were strongest in the combined group. TF variability performed weaker than the interval measures, the preHD results only correlated with the UHDRS-TMS. Reaction time was not correlated to disease burden or motor scores at all.

Associations with other measures. Linear models showed an association between nearly all investigated variables and estimated disease onset within 5 years ($p < 0.0001$) in the premanifest group.[12,16] The performance of the gene-positive subjects was associated

Figure 3 Structural brain correlations to tapping performance



(A–C) Statistical parametric map showing correlations between tap duration (TD) (speeded tapping [ST]), interonset interval (IOI) (ST), and deviation from interonset interval (ΔIOI) (metronome tapping [MT]) with gray (A) and white matter (B) in voxel-based morphometry (VBM) (results overlaid on a mean image from this dataset are shown, thresholded at $p < 0.05$, corrected for multiple comparisons using familywise error) and (C) cortical thickness (results are corrected for a false discovery rate at $p < 0.01$).

with the ratio striatal/ICV ($p < 0.0001$). The reaction time was the only variable that did not reveal either association.

Imaging correlations. Objective whole-brain correlations between tapping variability and brain volumes as observed by VBM revealed highly significant correlations across the combined gene-positive group (figure 3, A and B, and figure e-1). Increased TD variability correlated with gray matter atrophy bilaterally in the caudate and putamen and to a lesser extent with the right superior temporal and the left precentral gyrus. TD variability also correlated with bilateral loss of the internal and external capsule and the white matter of the superior temporal gyrus. Increased IOI variability was primarily associated with atrophy of the caudate and putamen bilaterally with slightly more involvement of the right side; an association was also seen with a small region of the right superior temporal gyrus. IOI variability correlated with the internal capsule bilaterally, the left external capsule, the right superior temporal, and the left frontal subgyral white matter. Increased ΔIOI variability correlated with gray matter loss of the caudate and putamen. Also white matter loss correlated with increased ΔIOI variability in the extrastriatal white matter including the internal capsule, as well as the left subgyral white matter of the frontal lobe.

Surface-based correlation analysis of tapping measures with changes in cortical thickness revealed correlations between the variability observed in tapping and cortical thickness diminution across the 2 Siemens scanners (figure 3C). In speeded tapping, variability of TD and IOI were both correlated with loss of cortical thickness. Strongest correlations were seen

for TD, primarily in the occipital, parietal, and primary motor cortex. IOI correlations were weaker and limited to occipital and parietal regions. Similar results were observed for ΔIOI in metronome tapping in the occipito-parietal region, while additional correlations were observed in the frontal cortex.

DISCUSSION Force-transducer-based tapping objectively quantified motor deficits in premanifest and symptomatic HD gene carriers and distinguished between all groups and subgroups. Correlations to disease burden, UHDRS-TMS, and the reduction of brain volume in VBM and cortical thickness were demonstrated, suggesting a link between structure and function. Our results extend earlier findings on tapping deficits in HD. Paulsen et al.[6] reported timing deficits in a tapping task up to a decade before predicted disease onset in a premanifest cohort. Tapping deficiencies in manifest HD and their correlation to the UHDRS-TMS have been described in smaller cohorts.[18,19] Deficits are reproducible in repeated measurements[19] and progress over time in manifest HD.[10,19]

TRACK-HD assessed a large cohort of premanifest and symptomatic gene carriers and controls. The UHDRS-TMS commonly serves as a primary or secondary outcome measure in clinical trials. However, the UHDRS-TMS is a categorical scale with limited sensitivity. It is susceptible to subjective error and interrater variability[20,21] and was designed for manifest HD.[22] Many studies define premanifest HD by a UHDRS-Diagnostic Confidence Level of 3 or lower. Subjects with up to 98% diagnostic certainty for manifest HD—based on the presence of characteristic motor signs—are thus considered premanifest. Accordingly, premanifest subjects may show noticeable motor signs with an impact on motor task performance. Study requirements in TRACK-HD limited clinical motor signs to a marginally noticeable level. Minor signs (UHDRS-TMS $\leq$5) were tolerated since instilled behavior has been reported in gene-negative offspring of HD families.[20] Accordingly, gene-negative family members in the PREDICT-HD study exhibited a mean UHDRS-TMS of 2.41 (SD 3.06).[23]

The index finger is crucial for many fine motor tasks and thus well-trained, minimizing the potential impact of motor learning. Variability of motor task execution has been observed in several tasks, e.g., grasping,[24,25] tongue protrusion,[7] gait,[26] and reaching.[9] Accordingly, variability of motor coordination appears to be a characteristic sign of HD.

Motor timing is another substantial component of motor coordination and thus precise motor functioning. There is also evidence for increased timing variability in HD,[27] even in a premanifest state.[28] Higher variability of isometric contraction duration was interpreted as an impairment of the speed control system in manifest HD.[29] Impaired time estimation in premanifest gene carriers correlated with the estimated years until onset.[30] Both speeded and metronome tapping assessments require motor timing efforts. However, the tasks were designed to be relatively simple, not only to be easily applicable in various settings, but also minimizing the impact of working memory dysfunction, which occurs in HD.[31] Demanding more attention, the metronome tapping task could be more influenced by memory dysfunction and cognitive deficits than the speeded tapping task. Nevertheless, both tasks detected deficits in tapping across all subgroups.

TRACK-HD provides the unique opportunity to correlate motor performance with structural brain changes employing 2 complementary imaging techniques under standardized, blinded conditions. We acknowledge that cortical thickness data were limited to 2 sites using Siemens scanners to avoid differing image contrast and variation in segmentation routines. Also, different methods for multiple comparison correction were used for the 2 techniques, which may partially account for lacking cortical correlations in VBM. However, the parameters were optimized for each technique.

The results suggest a strong link between structure and motor function that has not yet been demonstrated in a comparable cohort in HD. Nevertheless, we acknowledge that these correlations may reflect a common association with overall HD progression rather than a direct functional association. We are aware that etiologic conclusions may only be derived from functional imaging techniques.[32] The use of fMRI in multicenter studies remains a challenge for future developments, however, the literature provides us with ample evidence for an overlap between affected brain regions and tapping tasks.

Several brain regions predominantly affected in HD play an important role in internal time-keeping processes. Timing processes in self-paced tapping involve the SMA,[33] premotor cortex,[33,34] dorsolateral prefrontal cortex,[35] and basal ganglia.[36,37] Functional compensation mechanisms have been postulated in premanifest HD.[38,39]

White matter changes were suggested to represent the earliest measurable changes in HD and precede cell death.[3] Information processing speed assessed by intraindividual variability in a reaction time task was associated with decreased white matter volume.[40] As a repetitive task, speeded tapping requires rapid execution of extension-flexion movements and thus

rapid cerebral processing. Accordingly, we found speeded tapping measures to distinguish better between preHD-A and controls. Additionally, IOI (speeded tapping) correlated more strongly with internal capsule volume than ΔIOI (metronome tapping). Thus initial changes may be partially due to processes underlying movement preparation and execution, possibly white matter changes. Speeded tapping may therefore be of particular interest in the assessment of earliest changes. In contrast, the speeded tapping frequency showed the greatest contrast between preHD-B and HD1, and may serve as disease onset marker.

TD shows a distinct character with higher effect sizes in between-group and subgroup comparisons in speeded tapping; TD best distinguishes between preHD-A and controls among the metronome tapping variables. Interestingly, TD (speeded tapping) shows markedly stronger cortical thickness correlations than the other investigated variables; its specific distribution may thus be due to a stronger impact of cortical pathology.

In this cross-sectional study, force-transducer-based speeded and metronome tapping tasks provided sensitive, objective measures of motor dysfunction. Motor deficits in premanifest and premotor HD gene carriers were measurable in a subgroup of gene carriers with a median of 14 years (preHD-A) before estimated disease onset; earliest changes seem to be more sensitively detectable in speeded tapping, whereas some later stages of disease are more reliably distinguished by the metronome task. Tapping interval variability was the most robust quantitative motor measure and correlated with disease genotype and phenotype as well as structural changes within the brain. Although evidence for pathophysiologic changes underlying tapping impairment in HD is ample, distinct processes are diverse and remain speculative. Tapping devices are portable and can be easily applied in an outpatient setting by trained technicians. They may increase the sensitivity and reliability of motor measurements in clinical trials and supplement or even ultimately substitute categorical rating scales. Their sensitivity in detecting disease progression will be investigated prospectively in the TRACK-HD study.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by T. Acharya and Dr. D.R. Langbehn.

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