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Emerging differences between Huntington's disease-like 2 and Huntington's disease: A comparison using MRI brain volumetry

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ABSTRACT

Huntington's Disease-Like 2 (HDL2), caused by a CTG/CAG expansion in *JPH3* on chromosome 16q24, is the most common Huntington's Disease (HD) phenocopy in populations with African ancestry. Qualitatively, brain MRIs of HDL2 patients have been indistinguishable from HD. To determine brain regions most affected in HDL2 a cross-sectional study using MRI brain volumetry was undertaken to compare the brains of nine HDL2, 11 HD and nine age matched control participants. Participants were ascertained from the region in South Africa with the world's highest HDL2 incidence. The HDL2 and HD patient groups showed no significant differences with respect to mean age at MRI, disease duration, abnormal triplet repeat length, or age at disease onset. Overall, intracerebral volumes were smaller in both affected groups compared to the control group. Comparing the HDL2 and HD groups across multiple covariates, cortical and subcortical volumes were similar with the exception that the HDL2 thalamic volumes were smaller. Consistent with other similarities between the two diseases, these results indicate a pattern of neurodegeneration in HDL2 that is remarkably similar to HD. However smaller thalamic volumes in HDL2 raises intriguing questions into the pathogenesis of both disorders, and how these volumetric differences relate to their respective phenotypes.

1. Introduction

Huntington's disease like 2 (HDL2) is the most common Huntington's disease (HD) phenocopy in populations with an African ancestry and is emerging as the most common HD phenocopy in South America, the USA and parts of Europe (Margolis et al., 2004; Mariani et al., 2016; Walker et al., 2018). South Africa has the highest number of HDL2 cases described despite the under ascertainment of patients due to lack of resources in rural communities (Anderson et al., 2017b; Baine et al., 2016).

Huntington's Disease is caused by a CAG/CTG repeat expansion in exon 1 of the *huntingtin* gene on chromosome 4p16.3, while HDL2 is caused by a similarly sized CTG/CAG expansion in exon 2A of *junctophilin-3* (*JPH3*) on chromosome 16q24.3 (Holmes et al., 2001). Both are autosomal dominant disorders characterized by psychiatric disease, movement disorder and cognitive dysfunction which progress and inevitably result in death approximately 15 to 20 years after clinical onset (Margolis et al., 2001). Observations of the HDL2 phenotype are from retrospective and anecdotal cases and reviews (Anderson et al., 2017b). Notwithstanding these genetic differences and the need for systematic study of the HDL2 clinical phenotype, HDL2 is the disease that has been described to most resemble HD (Walker et al., 2003).

Furthermore, qualitative MRI studies have not been able to differentiate between HDL2 and HD. To date these rare reports suggest similar patterns of atrophy between these two disorders (Anderson et al., 2017b). A systematic review of 69 published cases of HDL2 reported 20 MRI scans of HDL2 patients described as indistinguishable from HD (Anderson et al., 2017b). An exception was a patient with HDL2 who

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presented with parkinsonism and myoclonus. The MRI of this case showed typical cerebral atrophy but relative sparing of the caudate nucleus (Bardien et al., 2007). A report of a single case of HDL2 having two MRIs five years apart described progressive atrophy of the same areas as seen in HD (Rodrigues et al., 2008). Hyperintense putaminal rims on T2 imaging have been described in three cases with HDL2 from the same family (Schneider et al., 2012). The putaminal rim sign has also been detected in a number of other degenerative movement disorders including Multi-System Atrophy (MSA), Neuro-Acanthocytosis, Dentatorubral-Pallidoluysian Atrophy (DRPLA) and Spinocerebellar Ataxia Type 17 (SCA17).

Despite the fact that HD and HDL2 are caused by mutations in different genes, which are linked to different functions within the cell, the majority of the qualitative MRI reports, neuropathological analysis, and clinical phenotype, highlight the similarities between both disorders. We therefore hypothesized that quantitative MRI analysis of HDL2 patients would reveal similar findings to those detected in HD patients. To test this hypothesis, we performed a blinded systematic imaging study of matched HD and HDL2 patients with a normal control group, taking advantage of the relatively high number of HDL2 cases that have been reported in the region surrounding Johannesburg, South Africa (Anderson et al., 2017b; Krause et al., 2015).Comparing the brain MRIs of these clinically similar diseases has the potential to guide further investigation into the differences and similarities between HD and HDL2 and forms part of an ongoing systematic characterization of the phenotype of HDL2.

2. Methods

Patients with HDL2 and HD were identified and diagnosed through the Division of Human Genetics, National Health Laboratory Service and the School of Pathology, The University of the Witwatersrand, in Johannesburg, South Africa. Controls were unrelated healthy acquaintances matched for gender, age and race. Participants were enrolled between January 2015 and June 2017 and all subjects had African or mixed ancestry including a significant African component. The Human Research Ethics Committee of The University of the Witwatersrand approved this cross-sectional study (M140872).

MRIs of subjects were performed at the University of the Witwatersrand Donald Gordon Medical Centre Radiology Department on a 1.5 T Philips Intera MR scanner (Philips Medical Systems, Eindhoven). There were no relevant scanner upgrades during the study. The MRI sequences used in this study are available in the supplement.

We used the Brain Research: Analysis of Images, Networks, and Systems (BRAINS) protocol, which has been validated and extensively used to measure intracerebral volumes for HD in the large PREDICT-HD study (Paulsen et al., 2008). Scans were processed by Brain Image Analysis, LLC using the cross-sectional analysis stream of NeuroAnalytica version 1.3.09, a commercial image analysis platform based on AutoWorkup (Pierson et al., 2011). A discriminant tissue classification was then performed (Harris et al., 1999). Artificial neural networks for each subcortical structure were applied (Powell et al., 2008). Additional information about this technique is available in the supplement.

Comparison of age at MRI, disease duration, abnormal repeat length, and age at onset among the groups was performed using a one-way ANOVA. Comparison of variables among the three groups, controlling for age at MRI and separately, for disease duration, expanded repeat length, and age of disease onset was performed using a General Linear Model. Post-hoc comparisons were performed using the Tukey-Kramer adjustment. The false discovery rate was controlled by the Benjamini-Hochberg procedure and significance was calculated at $p < .0084$. Data analysis was carried out using SAS version 9.4 for Windows.

Table 1
Table showing subject demographic data and MRI volumes. a. Subject ages, age of disease onset, duration of disease and triplet repeat length. b. Unadjusted volumetric analysis of selected subcortical structures, hippocampi and total intracranial volumes in cm^3. HD = Huntington's Disease, HDL2 = Huntington's Disease like 2, n = number SD = Standard Deviation.

1a Demographics and Genetics	HDL2	HD	Controls
Number of participants	9	11	9
Male: Female	5:4	6:5	5:4
	Mean (SD)	Mean (SD)	Mean (SD)
Age at MRI (years)	47.6 (9.1)	46.0 (12.4)	42.6 (9.1)
Abnormal repeat length (n)	47.0 (3.5)	44.9 (3.2)	–
Duration of disease (years)	5.6 (3.0)	6.6 (4.8)	–
Age at onset(years)	42.0 (10.2)	39.4 (13.1)	–
1b Region Volume (cm^3)	Mean (SD)	Mean (SD)	Mean (SD)
Left thalamus	5.156 (0.671)	6.453 (0.868)	6.628 (0.698)
Right thalamus	4.885 (0.805)	6.232 (0.745)	6.269 (0.643)
Left putamen	2.147 (0.452)	2.615 (0.233)	4.771 (0.637)
Right putamen	2.249 (0.389)	2.698 (0.263)	4.714 (0.502)
Left caudate	1.010 (0.455)	1.528 (0.485)	3.359 (0.548)
Right caudate	1.080 (0.475)	1.667 (0.488)	3.392 (0.629)
Left globus pallidus	0.812 (0.190)	0.749 (0.103)	1.297 (0.311)
Right globus pallidus	0.772 (0.150)	0.766 (0.101)	1.371 (0.323)
Left amygdala	0.747 (0.230)	0.743 (0.143)	0.841 (0.171)
Right amygdala	0.665 (0.170)	0.755 (0.141)	0.834 (0.266)
Left nucleus accumbens	0.159 (0.050)	0.174 (0.043)	0.266 (0.075)
Right nucleus accumbens	0.179 (0.067)	0.232 (0.068)	0.289 (0.059)
Intracranial volume	1437.9 (112.7)	1424.1 (118.5)	1424.6 (156.5)

3. Results

Images of nine HDL2, 11 HD and nine normal control participants were included in the study. None of the HDL2 participants were related. Three of the HD pedigrees each contributed two participants to the study. There were no significant differences among the groups with respect to mean age at MRI ($F [2,26] = 0.54$; $p = .59$), disease duration ($F [1,18] = 0.57$; $p = .57$), abnormal repeat length ($F [1,18] = 0.18$; $p = .18$), or age at onset ($F [1,18] = 0.63$; $p = .63$) (Table 1).

The main aim of the study was to contrast HD and HDL2 MRIs. Initially a qualitative comparison of MRIs could not distinguish between both pathologies (see Fig. 1.) The quantitative comparison was conducted using BRAINS. We conducted an initial comparison between HD and healthy controls in order to ensure comparability with previous studies and validation of the present methodology. Subsequently, the HDL2 group was compared to controls with the objective of providing the first MRI brain volumetry characterization of HDL2. Lastly, HD and HDL2 MRIs were compared.

3.1. Comparison between patients with HD and normal controls

When compared to the normal control group and controlling for the age at the time of the MRI, the HD group showed significant less grey matter volume in both of the parietal and left temporal lobes with significantly smaller caudate nuclei, putamen and globus pallidum bilaterally (see Figs. 2 and 3 and Table 1b). These smaller grey matter volumes were reflected in corresponding increases in CSF volumes (Fig. 4). Notably the mean thalamic volumes were not statistically different between the HD group and the normal control group ($p < .01$) (see Table 2).

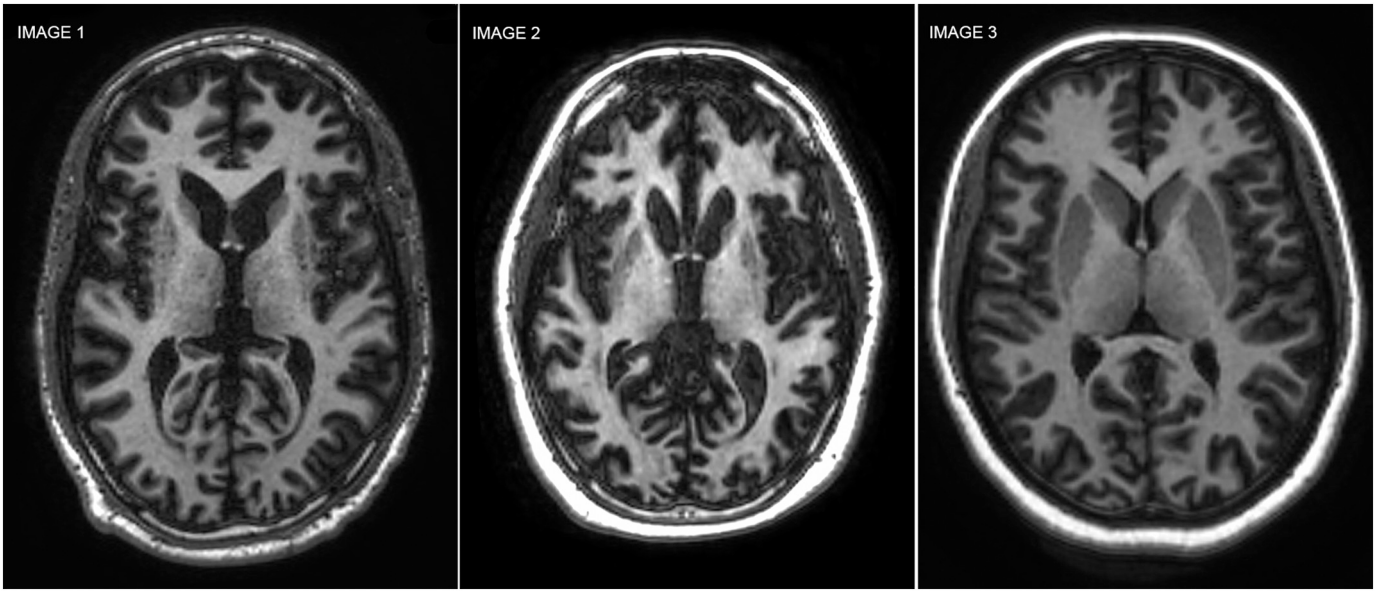


Fig. 1. Qualitative MRI Comparison. Three T1 axial 1.5 T MRIs comparing HDL2, HD and a normal control case. Image 1: 35-year-old HD subject with abnormal *HTT* allele = 49 triplet repeats. Image 2: 32-year-old HDL2 subject with abnormal *JPH3* = 53 triplet repeats. Image 3: 32-year-old normal control subject. The HDL2 and HD subjects show qualitatively similar grey and white matter atrophy with caudate nuclei and putaminal volume loss compared to the normal control.

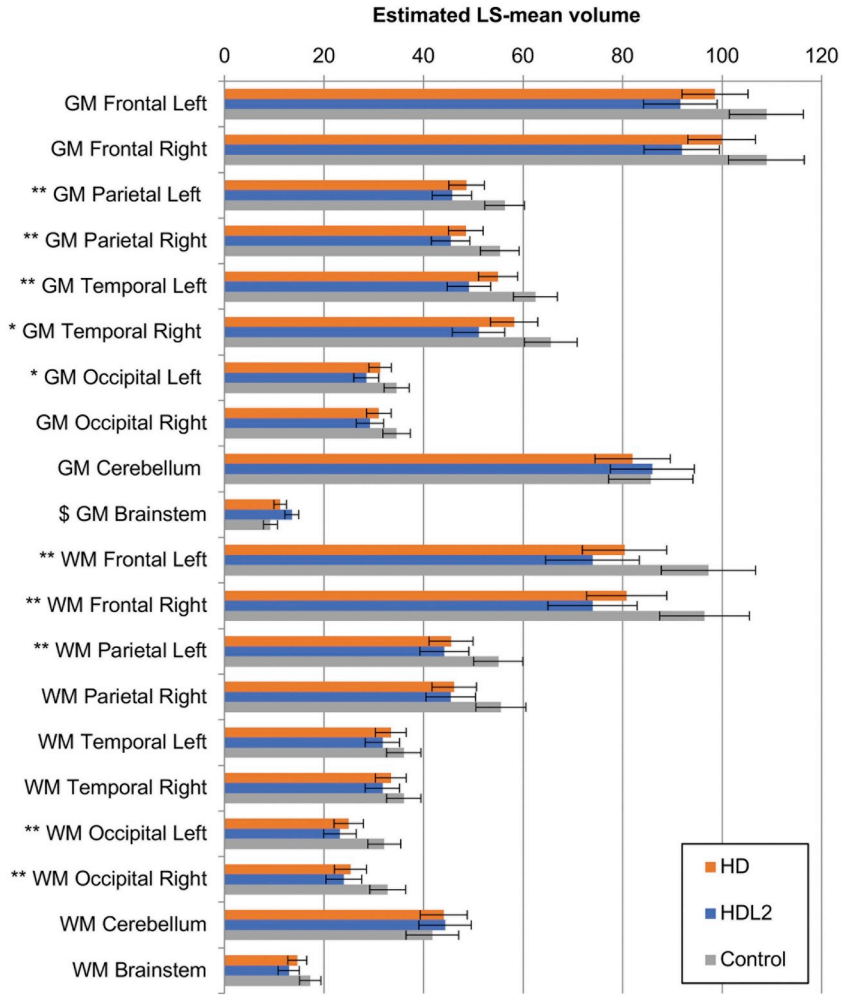


Fig. 2. HD, HDL2 and control groups grey matter and white matter volumes. The estimated least-squares (LS) means from the regression are depicted in a three-way comparison of grey and white matter volume. Error bars denote the 95% confidence intervals for the mean. Significance was set at $p < .008$. Symbols denote significant differences: **: HD, HDL2 < Control; *: HDL2 < Control; $: HD, Control < HDL2. GM = grey matter, WM = white matter.

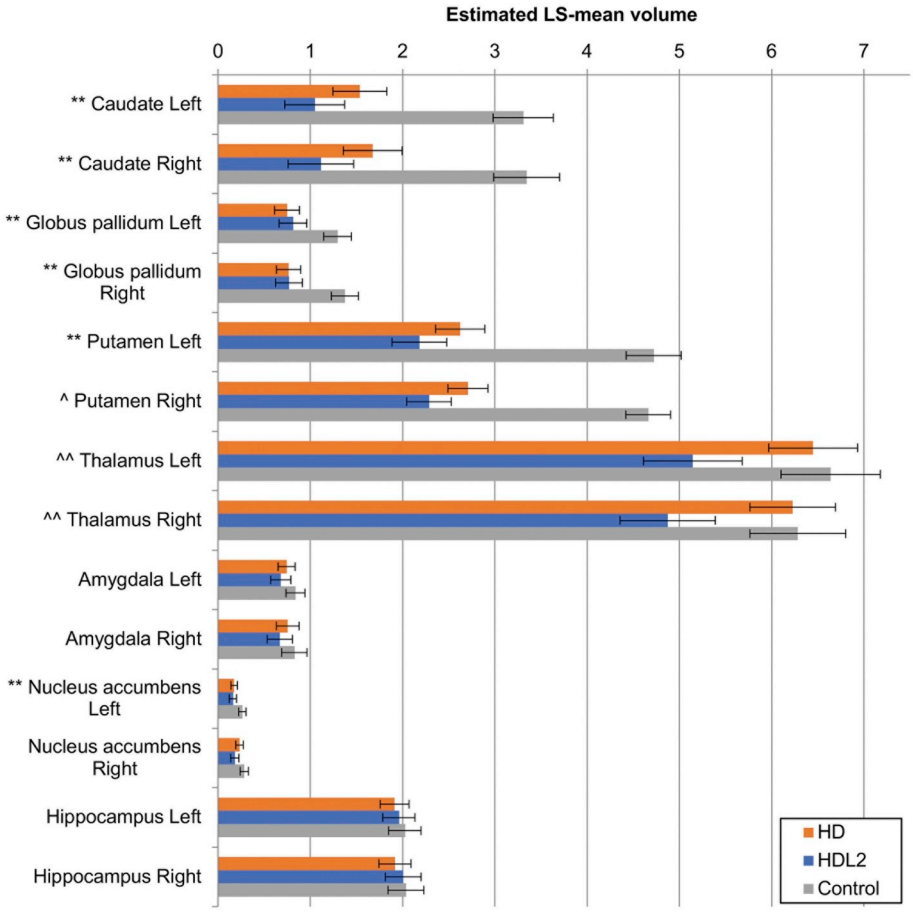


Fig. 3. HD, HDL2 and control groups basal ganglia, thalamic and hippocampal volumes. The estimated least-squares (LS) means from the regression are depicted in the figure in a three-way comparison among HD, HDL2 and control groups. Statistical significance is denoted by a symbol. Error bars denote the 95% confidence interval for the mean. Significance was set at $p < .008$. Symbols: **: HD, HDL2 < Control, ^: HDL2 < HD < Control, ^^: HDL2 < Control, HD where significance was reached. LS = Least-squares means, Nucleus acc = Nucleus accumbens.

3.2. Comparison between HDL2 and normal controls

Grey matter volume tended to be less in the HDL2 group compared to control groups when controlling for age at the time of the MRI (see Fig. 2). The HDL2 group showed significantly smaller grey matter volumes for both the parietal and temporal lobes and left occipital lobe and significantly smaller white matter volumes for both the frontal and occipital lobes and left parietal lobe compared to the normal control participants ($p < .008$). Almost all of the CSF spaces were significantly larger in the HDL2 group compared to the control group (see Fig. 4). Most of the basal ganglia including the thalamus were significantly smaller in the HDL2 group compared to the control group ($p < .008$) (see Table 1b and Fig. 3).

3.3. Comparison between HDL2 and HD

When comparing the HDL2 and HD groups, a similar pattern of grey and white matter volume was noted (see Fig. 2). The mean volumes of the caudate nucleus, globus pallidum, amygdala and the nucleus accumbens tended to be smaller in the HDL2 group compared to the HD group but this did not reach statistical significance when compared across all covariates (Table 1b and Fig. 3). When controlling for age at the time of the MRI, duration of disease, abnormal repeat length and age of onset, the HDL2 groups mean thalamic volumes were significantly smaller compared to the HD participants (Mean [STD] left and right thalamic volumes; HDL2 = left 5.156 cm^3 [0.671], right = 4.885 cm^3 [0.805], HD left = 6.453 cm^3 [0.86], right = 6.232 cm^3 [745]).

The HDL2 volumes were smaller when evaluating differences in the unadjusted putamen volumes in HDL2 and HD cases (Mean [STD] left and right putamen volumes; HDL2 = left 2.147 cm^3 [0.452], right = 2.249 cm^3 [0.389], HD left = 2.615 cm^3 [0.233], right = 2.698 cm^3 [0.263]). However, when applying the Benjamini-Hochberg procedure and applying a $p < .0084$, significance was not seen bilaterally for the putamen as was with the thalamus when controlling for age of onset. Furthermore, the thalamus (Left: $p < .0012$, Right: $p < .0006$) in comparison to the putamen (Left: $p < .011$, Right: $p < .0081$) had greater significant volume difference between the two diseases when controlling for age of disease onset (Table 2).

The unadjusted left and right caudate volumes suggest similar trends as seen in the thalamus and putamen when the unadjusted data are observed with the HDL2 volumes being smaller compared to the HD group caudate volumes (Mean [STD] left and right putamen volumes; HDL2 = left 1.010 cm^3 [0.455], right = 1.080 cm^3 [0.475], HD left = 1.528 cm^3 [0.485], right = 1.667 cm^3 [0.488]) (Table 1b). However, the LS mean caudate volumes are small: 3.2 for HD and 2.2 for the HDL2 groups and when applying the same procedure the difference between the HDL2 and HD caudate volumes did not reach significance when controlling for any of the covariates as noted in Table 2.

The relationship between duration of disease, abnormal repeat length, age at onset was separately determined for each volume measurement in both the HDL2 and HD groups. The trend was an inverse correlation for most measurements, as expected, but significance was not reached. In both diseases smaller volumes of the grey matter structures was seen with increasing duration of disease and larger repeat lengths.

Lastly, on blinded clinical review T2 images demonstrated bilateral putaminal rim hyperintensities in HD and HDL2 patients, but not in the control group.

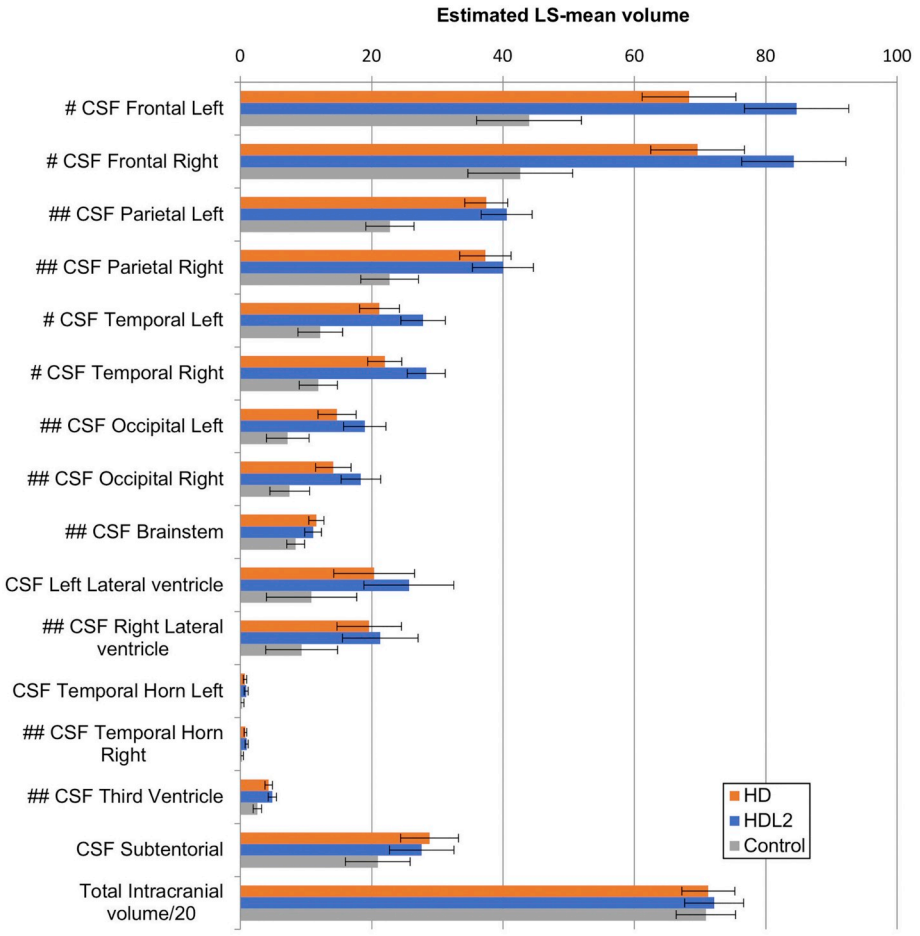


Fig. 4. HD, HDL2 and control cerebrospinal fluid and total intracranial volumes. The estimated least-squares (LS) means from the regression are depicted in the graph in a three-way comparison among the HD, HDL2 and control groups showing cerebrospinal fluid volumes and total intracranial volumes. Note that total intracranial volume was divided by 20 to fit to the graph scale. Statistical significance is shown with a symbol. Error bars denote the 95% confidence interval for the mean and significance was set at $p < .008$. Symbols denote #: Control < HD < HDL2. ##: HD, HDL2 < Control where significance was reached. LS = least squares mean, CSF = Cerebrospinal fluid.

4. Discussion

This is the first quantitative volumetric MRI study in patients with HDL2 and the first comparison to a HD group and an unaffected control group and done blind to the patients diagnosis. Consistent with the previously reported qualitative review of individual cases (Anderson et al., 2017b; Margolis et al., 2001). The analysis indicated similar atrophy of the grey and white matter structures including the basal ganglia and enlarged CSF spaces in the two disease groups compared to the normal control group. However, smaller thalamic volumes were noted in the HDL2 group compared to the HD group. There was no evidence of relative caudate sparing, as observed in one previous HDL2 case (Bardien et al., 2007).

The HD group showed white and grey matter loss, enlarged CSF spaces, and basal ganglia changes that replicated the findings of previous studies using similar analytic methods but much larger sample

Table 2
Table comparing the Huntington's Disease Like 2, Huntington's Disease and the Normal control groups basal ganglia mean volume significant differences across multiple covariates (controlling for age at MRI, controlling for duration of disease, controlling for abnormal repeat length and controlling for age at onset) Two-tailed significance: P < .008. *G. pallidus* = Globus Pallidus, HDL2 = Huntington's Disease Like 2, HD = Huntington's Disease, N. Accumbens = Nucleus accumbens.

Region	Comparison between HDL2, HD and control groups controlling for age at MRI		Comparison between HDL2 and HD groups controlling for duration of disease		Comparison between HDL2 and HD groups controlling for abnormal repeat length		Comparison between HDL2 and HD groups controlling for age at onset	
	Significant differences	*P* value	Significant differences	P value	Significant differences	P value	Significant differences	P value
Left Thalamus	HDL2 < HD, Control	0,0007	HDL2 < HD	0,0015	HDL2 < HD	0,0049	HDL2 < HD	0,0012
Right Thalamus	HDL2 < HD, Control	0,0005	HDL2 < HD	0,0008	HDL2 < HD	0,0032	HDL2 < HD	0,0006
Left Putamen	HDL2, HD < Control	< 0.0001	HDL2 < HD	0,0083	HDL2 < HD	0,0063	Not Significant	0,011
Right Putamen	HDL2 < HD < Control	< 0.0001	HDL2 < HD	0,0064	HDL2 < HD	0,0014	HDL2 < HD	0,0081
Left Caudate	HDL2, HD < Control	< 0.0001	Not Significant	0,023	Not Significant	0,027	Not Significant	0,034
Right Caudate	HDL2, HD < Control	< 0.0001	Not Significant	0,010	Not Significant	0,018	Not Significant	0,019
Left *G. pallidus*	HDL2, HD < Control	< 0.0001	Not Significant	0,45	Not Significant	0,41	Not Significant	0,42
Right G. Pallidus	HDL2, HD < Control	< 0.0001	Not Significant	0,81	Not Significant	0,80	Not Significant	0,97
Left Amygdala	Not Significant	0,11	Not Significant	0,35	Not Significant	0,27	Not Significant	0,35
Right Amygdala	Not Significant	0,27	Not Significant	0,22	Not Significant	0,16	Not Significant	0,25
Left N. Accumbens	HDL2, HD < Control	0,0016	Not Significant	0,38	Not Significant	0,16	Not Significant	0,54
Right N. Accumbens	Not Significant	0,011	Not Significant	0,018	Not Significant	0,10	Not Significant	0,10

sizes and provides support for the methods and patient population used in this study (Paulsen et al., 2008; Tabrizi et al., 2009; van den Bogaard et al., 2011). The key finding of this analysis is the similarity between the MRIs of HD and HDL2 patients, with the notable exception that the average thalamic volume was 21% smaller in the HDL2 group compared to the HD group. In contrast to this difference, the mean thalamic volume in the HD group was similar to those recorded in the normal control participants.

Initial neuroimaging studies found no difference in thalamic volumes between HD patients and controls (Rosas et al., 2003). Later studies have demonstrated thalamic volume loss in HD but have suggested that this reflects disease progression. Studies comparing MRI brain volumes in HD with normal controls often used different volumetric methods and showed HD thalamic volumes being between 2 and 8% less than the unaffected control groups (Coppen et al., 2018; Kassubek et al., 2004). Thalamic atrophy in HD appears to reflects whole brain atrophy and is proportional to overall degeneration (van den Bogaard et al., 2011). Therefore in keeping with previous reports of HD thalamic volumes, the mean thalamic volumes of the HD group in this study was 2% less than the control group. However, in the HD and HDL2 groups, regions like the putamen and caudate showed typically smaller volumes compared to the normal control group as has been described previously in HD (Tabrizi et al., 2009; van den Bogaard et al., 2011). The striking finding from this study was that HDL2 thalamic volume was significantly smaller than in the HD group when controlling for age at the time of the MRI, duration of disease, abnormal repeat length and age of onset of disease.

Attempts to find features differentiating HDL2 from HD are available, but findings have been anecdotal, inconsistent or disproved. For example, the hypothesis that HDL2 is a neuroacanthocytosis syndrome was recently refuted by a blinded controlled study (Anderson et al., 2017a). Descriptions of the HDL2's phenotype have introduced the possibility that HDL2 may disproportionately present with bradykinetic/parkinsonian features which likely reflects the unique phenotype and relatively long expanded repeat length, but this remains unverified (Margolis et al., 2001)(Schneider et al., 2012). The characterization of the clinical phenotype of HDL2 will remain incomplete while based only on retrospective case series (Anderson et al., 2017b). Thus, future research is needed, and our findings regarding the differences in thalamic volumes between HDL2 and HD may provide a new and exciting guide to explore into differentiating between these two mutations.

The possible clinical implications and pathogenic mechanisms causing greater thalamic atrophy in HDL2 would need to be accounted for. The pathogenesis of HDL2 is complex, with likely contributions from toxic properties of *JPH3* RNA with the repeat expansion, loss of expression of *JPH3*, and perhaps expanded tracts of polyglutamine expressed from a cryptic gene on the antisense strand at the HDL2 locus (Rudnicki et al., 2007; Seixas et al., 2012; Wilburn et al., 2011). The finding of smaller putamen and thalamic volumes in HDL2 compared to HD suggests differential neuronal and/or glial vulnerability in these areas to the HDL2 mutation compared to the HD mutation. This may have implications first in terms of phenotype. It has been suggested that there are clinical differences such as more myoclonus and parkinsonism although this needs further validation (Anderson et al., 2017b; Margolis et al., 2001). Secondly although little difference has been reported in the gross or histopathological findings between five patients with HDL2 compared to matched cases with HD (Rudnicki et al., 2008), it is possible that the thalamic differences may be the consequence of histopathological discrepancies between these mutations that require larger samples of HDL2 specimens (Rudnicki et al., 2008).

This study is based on the uniquely high prevalence of HDL2 in South Africa, and would be difficult to accomplish in any other location. Even in this region HDL2 is a rare disorder and therefore the sample size is small. The results do however establish the general neuroradiological similarity of HD and HDL2 and are consistent with their reportedly analogous clinical phenotypes. The selectively smaller thalamic volumes in HDL2 is an interesting finding, but the sample size imposes limits on data interpretation. In both HD and HDL2, the relationship between intracerebral volumes and duration of disease and abnormal repeat length do not reach significance, though most measurements trend to show smaller volumes with increasing duration of disease and larger abnormal repeat lengths. These are well established negative correlations for HD demonstrated in larger studies (Tabrizi et al., 2009). We would predict that in HDL2, like HD, these trends would be confirmed with larger cross-sectional cohorts of patients or with longitudinal analyses of smaller cohorts. In support of this, sequential MRIs five years apart have been reported for a single HDL2 case which qualitatively demonstrated progressive brain atrophy in a similar pattern to HD (Rodrigues et al., 2008).

Lastly, we found putaminal rim hyperintensities in all of the HD and HDL2 cases. This sign has been described before in HDL2 (Schneider et al., 2012). Other neurodegenerative disorders and normal controls have been shown to have putaminal rim hyperintensities and this is therefore unlikely to help distinguish HDL2 from other conditions (Lee et al., 2005; Tha et al., 2012). To our knowledge, the putaminal rim sign has not been commented on in HD previously.

5. Conclusion

Huntington's disease like 2 and HD are remarkably similar clinically and radiologically. When HDL2 is objectively compared to a HD group that is matched for age, abnormal repeat length and duration of disease there is a similar pattern emerging of smaller volumes in the grey and white matter as well as in the basal ganglia. The results presented here, now demonstrate the similarities between HDL2 and HD extend to spatial patterns of neurodegeneration, with the interesting exception of the thalamus, where selective thalamic volume loss tends to be greater in HDL2.

These findings raise intriguing possibilities about both the convergent and the divergent pathogenic pathways of the two diseases and opens future paths of research into how this relates to their phenotypes.

Disclosures and conflict of interest

Ronald Pierson is a shareholder in NeuroAnalytica and received fees from the University of the Witwatersrand for analysis of the MRIs.

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Data sharing and data accessibility

The authors encourage others to make use of this data and will make this large, anonymised data set available to any researchers or groups of good standing.

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Appendix A. Author contribution table

Name	Location	Role	Contribution
David G. Anderson	The University of the Witwatersrand Donald Gordon Medical Centre	Author	: Study concept and design, organization, acquisition of data, analysis and interpretation, writing of manuscript, critical revision of the manuscript for important intellectual content.
Mark Haagensen	The University of the Witwatersrand Donald Gordon Medical Centre	Author	: Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content
Aline Ferreira-Correia	Department of Psychology, School of Human and Community Development, University of the Witwatersrand	Author	: Acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content.
Ronald Pierson	Brain Image Analysis, LLC, Simi Valley CA USA	Author	:Analysis and interpretation, critical revision of the manuscript for important intellectual content.
Jonathan Carr	Division of Neurology, Department of Medicine, University of Stellenbosch, Cape Town	Author	Study supervision, critical revision of the manuscript for important intellectual content.
Amanda Krause	Division of Human Genetics, National Health Laboratory Service and School of Pathology, Faculty of Health Sciences, The University of the Witwatersrand	Author	: Study supervision, Analysis and interpretation, critical revision of the manuscript for important intellectual content, senior author.
Russell L. Margolis	Departments of Psychiatry and Neurology, Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.	Author	Study supervision, Analysis and interpretation, critical revision of the manuscript for important intellectual content, senior author.

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101666.

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