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Striatal morphology and neurocognitive dysfunction in Huntington disease: The IMAGE-HD study

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ABSTRACT

We aimed to investigate the relationship between striatal morphology in Huntington disease (HD) and measures of motor and cognitive dysfunction. MRI scans, from the IMAGE-HD study, were obtained from 36 individuals with pre-symptomatic HD (pre-HD), 37 with early symptomatic HD (symp-HD), and 36 healthy matched controls. The neostriatum was manually segmented and a surface-based parametric mapping protocol derived two pointwise shape measures: thickness and surface dilation ratio. Significant shape differences were detected between all groups. Negative associations were detected between lower thickness and surface area shape measure and CAG repeats, disease burden score, and UHDRS total motor score. In symp-HD, UPSIT scores were correlated with higher thickness in left caudate tail and surface dilation ratio in left posterior putamen; Stroop scores were positively correlated with the thickness of left putamen head and body. Self-paced tapping (slow) was correlated with higher thickness and surface dilation ratio in the right caudate in symp-HD and with bilateral putamen in pre-HD. Self-paced tapping (fast) was correlated with higher surface dilation ratio in the right anterior putamen in symp-HD. Shape changes correlated with functional measures subserved by corticostriatal circuits, suggesting that the neostriatum is a potentially useful structural basis for characterisation of endophenotypes of HD.

1. Introduction

1.1. The role of the striatum in Huntington disease

Huntington Disease (HD) is caused by a genetic mutation in the *huntingtin* gene, and leads to progressive and currently irreversible motor, psychiatric and cognitive decline (Vonsattel et al., 1985). Multiple studies are utilising clinical, cognitive, neuropsychiatric, and imaging data to better understand the progression of HD, and to identify biomarkers for use as endpoints in clinical trials (Paulsen et al.,

Abbreviations: BDI II, Beck Depression Inventory score Version II; DBS, Disease burden score; FrSBe, Frontal Systems Behaviour Scale; HADS A and HADS D, Hospital Anxiety and Depression Scales; HD, Huntington Disease; ITIPTAP fast average, inter-trial interval in participant passed tapping, fast 3 Hz; ITIPTAP slow average, inter-trial interval in participant passed tapping, slow 1.8 Hz; ITISTAP, inter-trial interval in speeded tapping; ICV, intracranial volume; pre-HD, pre-manifest, or pre-symptomatic HD; SCOPI, Schedule of Compulsions Obsessions and Pathological Impulses; symp-HD, symptomatic HD; UHDRS, Unified Huntington Disease Rating Scale; UPSIT, University of Pennsylvania Smell Identification Test

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2008; Tabrizi et al., 2009; Georgiou-Karistianis et al., 2013a, b). Atrophy of the neostriatum (caudate nucleus and putamen) has been well established in premanifest HD (pre-HD) more than a decade prior to disease onset (see (Paulsen et al., 2008; Tabrizi et al., 2009; van den Bogaard et al., 2011a; Georgiou-Karistianis et al., 2013a)), and becomes more pronounced as individuals approach clinical diagnosis (van den Bogaard et al., 2011b; Dominguez et al., 2013; Georgiou-Karistianis et al., 2013a, 2016).

The neostriatum is a crucial hub in corticostriatocortical re-entrant circuits that regulate cognition, emotion, behaviour and motor functions (Draganski et al., 2008). Structural changes in the striatum may disrupt these corticostriatal pathways (Looi and Walterfang, 2012) leading to changes in motor function and related cognitive and neuropsychiatric outcomes in HD (van Duijn et al., 2007). These circuits are structurally and functionally organised in the striatum in a topographic pattern (Haber, 2003; Bohanna et al., 2011).

HD studies that relate genetic and neuroanatomical measures to clinical outcomes may offer insight into disease mechanisms (Gottesman and Gould, 2003). In part, motor dysfunction arises from structural alteration to, or atrophy in, corticostriatal circuit components, including the striatum. Structural atrophy may also be related to the severity of genetic loading as characterised by polyglutamine (CAG) repeat length in the *huntingtin* gene, which has been used in the literature to compute a disease burden score [DBS (CAG length − 35.5) × age] (Georgiou-Karistianis et al., 2013b). CAG repeat length has long been known to be related to age of onset of disease, with longer repeat length related to earlier onset of motor symptoms of disease (Andrew et al., 1993; Langbehn et al., 2004). However, this is thought to account for only around 40–70% of the variance in age of disease onset, with other genes and environmental factors also presumed to play an important role (Wexler and U.S.VenezualaCollaborativeResearchProject, 2004; Ross and Tabrizi, 2011).

Changes in striatal morphology have long been observed both in neuropathological and imaging studies of HD (Vonsattel et al., 1985; van den Bogaard et al., 2011b; Looi et al., 2012; Younes et al., 2012; Tang et al., 2019). However, to our knowledge, very few studies have investigated the relationship between striatal shape or subregional specific volume changes and measures of dysfunction (Bohanna et al., 2011; Turner et al., 2016; Kim et al., 2017). Shape analysis is emerging as a potential endophenotype for multiple psychiatric and neurodegenerative diseases, allowing a more nuanced view of the interplay between structure and function (for review, see (Looi et al., 2014)). It has the advantage over pure volumetric analysis as it can elucidate subregional structural changes, in multiple disorders, which may not be apparent when looking at volume alone (Berner et al., 2019; Tang et al., 2019; Tate et al., 2019). Further characterisation of these changes will improve knowledge of HD-associated neurodegenerative pathways and provide further insight to relate quantitative measures of morphology (morphometry) to function. Measures of structural change in HD may also serve as biomarkers or surrogate endpoints for treatment trials (Georgiou-Karistianis et al., 2013b), and importantly, development of future disease-modifying treatments may be further informed by an understanding of the progression of subcortical neurodegeneration.

1.2. Aims and hypotheses

In this investigation we aimed to characterise neostriatal changes in individuals with pre-HD and symptomatic HD (symp-HD) compared to healthy controls, and to correlate changes with measures of clinical, motor, cognitive, and neuropsychiatric function. We hypothesised that quantified measures of neostriatal morphology would significantly differ between controls and individuals with pre-HD and symp-HD. We also hypothesised that neostriatal morphological changes would be associated with cognitive, neuropsychiatric and motor outcomes according to known functional connections.

2. Methods

2.1. Subjects and measures

Participants for this study, and all measurements, were acquired as part of the IMAGE-HD study (Georgiou-Karistianis et al., 2013a). Participants included 36 individuals with pre-HD, 37 with early symp-HD, and 36 healthy matched controls. Healthy controls were matched for age, sex, and IQ (Nelson and Willison, 1991) to the pre-HD individuals. All participants were right-handed and were free from brain injury, neurological and/or severe diagnosed psychiatric conditions (e.g. bipolar disorder, psychosis) other than HD. All pre-HD and symp-HD participants underwent a Unified Huntington Disease Rating Scale (UHDRS) motor assessment (HuntingtonStudyGroup, 1996); inclusion in the pre-HD group required a UHDRS total motor score of ≤ 5. Estimated years to clinical onset was based on the participant's age and the number of CAG repeats on the expanded allele (Langbehn et al., 2004).

A battery of neurocognitive tests were administered on the day of scanning that were selected based on their sensitivity in detecting differences between groups from previous large scale multi-site studies (Tabrizi et al., 2009; Stout et al., 2011). The tests assessed visuo-motor speed and attention (Symbol Digit Modalities Test, SDMT (Smith, 1982)), speeded reading (Stroop Word Test, (Stroop, 1935)), odour recognition (University of Pennsylvania Smell Identification Test, UPSIT (Doty et al., 1984)) and motor performance (speeded tapping and self-paced tapping tasks (Stout et al., 2011) - inter-trial interval in speeded tapping, ITISTAP; inter-trial interval in participant passed tapping, slow 1.8 Hz, ITIPTAP slow average; and inter-trial interval in participant passed tapping, fast 3 Hz, ITIPTAP fast average). Participants completed behavioural questionnaires which included assessments of behaviours associated with frontal-striatal brain dysfunction, including executive function (Frontal Systems Behaviour Scale, FrSBe (Stout et al., 2003)) and psychiatric disturbances (Schedule of Compulsions Obsessions and Pathological Impulses, SCOPI (Watson and Wu, 2005), Hospital Anxiety and Depression Scale, HADS A and HADS D (Zigmond and Snaith, 1983), Beck Depression Inventory score Version II, BDI II (Beck et al., 1996).

The IMAGE-HD study was approved by the Monash University and Melbourne Health Human Research Ethics Committees; informed written consent was obtained from each participant prior to testing in accord with the Helsinki Declaration. All testing was undertaken at the Royal Children's Hospital, Parkville, Melbourne, Australia. Ethics approval for this sub-project was obtained from Monash University and the Australian National University.

2.2. Imaging

Imaging was performed on a Siemens Magnetom Trio Tim System 3 Tesla scanner with a 32-channel head coil (Siemens AG, Erlangen, Germany) at the Murdoch Children's Research Institute (Royal Children's Hospital, Victoria, Australia). High-resolution T1-weighted images were acquired (192 slices, slice thickness of 0.9 mm, 0.8 mm x 0.8 mm in-plane resolution, 320 × 320 mm field of view, TI = 900 ms, TE = 2.59 ms, TR = 1900 ms, flip angle = 9°). No participants were excluded on the basis of poor quality scans or missing data.

2.3. Volumetric analysis

Neostriatal volumes for each scan were measured by a single trained researcher (FW) using manual segmentation according to a validated protocol (intra-rater intraclass correlation 0.88–0.98) (Looi et al., 2008, 2009) and ANALYZE 11.0 (Mayo Foundation, Rochester, MI, USA) software. Details of the protocol have been published previously (Looi et al., 2008, 2009)- briefly, these are performed in native space

Table 1
Demographic and selected data across groups.[a]

	Mean ± SD Controls (n = 36)	Pre-HD (n = 36)	Symp-HD (n = 37)
Covariates and clinical information:			
Sex (M:F)	12:24	14:22	21:16
Age (years)	42.4 ± 13.4	41.7 ± 9.9	52.1 ± 9.3
ICV (cm^3)	1456.4 ± 143.5	1414.7 ± 156.8	1400.8 ± 155.7
CAG repeat number		42 ± 2 (range 39–46)	43 ± 2 (range 40–50)
Disease Burden Score (DBS)		269.4 ± 52.7	378.5 ± 67.8
Years to onset		15.5 ± 7.0	
Years since diagnosis			2.0 ± 1.6
UHDRS motor score (range)		1 (0–4)	19 (6–60)
Significant differences: All 3 groups[b]			
Putaminal volume	5969 ± 797	5065 ± 1089	3449 ± 775
Caudate volume	7385 ± 1162	6052 ± 1574	4392 ± 981
Speeded tapping (ms)	219.9 ± 38.1	243.7 ± 45.0	364.5 ± 162.2
Self-paced tapping (1/SD ITI) 333ms	29.1 ± 8.3	23.8 ± 8.7	11.4 ± 5.7
Self-paced tapping (1/SD ITI) 550ms	23.8 ± 7.7	19.6 ± 7.4	10.5 ± 4.1
SDMT	56.3 ± 10.1	51.5 ± 8.6	36.0 ± 11.7
Two comparisons[c]			
UPSIT	34.0 ± 3.1	32.7 ± 5.0	26.2 ± 7.1
Stroop	109.8 ± 16.6	104.4 ± 17.5	82.5 ± 22.0

ICV: Intracranial volume; DBS: (CAG-35.5)*age; YtO: approximate years to onset, modified Langbehn method (Langbehn et al., 2004); YSD: Years since diagnosis; ITI: Inter-tap interval; SDMT: Symbol Digit Modalities Test; Age, sex and ICV were used as covariates in all analyses.

[a] For a full list see Georgiou-Karistianis et al. (2013a), although note that more subjects have been included in the symp-HD group since this initial publication.

[b] Symp-HD vs pre-HD, symp-HD vs controls, and pre-HD vs controls all $p \leq 0.017$.

[c] Symp-HD vs pre-HD and symp-HD vs controls, $p \leq 0.017$.

and manually trace both the caudate and putamen separately in the axial plane from a starting point at the level of the anterior commissure, then every slice superiorly until their upper boundaries. This method misses the nucleus accumbens/more limbic areas, and traces only the neostriatum proper.

Statistical analysis of volume and other baseline data was performed using SPSS 20.0 (Chicago, Ill., USA) and significance was set at $P < 0.05$. Multivariate analysis of covariance (MANCOVA) was used to test statistical significance between the subject groups with age, sex and intracranial volume (ICV) as covariates (Table 1). ICV was calculated from outputs from FMRIB's Software Library FSL 4.1.6 1, for more details see (Georgiou-Karistianis et al., 2013a). Preliminary checks were conducted to ensure there was no violation of assumptions of normality, homogeneity of variances, and reliable measurement of the covariate.

2.4. Shape analysis

A surface-based parametric mapping protocol derived two pointwise shape measures from the manual tracing above: thickness (radial distance) and the Jacobian determinant (surface dilation ratio) were derived across 2502 points on the surface of each of the left and right caudate and putamen. The protocol is freely available at http://enigma.ini.usc.edu/protocols/imaging-protocols/ (Gutman et al., 2012, 2015). Striatal shape atlases were created from the manual segmentations first, and then the ENIGMA shape pipeline was modified to use these instead of free-surfer based atlases. Briefly, thickness, or radial distance, is a local distance measure from the medial curve to the surface. The Jacobian determinant is the surface dilation ratio relative to template structure, or a measure of the local surface area (relative to a template structure made from all manually traced shapes combined). For clarity in results/discussion, radial distance will be referred to as "thickness" and the Jacobian determinant will be referred to as surface expansion/contraction. Only shape models that passed visual inspection and that conformed to T1-weighted MRI neuroanatomical boundaries using the ENIGMA Shape Analysis Quality Assessment Protocol were used (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Using the R package *lm* version 3.0.2, a multiple linear regression was fit at each thickness and Jacobian point to test for group differences and associations with clinical features. All analyses were adjusted for age, sex, and intracranial volume. A standard false discovery rate (FDR) correction was applied at the accepted level of 5% ($q = 0.05$), as implemented in the R function *p.adjusted*.

3. Results

3.1. Demographics and clinical details

Group differences were assessed with non-parametric tests (Table 1). There were significant differences between groups in measures of self-paced tapping (1.8 Hz and 3 Hz), SDMT, speeded tapping, UPSIT and Stroop ($p < 0.001$) and BDI-II ($p < 0.05$), but not in ICV, verbal IQ, SCOPI total OCD, FRSBE, or HADS anxiety or depression. Mann-Whitney U tests revealed significant differences between all three groups in all motor tests and in SDMT ($p \leq 0.017$). There were also significant differences between symp-HD and both controls and pre-HD in UPSIT and in Stroop ($p \leq 0.017$), and a significant difference between symp-HD and controls on the BDI-II ($p \leq 0.017$).

3.2. Volume and shape

There were significant differences in striatal volume between all three groups with control volumes larger than pre-HD, which were significantly larger than symp-HD (Table 1). Significant striatal shape differences were also detected between all groups (Fig. 1), with controls showing larger shape metrics (increased thickness and surface expansion) than pre-HD, and pre-HD larger than symp-HD. These shape differences mapped across large areas of the striatum, with more extensive differences detected using the Jacobian shape metric (local surface area expansion/contraction). The greatest shape differences were between controls and symp-HD, but there were also widespread shape differences between pre-HD and symp-HD and between pre-HD and controls. The greatest differences were in surface contraction and decreased thickness in the right putamen in pre-HD compared to controls and left putamen in symp-HD compared to pre-HD.

3.3. Correlations- shape

Significant negative associations were detected between striatal thickness and surface expansion/contraction measure and the number of CAG repeats, DBS, and UHDRS total motor score in pre-HD, symp-HD, or both (Fig. 2). Again, greater areas of association were seen with the Jacobian surface contraction/expansion measures than with the thickness metric. In pre-HD, there were widespread significant negative associations between lower thickness and surface contraction in caudate and putamen and both CAG repeat number and DBS. These associations were detected to a much lesser extent in symp-HD, with only

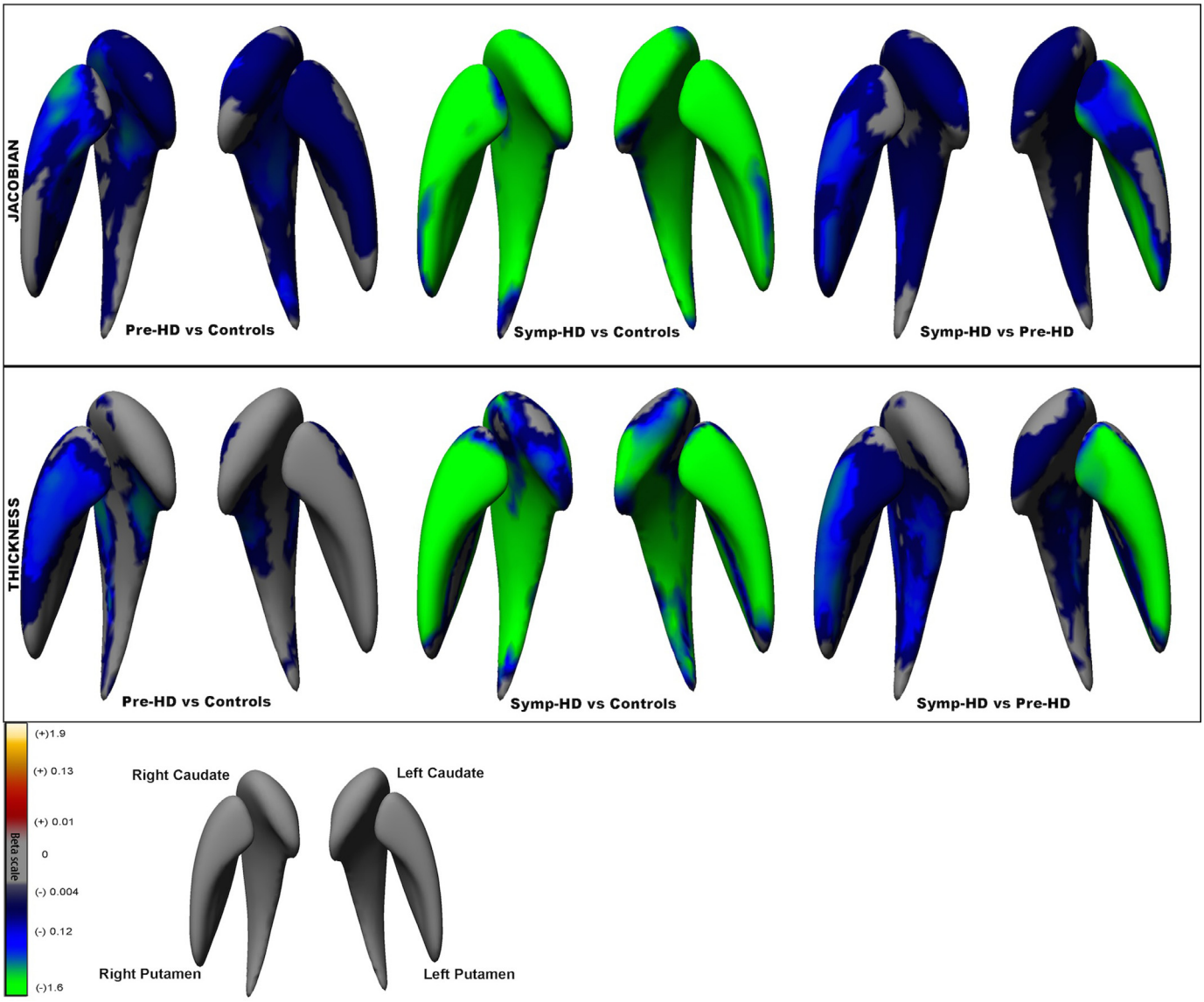

Fig. 1. Shape differences between groups. Top panel: Significant differences based on Jacobian determinant, indicating surface dilation due to subregional volume change. Bottom panel: Significant differences based on radial distance ("thickness"), or distance of the vertex from the medial curve of the structure. Beta value = regression coefficient, or "slope".

small areas of association between lower surface area shape measures and increasing DBS in patches of bilateral caudate, as well as left anterior putamen. Increasing CAG repeat number was only associated with lower surface area shape measures in left caudate head and anterior tail in symp-HD. Changes were similar but much less extensive when measuring thickness.

Of the other motor and neurocognitive measures tested against shape changes in neostriatum, only UPSIT, Stroop, and self-paced tapping (slow and fast) showed significant correlations (Fig. 3). There were significant associations between surface contraction in bilateral caudate and putamen in symp-HD and increasing UHDRS (motor) scores. These were limited to only patches of bilateral caudate head when thickness was tested.

In symp-HD, UPSIT scores were correlated with thickness of left caudate body and surface expansion in left posterior putamen, both in very limited regions. Stroop scores were positively correlated with the thickness of left putamen head and body. The regions of volume change are also very limited in these associations.

Self-paced tapping (slow) was correlated with surface expansion of the right caudate in symp-HD and with bilateral putamen in pre-HD, although when thickness was tested these correlations were confined to only anterior right caudate in symp-HD and right putamen in pre-HD. Self-paced tapping (fast) was correlated with right anterior putaminal higher surface expansion in symp-HD only.

4. Discussion

This study has confirmed significant differences between controls, pre-HD and symp-HD in neostriatal volume and shape metrics that quantify morphologic structural brain change. The regions of change in this area, while using different methods and investigating both pre-HD and symp-HD, confirm similar patterns of striatal atrophy (van den Bogaard et al., 2011b; Younes et al., 2012; Faria et al., 2016; Kim et al., 2017; Tang et al., 2019). It extends current research by finding that these morphologic changes correlate with CAG repeat number and DBS and that morphologic changes in specific areas in pre-HD and symp-HD are associated with motor and cognitive differences, which may provide insight into how subcortical morphometric changes relate to disease pathogenesis.

Interestingly, of the two measures used to identify shape changes,

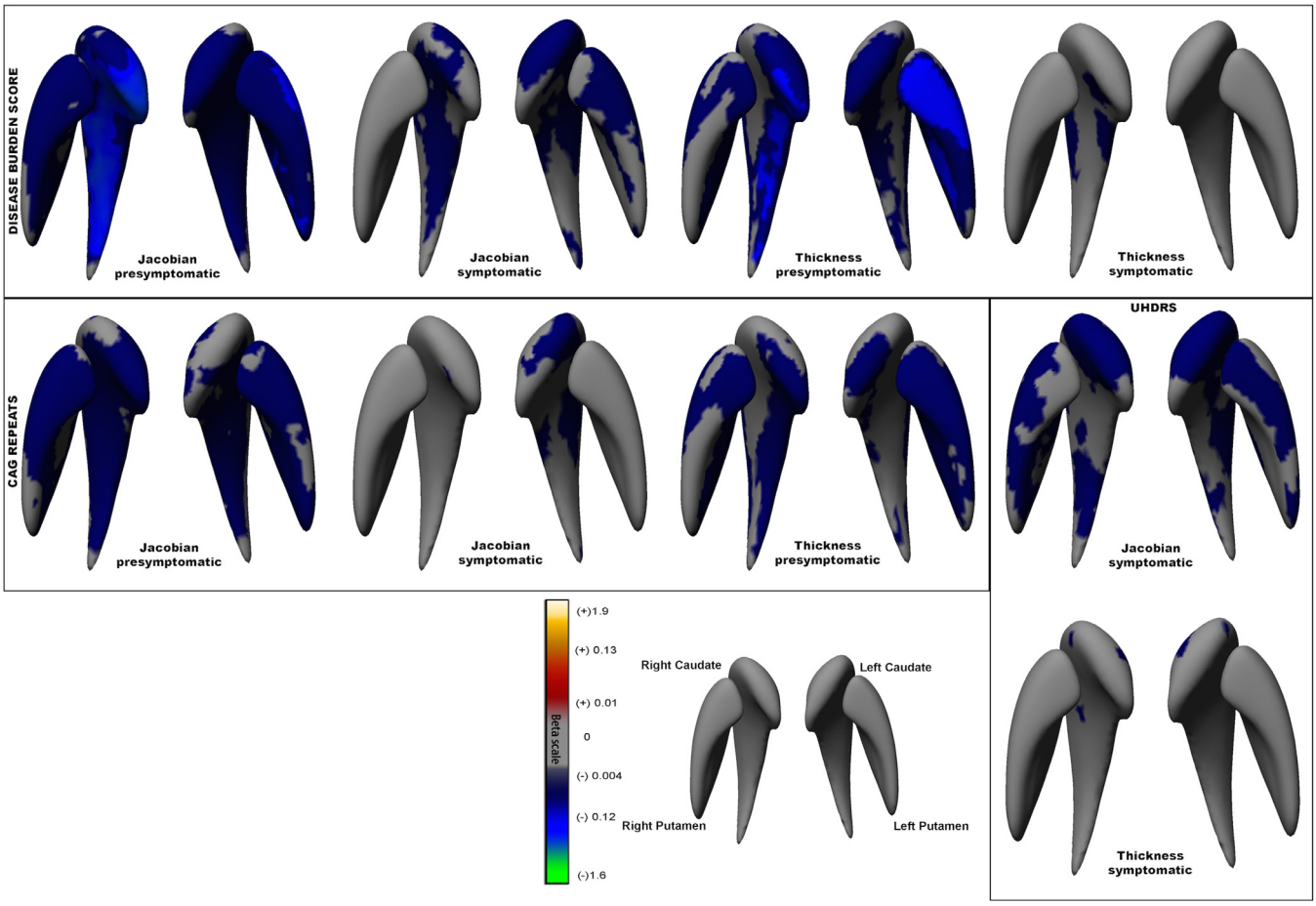

Fig. 2. Correlations between neostriatal shape and measures of disease burden. Panels indicate all significant correlations within each measure of disease burden: DBS, CAG repeats, and UHDRS motor scores. Jacobian = correlation based on surface dilation due to subregional volume change. Thickness = correlation based on radial distance, or distance of the vertex from the medial curve of the structure. Beta value = regression coefficient, or "slope".

the Jacobian measurement of shape change showed more extensive and stronger correlations than the radial thickness measure. As the Jacobian measurement incorporates more dimensions of the data than the simple scalar value of thickness, it may be better suited to discriminate relevant shape changes (Gutman et al., 2012, 2015). However, both measures remain useful in subcortical shape analysis (Tate et al., 2019): radial thickness directly corresponds to localised volume, whereas the Jacobian determinant can capture the stretching/shrinking along the main axis of a region, making them different but complementary measures.

4.1. CAG repeat length correlations with shape

Increasing number of CAG repeats correlated with surface contraction and decreased thickness throughout the neostriatum in pre-HD. In contrast, in symp-HD, the number of CAG repeats was only associated with surface contraction in left anterior caudate. This may be a statistical artefact due to the destructive nature of HD - by the time of clinical diagnosis, there is already marked neurodegeneration, particularly in the striatum, whereas there is much more variation in size of the striatum in pre-HD. However, there is also evidence that the factors that determine age of disease onset in pre-HD (largely but not exclusively CAG) do not explain all of the disease progression once it has become manifest (Aziz et al., 2018). In this study, reduced areas of shape correlation with CAG repeat length in symp-HD, but widespread correlations between shape and UHDRS throughout caudate and putamen, may also provide indirect evidence for the idea that CAG repeat length has less of an influence on disease progression. Similarly, there were also significant negative associations between neostriatal surface area shape measures and DBS. These correlations were greatest in pre-HD and less apparent in symp-HD.

4.2. Shape correlations with motor measures

Overall neostriatal volumes have been correlated with motor and cognitive outcomes in a number of studies in HD (Bechtel et al., 2010; Aylward et al., 2012; Delmaire et al., 2012; Misiura et al., 2017) but to our knowledge only two studies have examined striatal subregional morphology and motor outcomes in HD (Bohanna et al., 2011; Turner et al., 2016). Both studies investigated the IMAGE-HD cohort or a subset.

Bohanna and colleagues have previously found the greatest differences in volume and diffusion tensor imaging measures in dorsal areas of the striatum that have connections to primary motor and somatosensory cortices; subregion-specific volume was also strongly correlated with the UHDRS motor score (Bohanna et al., 2011).

Using a subset of the IMAGE-HD cohort, Turner and colleagues (Turner et al., 2016) measured EEG components of sensorimotor integration in 12 individuals with pre-HD and 7 with symp-HD and correlated these with shape changes in the striatum. All results occurred in the context of abnormal processing but normal task execution. Unregulated premotor activation was correlated with shape deflation of the dorsal putamen bilaterally, as well as deflation in anterior inferior putamen (left > right). This was thought to reflect the ability to recruit compensatory networks from frontal motor projection areas. In contrast, delayed timing of neural premotor activation was significantly

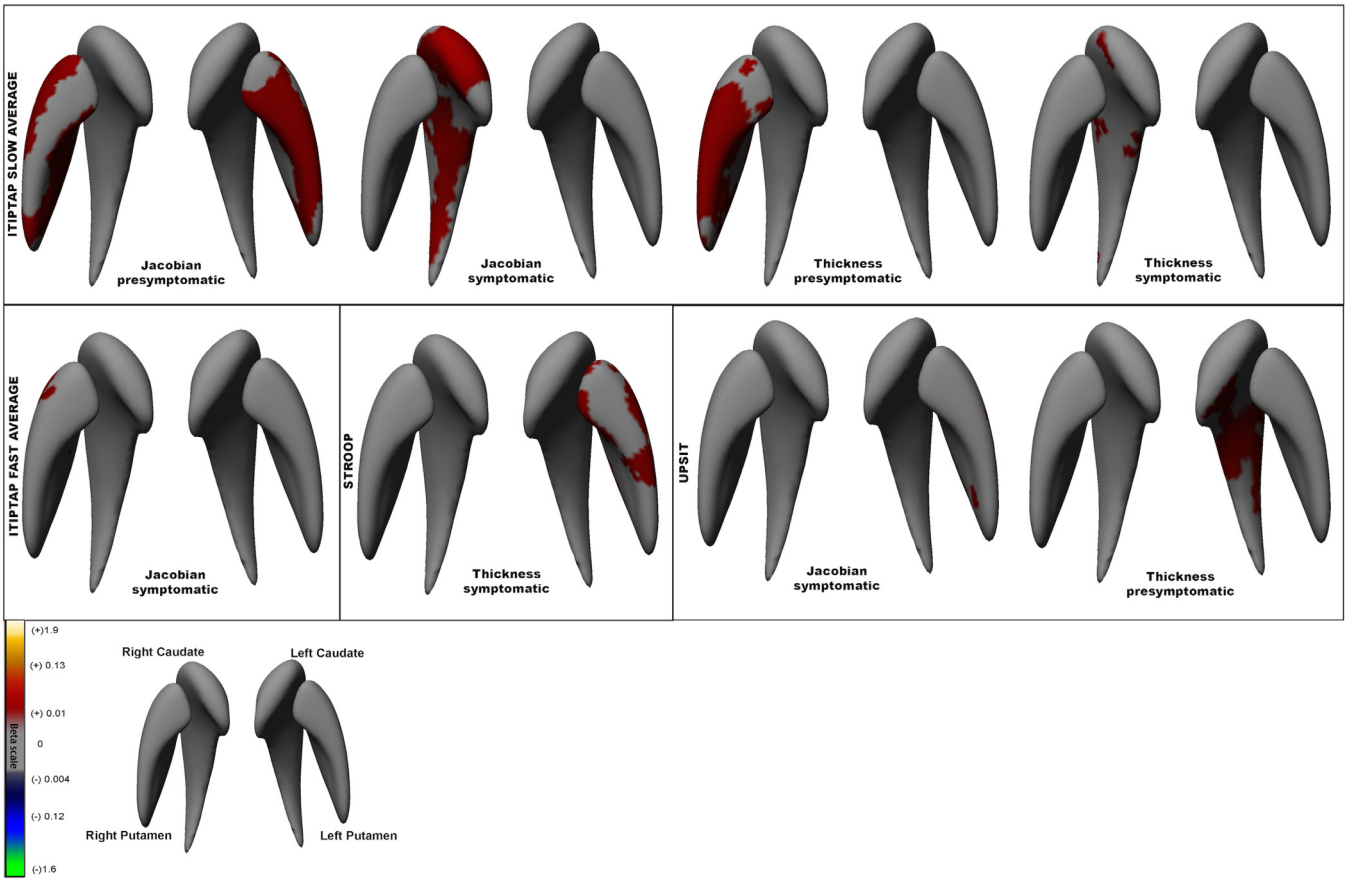

Fig. 3. Neostriatal shape correlations with motor and cognitive test scores. Panels indicate all significant correlations within each measure with significant results: ITIPTAP slow average (inter-trial interval in participant passed tapping, slow 1.8 Hz), ITIPTAP fast average (inter-trial interval in participant passed tapping, fast 3Hz), Stroop, and UPSIT. Jacobian = correlation based on surface dilation due to subregional volume change. Thickness = correlation based on radial distance, or distance of the vertex from the medial curve of the structure. Beta value = regression coefficient, or "slope".

correlated with shape deflation in the right caudate (anterolateral and dorsomedial areas only). Here, caudate shape deflation was thought to impair motor planning and execution (Turner et al., 2016).

Self-paced finger tapping has been previously shown to be impaired in both pre-HD and symp-HD individuals (Bechtel et al., 2010; Stout et al., 2011; Georgiou-Karistianis et al., 2013a). This task requires participants to listen to a tone presented at a certain rate (1.8 or 3.0 Hz), to tap along with this tone, and then to continue tapping at the same rate after cessation of the tone (Stout et al., 2011). "ITIPTAP slow average" measures the variance in self-paced tapping to a slow beat. In pre-HD, worsening accuracy in this measure was correlated with shape contraction throughout bilateral putamen (and reduced thickness in right putamen). Interestingly, in symp-HD this correlation was lost and instead worsening accuracy in self-paced tapping scores were correlated with right caudate shape contraction, throughout the entire caudate. This is consistent with the results found by Turner and colleagues above (Turner et al., 2016), suggesting that initially the bilateral putamen is able to recruit compensatory networks to help in motor tasks, but eventually this fails and consequently, right caudate atrophy impairs motor planning and execution, leading to worsening outcomes without any remaining compensatory measures. The regions of shape and volume change in these associations implicate the surface mapping of afferents from a wide range of circuits, including but not limited to the rostral premotor (to a lesser degree) and caudal motor corticostriatal circuits that converge on the striatum (Haber, 2003; Draganski et al., 2008).

Fast self-paced tapping is thought to be more difficult, requiring greater involvement of the frontal cortex rather than the striatum (Delmaire et al., 2012), which may explain why there are fewer significant correlations seen between self-paced tapping (fast) and striatal shape in our study, apart from in the anterior right putamen in a region that has connections to frontal cortex.

4.3. Shape correlations with neurocognitive measures

Of the neurocognitive measures tested, UPSIT and Stroop, but not SDMT, showed correlations with striatal shape metrics in symp-HD. There were no significant correlations detected between neostriatal shape and any cognitive measures in pre-HD or in controls. To our knowledge only one previous study has investigated the correlation between neostriatal shape change and neurocognitive measures; Kim and colleagues manually segmented the caudates of individuals with pre-HD and correlated shape changes here with composite measures of executive function and working memory. They found that scores in these domains mapped to anteromedial caudate (Kim et al., 2017).

The UPSIT is a complex task involving integration from a number of areas. Scores in UPSIT have been associated with diffusion tensor MRI mean diffusivity in the parietal lobe, medial temporal lobes, cingulum and insula, as well as caudate nucleus and anterior putamen (Delmaire et al., 2012). Here, we have found that in symp-HD, better scores in UPSIT are related to increased thickness of left mid-caudate and surface expansion in left posterior putamen. The regions of both shape and volume difference are very limited in these associations, and implicate the surface mapping of afferents from the orbitofrontal and dorsolateral-prefrontal corticostriatal circuits that converge on the left caudate, as well as known areas of connections with temporal lobe in left putamen (Haber, 2003; Draganski et al., 2008).

Similarly, the Stroop Word Test requires executive control

(MacLeod and MacDonald, 2000). In this study Stroop scores were positively correlated with left anterior putaminal thickness in symp-HD, in regions mapping to orbitofrontal and dorsolateral-prefrontal corticostriatal circuits (Haber, 2003; Draganski et al., 2008). Of note, correlations with both Stroop and UPSIT were in the left neostriatum only-the dominant hemisphere for all subjects.

Integrity of tracts between the putamen and prefrontal areas are thought to be critical for executive function (Liston et al., 2006). Damage to these tracts and others, as reflected in the shape abnormalities here, can affect not only the more obvious motor symptoms of HD but also subtler circuitry controlling executive function. The small regions of associations here compared to the larger areas of association in Kim et al.'s study (Kim et al., 2017) likely reflect the composite nature of their measures. Our study however remains an important addition to the current body of work because it adds precise anatomical detail to this knowledge of circuitry, and extends into further measures of caudate and putamen, as well as motor, cognitive and clinical measures.

4.4. Limitations

We focused on the morphology of the striatum as a sentinel measure of structural change within corticostriatal circuits, which we believe is more easily quantified than the entirety of the corticostriatal pathways. Inferences regarding the effect of shape differences on known underlying subfields are limited by our shape analysis technique. Some inferences may be made based on neuroanatomical sources (Haber, 2003; Draganski et al., 2008), but ongoing work involves the challenging task of mapping known neuroanatomical subfields to the surface of our subcortical shape models. Future studies may provide additional insights into the underlying subfield effects detected by this powerful shape analysis technique.

4.5. Conclusions/clinical implications

We have replicated and extended on previous work showing that quantified measures of neostriatal morphology differ significantly across controls, pre-HD and symp-HD. We found the thickness and surface expansion/dilation measures correspond to the surface mapping of afferents from corticostriatal circuits in HD. Furthermore, neostriatal shape correlated with motor, neurocognitive and clinical measures subserved by such circuits, suggesting that the neostriatum is a potentially useful structural basis for characterisation of endophenotypes of HD. Future work in HD should investigate the spatiotemporal progression of striatal atrophy and its genetic and clinical correlates: to assess the usefulness of such quantifiable endophenotypes (striatal structure and frontostriatal function), to understand the pathophysiology of the disorder, monitor disease progression and ultimately, assess response to clinical interventions (Looi and Santillo, 2017).

Conflict of Interest

Dr Stout has received funding from CHDI Foundation unrelated to this research. She is also director of Stout Neuropsych Pty Ltd., which has research contracts with Omeros and Teva Pharmaceuticals, none of which are relevant to this research. In addition she has received funds from Prana Biotechnology, University of California Davis, and the University of Michigan, none relevant to this research. Dr Looi self-funded travel and computer infrastructure costs to coordinate this research through the Australian United States Scandinavian-Spanish Imaging Exchange (AUSSIE), based at the Australian National University Medical School. Dr Walterfang has received funding for research from and has received honoraria from Actelion, Vtesse and Biomarin pharmaceuticals, unrelated to this research.

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Contributors

F.A. Wilkes performed the manual segmentation of the neostriatum, directed the imaging analysis and wrote the bulk of the manuscript. Z. Abaryan, C.R.K. Ching and B.A. Gutman performed the imaging analysis under the supervision of P.M. Thompson. J.C. Stout, P.Chua, G.F. Egan, and N. Georgiou-Karistianis were integral to the development and implementation of the overall IMAGE-HD project, of which this study is a sub-project. N. Georgiou-Karistianis is the primary investigator of the IMAGE-HD project and along with M. Walterfang and D. Velakoulis is a PhD co-supervisor of F.A. Wilkes; J.C.L. Looi is F.A. Wilkes' main PhD supervisor. All authors had significant intellectual and practical input into the final manuscript.

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