Psychiatry Research: Neuroimaging 335 (2023) 111694

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Hippocampal morphology in Huntington's disease, implications for plasticity and pathogenesis: The IMAGE-HD study

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ARTICLE INFO

Keywords:
Huntington's disease
Hippocampus
SSRIs
Depression

ABSTRACT

While striatal changes in Huntington's Disease (HD) are well established, few studies have investigated changes in the hippocampus, a key neuronal hub. Using MRI scans obtained from the IMAGE-HD study, hippocampi were manually traced and then analysed with the Spherical Harmonic Point Distribution Method (SPHARM-PDM) in 36 individuals with presymptomatic-HD, 37 with early symptomatic-HD, and 36 healthy matched controls. There were no significant differences in overall hippocampal volume between groups. Interestingly we found decreased bilateral hippocampal volume in people with symptomatic-HD who took selective serotonin reuptake inhibitors compared to those who did not, despite no significant differences in anxiety, depressive symptoms, or motor incapacity between the two groups. In symptomatic-HD, there was also significant shape deflation in the right hippocampal head, showing the utility of using manual tracing and SPHARM-PDM to characterise subtle shape changes which may be missed by other methods. This study confirms previous findings of the lack of hippocampal volumetric differentiation in presymptomatic-HD and symptomatic-HD compared to controls. We also find novel shape and volume findings in those with symptomatic-HD, especially in relation to decreased hippocampal volume in those treated with SSRIs.

Abbreviations

Beck Depression Inventory Score Version II BDI II
brain derived neurotrophic factor BDNF
dentate gyrus DG
Disease Burden Score DBS
Hospital Anxiety and Depression Scale HADS A and HADS D
Huntington's Disease HD
intracranial volume ICV
Magnetic Resonance Imaging MRI
premanifest, or pre-symptomatic HD pre-HD
selective serotonin reuptake inhibitors SSRIs
Spherical Harmonic Point Distribution Method SPHARM-PDM
the subgranular zone of the dentate gyrus in the hippocampal complex SGZ
the subventricular zone SVZ
symptomatic HD symp-HD
Unified Huntington's Disease Rating Scale UHDRS
University of Pennsylvania Smell Identification Test UPSIT

1. Introduction

Huntington's disease (HD) is a neurodegenerative condition known to start in the neostriatum before progressing to more marked

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https://doi.org/10.1016/j.pscychresns.2023.111694
Received 10 March 2023; Received in revised form 10 June 2023; Accepted 26 July 2023
Available online 2 August 2023

degeneration in the neostriatum and other brain areas, with resultant motor, cognitive, and neuropsychiatric impairment (Vonsattel et al., 1985). From a neuropsychiatric perspective, depression, anxiety, irritability, apathy, obsessions and compulsions, perseveration and psychosis have all been reported in HD (Paulsen et al., 2001; Thompson et al., 2012; van Duijn, et al. 2014, et al. 2007). Depression and anxiety are common in people with HD, with 60% of people experiencing low mood and 71% experiencing anxiety over the course of some longitudinal studies (Thompson et al., 2012), but also in pre-symptomatic HD (pre-HD) (Julien et al., 2007). HD presents with psychosis earlier, as well as in later stages with dementia. People with HD may be on antidepressants as well as antipsychotics (used for both chorea and psychiatric symptoms) (Begeti et al., 2016; Stahl and Feigin 2020). Currently available agents for symptomatic control in HD are minimal, and there is no current cure despite intensive research (Stahl and Feigin 2020).

There is evidence of the impairment of short and long-term functional neuronal plasticity through a number of mechanisms in human and animal models of HD that may affect learning and memory (Weerasinghe-Mudiyanselage et al., 2022). Specifically in HD, neurodegenerative alterations in cortico-striatal loops lead to a lack of bidirectional synaptic plasticity with the hippocampus and disrupt the critical filtering function of the striatum. This causes an inability to acquire relevant new cortical information, preventing environmental adaptability including loss of cognitive flexibility and perseverative behaviour (Ghiglieri et al., 2011). Adult hippocampal neurogenesis-related basal serotonergic dysfunction in the hippocampus is thought to be related to depressive-like behaviour and memory deficits in HD mouse models (Ransome et al., 2012). Accordingly, we hypothesised that hippocampal structural changes may be associated with both cognitive dysfunction affecting new learning and memory, as well as depression and related symptomatology. In this study, we aimed to investigate HD pathology in the hippocampus, a key neuronal hub that has associations with clinical HD symptoms including cognitive impairment and psychiatric conditions such as depression and anxiety.

1.1. The hippocampus

The hippocampus is crucial for learning and memory (Tulving 2002), in particular for combining spatial and non-spatial memories into "what happened where", based on structural and functional coordination of memory-related information processing (Knierim et al., 2014). Hippocampal atrophy is a cardinal aspect of Alzheimer disease alongside impaired memory (Zeng et al., 2021), whereas better spatial memory has been reported in conjunction with larger hippocampal size in London cab drivers (Maguire et al., 2000). Of note, the hippocampus and the striatum are involved in parallel interacting memory systems (McDonald and White 1994; White 2009; White and McDonald 2002). The caudate is thought to play a critical role in egocentric navigation whereas the hippocampus is crucially involved in allocentric navigation (McDonald and White 1994; White 2009; White and McDonald 2002), although in some cases in HD the hippocampus can compensate for caudate dysfunction in this memory pathway (Possin et al., 2017; Voermans et al., 2004).

Additionally, the hippocampus and striatum are anatomically associated to the two key regions where adult neurogenesis is known to occur: the sub-granular zone of the dentate gyrus in the hippocampal complex (SGZ), and the sub-ventricular zone (SVZ), which lies just above the caudate (Barani et al., 2007). Progenitor cells in the SGZ can migrate to the granule cell layer and differentiate into granular neurons which are functionally integrated into the hippocampal circuitry. Treatment with selective serotonin reuptake inhibitors (SSRIs) in transgenic mouse models of HD increases both brain derived neurotrophic factor (BDNF) levels and neurogenesis in SGZ and SVZ, attenuates the progression of brain atrophy and behavioural abnormalities, and increases survival (Duan et al., 2008; Grote et al., 2005; Peng et al., 2008). Despite work in animal models and the common use of antidepressants, especially SSRIs, in HD (Rowe et al., 2012) there has been limited research into the effect of SSRIs on the natural history of human HD progression.

Shape and volume analysis have been applied to the hippocampus in a number of neurodevelopmental and degenerative disorders (Lindberg et al., 2012; Solowij et al., 2013; Wood et al., 2010). There has been considerable interest in hippocampal plasticity, as cognitive training has been shown to increase left hippocampal activation in mild cognitive impairment (Rosen et al., 2011) and aerobic exercise training has been shown to increase anterior hippocampal size and improve spatial memory (Erickson et al., 2011). Notably, the increase in volume is associated with greater serum levels of BDNF (Erickson et al., 2011). Antidepressant use and recovery from depression also causes increased neurogenesis and altered BDNF in the hippocampus (Boldrini et al., 2009; McKinnon et al., 2009; Nogovitsyn et al., 2020; Phillips et al., 2015).

1.2. Volume and shape of the hippocampus in HD

Several studies have addressed hippocampal volume, with fewer addressing hippocampal shape in HD. In pre-HD, some studies have found no significant volume difference from controls at baseline or within group change detectable over one or more years (Aylward et al., 2013; Majid et al., 2011; Tang et al., 2019), nor shape differences in the hippocampus at baseline compared to controls (Younes et al., 2012). In symptomatic HD (symp-HD) baseline differences in volume compared to healthy controls have been seen (Coppen et al., 2018; van den Bogaard, et al. 2011), but no longitudinal changes in hippocampal volume over a period of up to six years (Ramirez-Garcia et al., 2020; Wijeratne et al., 2018). Other studies have found a significantly lower left hippocampus volume only in pre-HD versus controls, compared to lower volumes bilaterally in symp-HD (van den Bogaard, et al. 2011). This was also reflected in small areas of bilateral shape deflation in the hippocampal head and tail in symp-HD only (van den Bogaard, et al. 2011). In other studies of people in the pre-HD phase who are stratified according to genetic load and age, the extent of bilateral shape alterations in posterior hippocampus has been associated with level of genetic load (Faria et al., 2016). In a pre-HD study in which the hippocampus was split into subregions (CA1, CA2, CA3/dentate gyrus [DG] and subiculum) small but significant surface differences were seen in the left hemisphere across all three stratified pre-HD groups compared to controls, whereas in the right hemisphere significant differences were seen only in the middle and high load groups (Tang et al., 2019). In the lowest load groups, differences were mostly noted in CA2, while for higher loads the differences affected CA3/DG bilaterally, CA2 in the left hemisphere and CA1 in the right hemisphere (Tang et al., 2019). In summary, volume changes in the hippocampus in HD are minimal or limited while shape analyses indicate some specific regional shape changes in the hippocampus.

Several studies have further investigated the correlation between imaging differences in the hippocampus in HD and functional measures related to other affected neuronal pathways. Poorer performance in the University of Pennsylvania Smell Identification Test (UPSIT) has been associated with higher mean diffusivity in the hippocampus bilaterally (Delmaire et al., 2012), as well as with the volume of the superior right hippocampus in a voxel based morphometry study (Scahill et al., 2013). While the neuronal pathways for olfaction do not show a direct connectivity to the hippocampus, there are links to components of the cortico-subcortical loops through thalamic processing (Zhou et al., 2019). In other neurodegenerative disorders, UPSIT scores have been found to be associated with hippocampal volume in mild cognitive impairment (Yu et al., 2019), with tau pathology in the hippocampus and other regions in Alzheimer disease (Klein et al., 2021), and with hippocampal dopamine innervation in Parkinson disease (Bohnen et al., 2008).

While HD has the most marked effects on the neostriatum, it also has more subtle effects on other subcortical areas. Our aim was to investigate changes in the hippocampus and in particular their relationship with related psychiatric and neurocognitive outcomes. We hypothesised that there would be hippocampal shape differences between pre-HD and controls, and between symp-HD and controls, and that these differences would be related to depressive symptoms and cognition (Delmaire et al., 2012).

2. Method

2.1. Subjects

Subjects in this study were 36 individuals with pre-HD, 37 with early symp-HD, and 36 healthy matched controls. Healthy controls were matched for age, sex and IQ to the pre-HD individuals. All participants were right-handed and were free from brain injury, neurological and/or severe diagnosed psychiatric conditions other than HD. Medications that the subjects were taking at the time of the study were also recorded, including the dose and the reason for taking. The majority of subjects took no medication, but there were a few, largely in the symp-HD group, who took antidepressant medication, predominantly SSRIs. This will be discussed in detail below.

2.2. Measures

A number of tests were taken by the individuals including: motor measures: Unified Huntington's Disease Rating Scale (UHDRS) motor score (Kieburtz et al., 1996), self-paced tapping (1.8 Hz and 3 Hz) and speeded tapping (Stout et al., 2011); cognitive measures: verbal IQ, Symbol digit modalities test (Smith 1982), UPSIT (Doty et al., 1984) and Stroop (Stroop 1935); and psychiatric measures: Beck Depression Inventory Score Version II (BDI-II) (Beck et al., 1996), Schedule of Compulsions Obsessions and Pathological Impulses (Watson and Wu 2005), Frontal Systems Behaviour Scale (Stout et al., 2003), and Hospital Anxiety and Depression Scale (HADS) anxiety and depression subscales (HADS-A and HADS-D) (Zigmond and Snaith 1983). Magnetic resonance imaging (MRI) scans were taken of all subjects on a 3T scanner in the Royal Melbourne Children's Hospital. For this sub-study we used UHDRS as a measure of motor incapacity from disease, and chose to investigate the relationship between hippocampal volume and shape and UPSIT, BDI-II, HADS-A, and HADS depression.

The IMAGE-HD study was approved by the Monash University and Melbourne Health Human Research Ethics Committees and 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 neuroimaging sub-project was also obtained from both Monash University and from the Australian National University.

2.3. Manual tracing

Hippocampi were manually traced by a single trained researcher (FW) according to a previously published protocol (Velakoulis et al., 1999; Watson et al., 1992). Briefly, all MRI images were aligned along the AC-PC (anterior commissure- posterior commissure) plane in the FMRIB Software Library. Tracing was then performed using Analyze software using a protocol modified from Watson and colleagues (Watson et al., 1992). In brief, tracing occurred in the coronal plane from posterior to anterior, from the head of the hippocampus just before the crux of the fornix becomes indistinctly separated from the thalamus. The inferior border is the interface between the hippocampal grey matter and the parahippocampal gyrus white matter. The lateral border is the temporal/inferior horn of the lateral ventricle. The superior border included any white matter superior to the hippocampal grey matter-more posteriorly this is the fornix and then this forms the fimbria and alveus more anteriorly. The subiculum is not included in this protocol. (Velakoulis et al., 1999; Watson et al., 1992). Reliability of image analysis was assessed by intraclass correlation, which was evaluated by repeating right and left sided hippocampal measurements on 10 randomly selected scans (20 comparisons). Intra-rater intra-class correlations were 0.88–0.98.

2.4. Volumetric analysis

Statistical analysis of volume and other baseline data was performed using SPSS 20.0 (Chicago, Ill., USA) and significance was set at $P<0.05$. Differences between groups for clinical and demographic data were tested with parametric (ANOVA) and non-parametric (Chi-square, Kruskal-Wallis, Mann Whitney U) tests as appropriate. Multivariate analysis of covariance (MANCOVA) was used to test differences in hippocampal volume between the subject groups with age, sex and ICV as covariates, as these were either significantly different between groups or have expected effects on hippocampal volume. Preliminary checks were conducted to ensure there was no violation of assumptions of normality, homogeneity of variances, and reliable measurement of the covariate. Bonferroni corrections for multiple comparisons were used where appropriate.

2.4.1. SPHARM-PDM shape analysis

Traced structures were processed for baseline shape analysis using the SPHARM-PDM analysis software (https://www.nitrc.org/projects/spharm-pdm/) (Styner et al., 2006). Briefly, hippocampal segmentations were smoothed with a 1 mm Gaussian kernel and spherical harmonics were used to generate meshes with 1002 corresponding surface points. Average left and right meshes were created using the control participants and hippocampal meshes were aligned to the mean shape using Procrustes alignment. For each participant the signed magnitude of displacement was calculated along the surface normal from the mean shape. The displacement vector was used in subsequent shape analysis. Displacement vector values were used as the dependant variables in all analyses, and thus all analyses were conducted across the 1002 corresponding points for each structure. In all analyses age, sex and ICV were used as covariates. Pearson's correlation analyses were performed with the independent variable calculated as the magnitude of displacement between surface normals at each vertex from the mean shape. Covariates and correction for multiple comparisons were performed as for the group comparisons. P-values across each shape were corrected using a false discovery rate (FDR) with $p < 0.05$. For the purposes of results and discussion, significant differences were only considered at the FDR corrected level.

3. Results

3.1. Demographic and volumetric data

Demographic and selected data across groups are shown in Table 1. Although there appears to be a difference in the proportion of men and women between groups, this does not reach statistical significance. As expected, there are significant differences in age and measures of motor incapacity between groups: people with symp-HD are older than the other two groups, and have higher scores on the UHDRS motor subscale. Patterns of SSRI use were also significantly different between controls, pre-HD, and symp-HD. Thirty-five percent of participants in the symp-HD group were taking an SSRI during the period of the study (13 people, most of whom took citalopram 20 mg, sertraline 50–200 mg, or fluoxetine 20–40 mg). In contrast, 11% of people with pre-HD took SSRIs (four people, one of whom took escitalopram, one citalopram, and two sertraline) and only 3% of controls (one person, who took citalopram). All were taking the medication for depression except for one person taking fluoxetine for anxiety.

Within the outcomes of interest, there were significant differences in

Table 1
Demographic and selected data across groups.

	Mean ± SD Controls (n = 36)	Pre-HD (n = 36)	Symp-HD (n = 37)
Sex (M:F)	12:24	14:22	21:16
Age (years)	42.4 ± 13.4	41.7 ± 9.9	52.1 ± 9.3*
ICV (10cm^3)	1.46±0.14	1.41±0.16	1.40±0.16
UHDRS motor score (range)		1 (0–4)**	19 (6–60)**
SSRI use	3%	11%	35%
UPSIT	34.0 ± 3.1	32.7 ± 5.0	26.2 ± 7.1*
BDI-II	4.0 ± 4.1	8.7 ± 9.8	8.2 ± 7.2
HADS-A	5.0 ± 2.8	6.6 ± 3.5	5.5 ± 3.4
HADS-D	2.6 ± 3.1	2.7 ± 3.0	2.8 ± 2.4
Right hipp. vol. (cm^3)	3.2 ± 0.4	3.2 ± 0.4	3.1 ± 0.5
Left hipp. vol. (cm^3)	3.1 ± 0.3	3.0 ± 0.4	2.9 ± 0.5

ICV: Intracranial volume; UHDRS: Unified Huntington's Disease Rating Scale; SSRI: selective serotonin reuptake inhibitor; UPSIT: University of Pennsylvania Smell Identification test. Maximum score is 40, with lower scores indicating worse olfaction; BDI-II: Beck depression inventory score version II. Minimum score for mild depression is 14 points, for moderate depression is 20 points, and for major depression is 29 points; HADS-A: Hospital anxiety and depression scale- anxiety. Maximum score is 21; HADS-D: Hospital anxiety and depression scale- depression. Maximum score 21; hipp. vol.: hippocampal volume. Also note that two participants were excluded from the volume analysis due to high motion artefact interfering with manual tracing.
*Significant differences compared to controls, $p<0.001$.
**Significant differences between pre-HD and symp-HD, $p<0.001$.

UPSIT scores between groups, with symp-HD scoring significantly more poorly than controls and pre-HD. There were no significant differences between groups in any of the anxiety or depression scores. There were also no significant differences in hippocampal volume between groups. Multivariate analysis of covariance here revealed a significant main effect of ICV on hippocampal volume ($p < 0.001$), but no significant main effect of group or sex or age. When controlling for age and group status, there were no significant partial correlations between hippocampal volume (right or left) and scores on any of UPSIT, BDI-II, HADS-A or HADS-D.

Given the low numbers for SSRI use in controls and in pre-HD, the relationship between SSRI use and outcomes (psychiatric measures and hippocampal volumes) was only assessed in symp-HD. When stratifying into SSRI users versus non-users, a significant difference in both right and left hippocampal volume was found, despite there being no significant differences between proportion of men and women, age, years since diagnosis, ICV, or motor, anxiety or depressive symptoms (Table 2). This significant difference remained when using age, sex, and ICV as covariates. As in the hippocampal volume analysis for all three groups, multivariate analysis of covariance within symp-HD SSRI users and non-users revealed a significant main effect of ICV as well as group on hippocampal volume, but no significant main effects of age or sex.

Table 2
SSRI use and relationship with psychiatric symptoms, hippocampal volume, and motor incapacity in symp-HD (±SD).

	SSRI users (±SD)	SSRI non-users (±SD)
Demographic data		
Sex (M:F)	7:6	13:9
Years since diagnosis	2.5 ± 1.4	1.7 ± 1.6
Age (y)	54.1 ± 10.6	50.9 ± 8.7
ICV (10cm^3)	1.35±0.14	1.41±0.15
UHDRS motor score	22.5 ± 12.9	17.9 ± 12.3
BDI-II	4.0 ± 4.1	8.7 ± 9.8
HADS-A	6.2 ± 3.9	5.1 ± 3.2
HADS-D	3.2 ± 2.7	2.7 ± 2.2
Right hipp. vol. (cm^3)*	2.8 ± 0.3	3.2 ± 0.5
Left hipp. vol. (cm^3)*	2.6 ± 0.3	3.0 ± 0.5

UHDRS: Unified Huntington's Disease Rating Scale; UPSIT: University of Pennsylvania Smell Identification test; BDI-II: Beck depression inventory mark II; HADS-A: Hospital anxiety and depression scale- anxiety; HADS-D: Hospital anxiety and depression scale- depression; SSRI: selective serotonin reuptake inhibitor; hipp. vol.: hippocampal volume.
*Significant differences between groups, $p<0.05$.
Note that two participants were excluded from the volume analysis due to high motion artefact interfering with manual tracing.

3.2. Baseline shape differences

Hippocampal shape differences can be seen in Fig. 1. There were no significant differences between groups in left hippocampal shape. In the right hippocampus there was a significant shape deflation in the anterior hippocampal head in symp-HD compared to controls, in an area corresponding to CA3. There were no correlations between hippocampal shape and scores on any of the clinical measures. There were also no significant correlations between SSRI use and hippocampal shape in symp-HD.

4. Discussion

We used manual tracing of the hippocampus to investigate hippocampal shape and volume in HD and the relationship with neuropsychiatric symptoms. We found no differences in hippocampal volume between controls and pre-HD or symp-HD, but baseline shape deflation was demonstrated in the right hippocampal head in symp-HD compared to controls. We also report lower hippocampal volume in people with symp-HD who were on SSRIs compared to those who weren't, but no significant shape differences between these groups.

4.1. Volumetric differences in hippocampus

We found no significant differences in hippocampal volume between groups. Previous studies have identified mixed results in this regard,

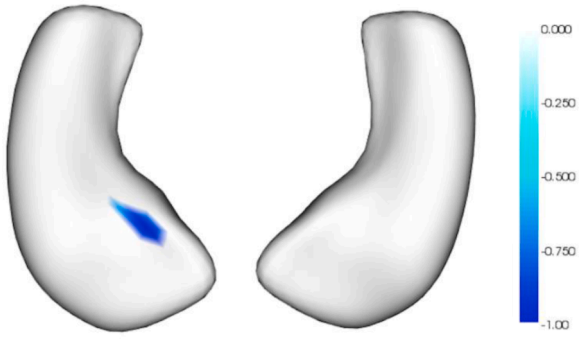

Fig. 1. Significant differences in hippocampal shape in symp-HD compared to controls. Superior view of the bilateral hippocampus. Right hippocampus is on the left of image, left hippocampus to the right of image. Blue = shape contraction, scale is in mm.

with some finding unilateral or bilateral changes in pre-HD close to disease onset, and/or bilateral changes in symp-HD (Ciarochi et al., 2016; Coppen et al., 2018; van den Bogaard, et al. 2011). Other studies found no such differences (Aylward et al., 2013; Majid et al., 2011; Ramirez-Garcia et al., 2020; Wijeratne et al., 2018). The low number of cases in our study, and the fact that they were in the early stages of symp-HD may have contributed to this finding. However, we have also used manual tracing, which while labour intensive provides more fine-grained detail than automated methods, and thus better ability to characterise changes in hippocampal morphology in this cohort (Fung et al., 2019; Germeyan et al., 2014).

4.2. Clinical correlations

No significant associations between hippocampal size and depression or anxiety symptoms were identified in this dataset (BDI-II, HADS-A or HADS-D). This may be related to the exclusion of participants with major mental illness, since the average scores on these measures for the three groups were below the cut off value for clinical levels of depression or anxiety (Smarr and Keefer 2011). Despite this lack of association there was a significant difference in hippocampal volume in symp-HD SSRI users compared to non-users. Lower bilateral hippocampal volume was found in people with symp-HD who took SSRIs, although there was no significant difference between the groups in depressive or anxiety symptoms or in motor symptoms, nor in the sex distribution of both groups, age, or time since diagnosis.

At first glance, our finding of decreased hippocampal volume in people with symp-HD taking SSRIs appears to be inconsistent with previous studies in humans and in mouse models of HD. Human studies have suggested that there is a smaller hippocampal volume in people with depression after disease onset (McKinnon et al., 2009; Nolan et al., 2020), and in particular that hippocampal tail volumes are decreased in participants with depression, while those who achieve early sustained remission on antidepressants have significantly greater hippocampal tail volumes (Nogovitsyn et al., 2020). Similarly, in mouse models of HD, treatment with SSRIs increases neurogenesis in the SGZ and attenuates brain atrophy (Duan et al., 2008; Grote et al., 2005; Peng et al., 2008). Here, we have found a lower hippocampal volume in people with symp-HD who are on SSRIs, which is not related to time since diagnosis, sex, motor incapacity, or anxious or depressive symptoms.

Within the ageing and dementia literature an increasing number of studies have shown a link between depression, SSRI use, and dementia and hippocampal atrophy. Depression is known to increase risk of dementia (Brenowitz et al., 2021; Sáiz-Vázquez et al., 2021), and depression in old age may be a prodrome to dementia (Almeida et al., 2017; Tateno et al., 2023). While it is difficult to separate the contribution of SSRIs to hippocampal atrophy or dementia given the risk of "confounding by indication" (see commentary by (Kodesh et al., 2020)), there appears to be an additional association of SSRI use with hippocampal atrophy (Geerlings et al., 2012) and risk of dementia (Kodesh et al., 2020; Leng et al., 2018; Wang et al., 2016, et al. 2018). Our results point to a similar process in HD, which is a significant new finding and requires further exploration, particularly as it has implications for devastating patient outcomes like dementia.

Caveats to the above findings however must be discussed. Psychiatric disease was an exclusion criterion for participation in the study, and participants in the study who were on antidepressants did not have significant depressive symptoms. The cut off score for depression in HADS-D is 8 (Zigmond and Snaith 1983), while for BDI-II the minimum score for moderate depression is 20 and severe depression requires a score of 29 or higher (Beck et al., 1996). Here, median scores for all our participants were below threshold for clinically significant symptoms, and therefore we cannot extrapolate these results to depressed versus non-depressed people. This may also have masked partial treatment of depression and related lower hippocampal volumes, which have not been modified by SSRI treatment. The low participant numbers in this study may have contributed to the absence of significant shape correlations with SSRI use. Similarly, although there was no significant difference in age or time since diagnosis between the two groups, there was a trend towards older age, longer time since diagnosis, and increased motor burden in people with symp-HD who were taking SSRIs. It remains possible that both the decreased hippocampal volume and the SSRI use in symp-HD are markers of disease progression rather than causally linked. Further replication with larger numbers is required.

Correlation between scores on UPSIT and hippocampal size/shape were not observed, in spite of some HD studies which have found correlations with diffusion tensor imaging (Delmaire et al., 2012) and volume changes in this region (Scahill et al., 2013). UPSIT scores were significantly worse in people with symp-HD compared to pre-HD and controls, which did not differ significantly between each other. UPSIT is a score out of 40, counting the number identified correctly of 40 different smells. Controls scored an average of 34 correct, pre-HD scored 33, and symp-HD only 26. Of note, "normal" scores in the UK are defined as 34–40 for males and 35–40 for females, "mild microsmia" as 30–33 (males) and 31–34 (females), "microsmia" as 26–29 in both sexes, "severe microsmia" as 19–25 in both sexes, and "anosmia" as anything less than 19 (Muirhead et al., 2013). The clustering of scores in the less disabled range for all groups including symp-HD may have meant that there was less variation for a correlation with hippocampal shape to be seen. Interestingly, UPSIT scores vary by culture, and are known to be lower in Australian subjects than in UK or North American subjects (Mackay-Sim 2001).

4.3. Hippocampal shape analysis

We found significant deflation in the right hippocampal head in symp-HD compared to controls in this cross-sectional analysis. Previous studies have variously found small bilateral areas of lower volume compared to controls in the hippocampal head and tail in symp-HD (van den Bogaard, et al. 2011). In studies with larger numbers of pre-HD participants, significant bilateral decreases in hippocampal tail were observed in those closer to disease onset (Faria et al., 2016; Tang et al., 2019), and smaller changes in the hippocampal body in those further away from disease onset, commencing in the left hemisphere (Tang et al., 2019).

Areas of shape change correspond roughly to shape deflation in CA3 of the hippocampal head (noting that the subiculum is not included in this method of tracing the hippocampus). This is in contrast to a previous study which found shape decreases in CA2 initially in pre-HD further from disease onset, then decreases in CA3/dentate gyrus closer to disease onset (Tang et al., 2019). Hippocampal shape changes in HD may help to shed light on whether neuronal degeneration in HD occurs in a pattern that spreads out from the striatum (Poudel et al., 2019) or begins from multiple foci of cell autonomous neurodegeneration (Tang et al., 2019). If network spread were the case, we would hypothesise that areas of the hippocampus with connections to the striatum would degenerate first in pre-HD and symp-HD, with those regions showing decrease corresponding to hippocampal structures that receive input from distal regions (dentate gyrus/CA3, CA1). Our results favour network spread, as degeneration occurs in the anterior hippocampus, which is topographically connected to striatum, and in CA3 which receives neuronal inputs from other parts of the brain.

4.4. Limitations

The use of manual versus automated techniques is labour-intensive and subspecialised, yet we believe that the use of a rigorously anatomical basis for tracing and description of the hippocampal borders remains the gold standard. Manual tracing rather than automated segmentations remain more anatomically accurate, particularly when there are distortions of normal anatomy (Fung et al., 2019; Germeyan et al., 2014). The relatively small cohort size here, particularly when

investigating possible impacts of SSRIs, also limits interpretation of the findings.

4.5. Conclusions/clinical implications

We confirmed and extended findings of hippocampal change in HD by showing shape deflation in an input region of the right hippocampal head in symp-HD, suggesting shape change following degeneration from the striatum. We also found a significantly lower hippocampal volume in people with symp-HD who were medicated with SSRIs, an intriguing finding which warrants further investigation. These findings contribute to our understanding of the pathogenesis of HD and indicate new areas of investigation. The importance of shape analysis to investigate regional change, rather than volumetric analysis, has the potential to provide important insights into brain network changes in neurodegenerative disease.

Funding

This work was supported by the CHDI Foundation, Inc. (USA) (grant number A – 3433); the National Health and Medical Research Council (NHMRC) (grant number 606650); the RANZCP New Investigator Grant 2013 (FAW); and the University of Melbourne – computer and software support. We thank all participants for their involvement in the study.

CRediT authorship contribution statement

F.A. Wilkes was involved in conceptualisation, data curation, formal analysis, investigation and methodology of this imaging sub-project of the IMAGE-HD project. She also wrote the original draft and orchestrated the review and editing of the final manuscript. D. Jakabek was central to formal analysis, investigation and methodology of this sub-project, as well as being involved in the review and editing of the final manuscript. G. Poudel, J.C. Stout, P.Chua, and G.F. Egan were involved in conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, and project administration of the main IMAGE-HD project, from which this article draws its data. They were also all involved in the review and editing of the final version of this manuscript. N. Georgiou-Karistianis is the primary investigator of the IMAGE-HD project and so was integral to all of the above roles related to the IMAGE-HD main project, as well as visualisation of the main project and this sub-project, review and editing of the manuscript, and supervision of F.A. Wilkes as her PhD co-supervisor. M. Walterfang and D. Velakoulis were involved in conceptualisation of this sub-project, as well as supervision of F.A. Wilkes as her PhD co-supervisors. They were also involved in the review and editing of the final manuscript. J.C.L. Looi was involved in conceptualisation of this sub-project, supervision of F.A. Wilkes as her main PhD supervisor, and review and editing of the final manuscript. All authors had significant intellectual and practical input into the final manuscript.

Declaration of Competing Interest

In the past three years, Dr Stout has received funding from CHDI Foundation unrelated to this research. She is also director of Zindametrix Pty Ltd., which has research contracts with several pharma companies to assist in implementing cognitive assessments in HD clinical trials, none of which are relevant to this research. In addition, she has received an honorarium from Teva Australia for participation in a scientific advisory board, none related 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.

References

Almeida, O.P., Hankey, G.J., Yeap, B.B., Golledge, J., Flicker, L., 2017. Depression as a modifiable factor to decrease the risk of dementia. Transl. Psychiatry 7 (5), e1117.
Aylward, E.H., Harrington, D.L., Mills, J.A., Nopoulos, P.C., Ross, C.A., Long, J.D., Liu, D., Westervelt, H.K., Paulsen, J.S., 2013. Regional atrophy associated with cognitive and motor function in prodromal Huntington disease. J. Huntingtons Dis. 2 (4), 477–489.
Barani, I.J., Benedict, S.H., Lin, P.-S., 2007. Neural stem cells: implications for the conventional radiotherapy of central nervous system malignancies. Int. J. Radiat. Oncol. Biol. Phys. 68 (2), 324–333.
Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual For the Beck Depression Inventory - II. Psychol. Corp, San Antonio.
Begeti, F., Schwab, L.C., Mason, S.L., Barker, R.A., 2016. Hippocampal dysfunction defines disease onset in Huntington's disease. J. Neurol. Neurosurg. Psychiatry 87 (9), 975–981.
Bohnen, N.I., Gedela, S., Herath, P., Constantine, G.M., Moore, R.Y., 2008. Selective hyposmia in Parkinson disease: association with hippocampal dopamine activity. Neurosci. Lett. 447 (1), 12–16.
Boldrini, M., Underwood, M.D., Hen, R., Rosoklija, G.B., Dwork, A.J., John Mann, J., Arango, V, 2009. Antidepressants increase neural progenitor cells in the human hippocampus. Neuropsychopharmacology 34 (11), 2376–2389.
Brenowitz, W.D., Zeki Al Hazzouri, A., Vittinghoff, E., Golden, S.H., Fitzpatrick, A.L., Yaffe, K, 2021. Depressive symptoms imputed across the life course are associated with cognitive impairment and cognitive decline. J. Alzheimers Dis. 83 (3), 1379–1389.
Ciarochi, J.A., Calhoun, V.D., Lourens, S., Long, J.D., Johnson, H.J., Bockholt, H.J., Liu, J., Plis, S.M., Paulsen, J.S., Turner, J.A., 2016. Patterns of co-occurring gray matter concentration loss across the huntington disease prodrome. Front. Neurol. 7, 147.
Coppen, E.M., Jacobs, M., van den Berg-Huysmans, A.A., van der Grond, J., Roos, R.A.C., 2018. Grey matter volume loss is associated with specific clinical motor signs in Huntington's disease. Parkinsonism Relat. Disord. 46, 56–61.
Delmaire, C., Dumas, E., Sharman, M., van den Bogaard, S., Valabregue, R., Jauffret, C., Justo, D., Reilmann, R., Stout, J., Craufurd, D., 2012. The structural correlates of functional deficits in early Huntington's disease. Hum. Brain Mapp. 34 (9), 2141–2153.
Doty, R.L., Shaman, P., Kimmelman, C.P., Dann, M.S., 1984. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. Laryngoscope 94 (2 Pt 1), 176–178.
Duan, W.Z., Peng, Q., Masuda, N., Ford, E., Tryggestad, E., Ladenheim, B., Zhao, M., Cadet, J.L., Wong, J., Ross, C.A., 2008. Sertraline slows disease progression and increases neurogenesis in N171-82Q mouse model of Huntington's disease. Neurobiol. Dis. 30 (3), 312–322.
Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. U.S.A. 108 (7), 3017–3022.
Faria, A.V., Ratnanather, J.T., Tward, D.J., Lee, D.S., van den Noort, F., Wu, D., Brown, T., Johnson, H., Paulsen, J.S., Ross, C.A., 2016. Linking white matter and deep gray matter alterations in premanifest Huntington disease. Neuroimage Clin. 11, 450–460.
Fung, Y.L., Ng, K.E.T., Vogrin, S.J., Meade, C., Ngo, M., Collins, S.J., Bowden, S.C., 2019. Comparative utility of manual versus automated segmentation of hippocampus and entorhinal cortex volumes in a memory clinic sample. J. Alzheimers Dis. 68 (1), 159–171.
Geerlings, M.I., Brickman, A.M., Schupf, N., Devanand, D.P., Luchsinger, J.A., Mayeux, R., Small, S.A., 2012. Depressive symptoms, antidepressant use, and brain volumes on MRI in a population-based cohort of old persons without dementia. J. Alzheimers Dis. 30 (1), 75–82.
Germeyan, S.C., Kalikhman, D., Jones, L., Theodore, W.H., 2014. Automated versus manual hippocampal segmentation in preoperative and postoperative patients with epilepsy. Epilepsia 55 (9), 1374–1379.
Ghiglieri, V., Sgobio, C., Costa, C., Picconi, B., Calabresi, P., 2011. Striatum-hippocampus balance: from physiological behavior to interneuronal pathology. Prog. Neurobiol. 94 (2), 102–114.
Grote, H.E., Bull, N.D., Howard, M.L., van Dellen, A., Blakemore, C., Bartlett, P.F., Hannan, A.J., 2005. Cognitive disorders and neurogenesis deficits in Huntington's disease mice are rescued by fluoxetine. Eur. J. Neurosci. 22 (8), 2081–2088.
Julien, C.L., Thompson, J.C., Wild, S., Yardumian, P., Snowden, J.S., Turner, G., Craufurd, D., 2007. Psychiatric disorders in preclinical Huntington's disease. J. Neurol. Neurosurg. Psychiatry 78 (9), 939–943.
Kieburtz, K., Penney, J.B., Como, P., Ranen, N., Shoulson, I., Feigin, A., Abwender, D., Greenamyre, J.T., Higgins, D., Marshall, F.J., 1996. Unified Huntington's disease rating scale: reliability and consistency. Mov. Disord. 11 (2), 136–142.
Klein, J., Yan, X., Johnson, A., Tomljanovic, Z., Zou, J., Polly, K., Honig, L.S., Brickman, A.M., Stern, Y., Devanand, D.P., 2021. Olfactory impairment is related to tau pathology and neuroinflammation in Alzheimer's disease. J. Alzheimers Dis. 80 (3), 1051–1065.
Knierim, J.J., Neunuebel, J.P., Deshmukh, S.S., 2014. Functional correlates of the lateral and medial entorhinal cortex: objects, path integration and local-global reference frames. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (1635), 20130369.
Kodesh, A., Sandin, S., Reichenberg, A., Rotstein, A., Pedersen, N.L., Ericsson, M., Karlsson, I.K., Davidson, M., Levine, S.Z., 2020. Antidepressants and the risk of dementia: appropriate consideration of confounding by indication. Am. J. Geriatr. Psychiatry 28 (4), 499–500.

Leng, Y., Diem, S.J., Stone, K.L., Yaffe, K., 2018. Antidepressant use and cognitive outcomes in very old women. J. Gerontol. A Biol. Sci. Med. Sci. 73 (10), 1390–1395.
Lindberg, O., Walterfang, M., Looi, J.C.L., Malykhin, N., Ostberg, P., Zandbelt, B., Styner, M., Paniagua, B., Velakoulis, D., Orndahl, E., 2012. Hippocampal shape analysis in Alzheimer's disease and frontotemporal lobar degeneration subtypes. J. Alzheimers Dis. 30 (2), 355–365.
Mackay-Sim, A., Doty, R.L., 2001. The University of Pennsylvania Smell Identification Test: normative adjustment for Australian subjects. Austr. J. Oto-Laryngol. 4, 174–177.
Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., Frith, C.D., 2000. Navigation-related structural change in the hippocampi of taxi drivers. Proc. Natl. Acad. Sci. USA. 97 (8), 4398–4403.
Majid, D.S.A., Aron, A.R., Thompson, W., Sheldon, S., Hamza, S., Stoffers, D., Holland, D., Goldstein, J., Corey-Bloom, J., Dale, A.M., 2011. Basal ganglia atrophy in prodromal Huntington's disease is detectable over one year using automated segmentation. Mov. Disord. 26 (14), 2544–2551.
McDonald, R.J., White, N.M., 1994. Parallel information processing in the water maze: evidence for independent memory systems involving dorsal striatum and hippocampus. Behav. Neural Biol. 61 (3), 260–270.
McKinnon, M.C., Yucel, K., Nazarov, A., MacQueen, G.M., 2009. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. J. Psychiatry Neurosci. 34 (1), 41–54.
Muirhead, N., Benjamin, E., Saleh, H., 2013. Is the University of Pennsylvania smell identification test (UPSIT) valid for the UK population? Otorhinolaryngolog. 6 (2), 99–103.
Nogovitsyn, N., Muller, M., Souza, R., Hassel, S., Arnott, S.R., Davis, A.D., Hall, G.B., Harris, J.K., Zamyadi, M., Metzak, P.D., 2020. Hippocampal tail volume as a predictive biomarker of antidepressant treatment outcomes in patients with major depressive disorder: a CAN-BIND report. Neuropsychopharmacology 45 (2), 283–291.
Nolan, M., Roman, E., Nasa, A., Levins, K.J., O'Hanlon, E., O'Keane, V., Willian Roddy, D, 2020. Hippocampal and Amygdalar Volume Changes in Major Depressive Disorder: A Targeted Review and Focus on Stress 4, 2470547020944553.
Paulsen, J.S., Ready, R.E., Hamilton, J.M., Mega, M.S., Cummings, J.L., 2001. Neuropsychiatric aspects of Huntington's disease. J. Neurol. Neurosurg. Psychiatry 71 (3), 310–314.
Peng, Q., Masuda, N., Jiang, M., Li, Q., Zhao, M., Ross, C.A., Duan, W., 2008. The antidepressant sertraline improves the phenotype, promotes neurogenesis and increases BDNF levels in the R6/2 Huntington's disease mouse model. Exp. Neurol. 210 (1), 154–163.
Phillips, J.L., Batten, L.A., Tremblay, P., Aldosary, F., Blier, P., 2015. A prospective, longitudinal study of the effect of remission on cortical thickness and hippocampal volume in patients with treatment-resistant depression. Int. J. Neuropsychopharmacol. 18 (8).
Possin, K.L., Kim, H., Geschwind, M.D., Moskowitz, T., Johnson, E.T., Sha, S.J., Apple, A., Xu, D., Miller, B.L., Finkbeiner, S., 2017. Egocentric and allocentric visuospatial working memory in premotor Huntington's disease: a double dissociation with caudate and hippocampal volumes. Neuropsychologia 101, 57–64.
Poudel, G.R., Harding, I.H., Egan, G.F., Georgiou-Karistianis, N., 2019. Network spread determines severity of degeneration and disconnection in Huntington's disease. Hum. Brain Mapp. 40 (14), 4192–4201.
Ramirez-Garcia, G., Galvez, V., Diaz, R., Bayliss, L., Fernandez-Ruiz, J., Campos-Romo, A., 2020. Longitudinal atrophy characterization of cortical and subcortical gray matter in Huntington's disease patients. Eur. J. Neurosci. 51 (8), 1827–1843.
Ransome, M.I., Renoir, T., Hannan, A.J., 2012. Hippocampal neurogenesis, cognitive deficits and affective disorder in Huntington's disease. Neural Plast.
Rosen, A.C., Sugiura, L., Kramer, J.H., Whitfield-Gabrieli, S., Gabrieli, J.D., 2011. Cognitive training changes hippocampal function in mild cognitive impairment: a pilot study. J. Alzheimers Dis. 26, 349–357.
Rowe, K.C., Paulsen, J.S., Langbehn, D.R., Wang, C., Mills, J., Beglinger, L.J., Smith, M. M., Epping, E.A., Fiedorowicz, J.G., Duff, K., 2012. Patterns of serotonergic antidepressant usage in prodromal Huntington disease. Psychiatry Res. 196 (2–3), 309–314.
Sáiz-Vázquez, O., Gracia-García, P., Ubillos-Landa, S., Puente-Martínez, A., Casado-Yusta, S., Olaya, B., Santabárbara, J., 2021. Depression as a risk factor for Alzheimer's disease: a systematic review of longitudinal meta-analyses. J. Clin. Med. 10 (9).
Scahill, R.I., Hobbs, N.Z., Say, M.J., Bechtel, N., Henley, S.M., Hyare, H., Langbehn, D.R., Jones, R., Leavitt, B.R., Roos, R.A., 2013. Clinical impairment in premanifest and early Huntington's disease is associated with regionally specific atrophy. Hum. Brain Mapp. 34 (3), 519–529.
Smarr, K.L., Keefer, A.L, 2011. Measures of depression and depressive symptoms: beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res (Hoboken) 63 (Suppl 11), S454–S466.
Smith, A., 1982. Symbol Digit Modality Test (SDMT): Manual (Revised). Psychological Services, Los Angeles.
Solowij, N., Walterfang, M., Lubman, D.I., Whittle, S., Lorenzetti, V., Styner, M., Velakoulis, D., Pantelis, C., Yuecel, M., 2013. Alteration to hippocampal shape in cannabis users with and without schizophrenia. Schizophr. Res. 143 (1), 179–184.
Stahl, C.M., Feigin, A., 2020. Medical, surgical, and genetic treatment of Huntington disease. Neurol. Clin. 38 (2), 367–378.
Stout, J.C., Paulsen, J.S., Queller, S., Solomon, A.C., Whitlock, K.B., Campbell, J.C., Carlozzi, N., Duff, K., Beglinger, L.J., 2011. Neurocognitive signs in prodromal Huntington disease. Neuropsychol 25 (1), 1–14.
Stout, J.C., Ready, R.E., Grace, J., Malloy, P.F., Paulsen, J.S., 2003. Factor analysis of the frontal systems behavior scale (FrSBe). Assessment 10 (1), 79–85.
Stroop, J.R., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol. 18 (6), 643–662.
Styner, M., Oguz, I., Xu, S., Brechbühler, C., Pantazis, D., Levitt, J., Shenton, M., Gerig, G., 2006. Framework for the statistical shape analysis of brain structures using SPHARM-PDM. Insight J. 1071, 242–250.
Tang, X., Ross, C.A., Johnson, H., Paulsen, J.S., Younes, L., Albin, R.L., Ratnanather, J.T., Miller, M.I., 2019. Regional subcortical shape analysis in premanifest Huntington's disease. Hum. Brain Mapp 40 (5), 1419–1433.
Tateno, A., Nogami, T., Sakayori, T., Yamamoto, K., Okubo, Y., 2023. Depression as a prodromal symptom of neurodegenerative diseases. J. Nippon Med. Sch. 90 (2), 157–164.
Thompson, J.C., Harris, J., Sollom, A.C., Stopford, C.L., Howard, E., Snowden, J.S., Craufurd, D., 2012. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. J. Neuropsychiatry Clin. Neurosci. 24 (1), 53–60.
Tulving, E., 2002. Episodic memory: from mind to brain. Annu. Rev. Psychol. 53, 1–25.
van den Bogaard, S.J.A., Dumas, E.M., Ferrarini, L., Milles, J., van Buchem, M.A., van der Grond, J., Roos, R.A.C., 2011. Shape analysis of subcortical nuclei in Huntington's disease, global versus local atrophy - results from the TRACK-HD study. J. Neurol. Sci. 307 (1–2), 60–68.
van Duijn, E., Craufurd, D., Hubers, A.A., Giltay, E.J., Bonelli, R., Rickards, H., Anderson, K.E., van Walsem, M.R., van der Mast, R.C., Orth, M., 2014. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). J. Neurol. Neurosurg. Psychiatry 85 (12), 1411–1418.
van Duijn, E., Kingma, E.M., van der Mast, R.C., 2007. Psychopathology in verified Huntington's disease gene carriers. J. Neuropsychiatry Clin. Neurosci. 19 (4), 441–448.
Velakoulis, D., Pantelis, C., McGorry, P.D., Dudgeon, P., Brewer, W., Cook, M., Desmond, P., Bridle, N., Tierney, P., Murrie, V., 1999. Hippocampal volume in first-episode psychoses and chronic schizophrenia - a high-resolution magnetic resonance imaging study. Arch. Gen. Psychiatry 56 (2), 133–141.
Voermans, N.C., Petersson, K.M., Daudey, L., Weber, B., van Spaendonck, K.P., Kremer, H.P.H., Fernandez, G., 2004. Interaction between the human hippocampus and the caudate nucleus during route recognition. Neuron 43 (3), 427–435.
Vonsattel, J.P., Myers, R.H., Stevens, T.J., Ferrante, R.J., Bird, E.D., Richardson, E.P., 1985. Neuropathological classification of Huntington's disease. J. Neuropathol. Exp. Neurol. 44 (6), 559–577.
Wang, C., Gao, S., Hendrie, H.C., Kesterson, J., Campbell, N.L., Shekhar, A., Callahan, C. M., 2016. Antidepressant use in the elderly is associated with an increased risk of dementia. Alzheimer Dis. Assoc. Disord. 30 (2), 99–104.
Wang, Y.C., Tai, P.A., Poly, T.N., Islam, M.M., Yang, H.C., Wu, C.C., Li, Y.J., 2018. Increased risk of dementia in patients with antidepressants: a meta-analysis of observational studies. Behav. Neurol. 2018, 5315098.
Watson, C., Andermann, F., Gloor, P., Jones-Gotman, M., Peters, T., Evans, A., Olivier, A., Melanson, D., Leroux, G., 1992. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 42 (9), 1743–1750.
Watson, D., Wu, K.D., 2005. Development and validation of the schedule of compulsions, obsessions, and pathological impulses (SCOPI). Assessment 12 (1), 50–65.
Weerasinghe-Mudiyanselage, P.D.E., Ang, M.J., Kang, S., Kim, J.S., Moon, C., 2022. Structural plasticity of the hippocampus in neurodegenerative diseases. Int. J. Mol. Sci. 23 (6).
White, N.M., 2009. Some highlights of research on the effects of caudate nucleus lesions over the past 200 years. Behav. Brain Res. 199 (1), 3–23.
White, N.M., McDonald, R.J., 2002. Multiple parallel memory systems in the brain of the rat. Neurobiol. Learn. Mem. 77 (2), 125–184.
Wijeratne, P.A., Young, A.L., Oxtoby, N.P., Marinescu, R.V., Firth, N.C., Johnson, E.B., Mohan, A., Sampaio, C., Scahill, R.I., Tabrizi, S.J., 2018. An image-based model of brain volume biomarker changes in Huntington's disease. Ann. Clin. Transl. Neurol. 5 (5), 570–582.
Wood, S.J., Kennedy, D., Phillips, L.J., Seal, M.L., Yuecel, M., Nelson, B., Yung, A.R., Jackson, G., McGorry, P.D., 2010. Hippocampal pathology in individuals at ultra-high risk for psychosis: a multi-modal magnetic resonance study. Neuroimage 52 (1), 62–68.
Younes, L., Ratnanather, T., Brown, T., Aylward, E., Nopoulos, P., Johnson, H., Magnotta, V.A., Paulsen, J.S., Margolis, R.L., 2012. Regionally selective atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis. Hum. Brain Mapp.
Yu, H.L., Chen, Z.J., Zhao, J.W., Duan, S.R., Zhao, J.K., 2019. Olfactory impairment and hippocampal volume in a Chinese MCI clinical sample. Alzheimer Dis. Assoc. Disord. 33 (2), 124–128.
Zeng, H.M., Han, H.B., Zhang, Q.F., Bai, H., 2021. Application of modern neuroimaging technology in the diagnosis and study of Alzheimer's disease. Neur. Regen. Res. 16 (1), 73–79.
Zhou, G., Lane, G., Cooper, S.L., Kahnt, T., Zelano, C., 2019. Characterizing functional pathways of the human olfactory system. eLife 8.
Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67 (6), 361–370.