COMPARATIVE QUANTITATIVE STUDY OF 'SIGNATURE' PATHOLOGICAL LESIONS IN THE HIPPOCAMPUS AND ADJACENT GYRI OF TWELVE NEURODEGENERATIVE DISORDERS

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Running Head: Hippocampal pathology in neurodegenerative disease

Abstract

The hippocampus (HC) and adjacent gyri are implicated in dementia in several neurodegenerative disorders. To compare HC pathology among disorders, densities of 'signature' pathological lesions were measured at a standard location in eight brain regions of twelve disorders. Principal components analysis (PCA) of the data suggested disorders could be divided into three groups: (1) Alzheimer's disease (AD), Down's syndrome (DS), sporadic Creutzfeldt-Jakob disease (sCJD), and variant CJD (vCJD) in which either β-amyloid (Aβ) or prion protein (PrP^{sc}) deposits were distributed in all sectors of the HC and adjacent gyri, high densities being recorded in parahippocampal gyrus (PHG) and subiculum, (2) Pick's disease (PiD), sporadic frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions (FTLD-TDP), and neuronal intermediate filament inclusion disease (NIFID) in which relatively high densities of neuronal cytoplasmic inclusions (NCI) were present in dentate gyrus (DG) granule cells, and (3) Parkinson's disease dementia (PD-Dem), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA) in which densities of signature lesions were relatively low. Variation in density of signature lesions in DG granule cells and CA1 were the most important sources of neuropathological variation among disorders. Hence, HC and adjacent gyri are differentially affected in dementia reflecting either variation in vulnerability of hippocampal neurons to specific molecular pathologies or in the spread of pathological proteins to the HC. Information regarding the distribution of pathology could ultimately help to explain variations in different cognitive domains, such as memory, observed in the various disorders.

Key Words: Neurodegenerative disease, Hippocampus (HC), Dentate gyrus (DG), Cellular inclusions, tauopathies, synucleinopathies

Introduction

The hippocampus (HC) is involved in a variety of cognitive functions including behavioral inhibition (Gray 1987; Gray and McNaughton 2000; Vinogradova 2001), memory (Scoville and Milner 1957), and spatial location (O'Keefe and Nadel 1978). In cognitively normal elderly individuals, CT/MRI studies reveal that HC atrophy occurs in approximately 29% of cases (de Leon et al. 1997) while neuronal loss occurs in lamina II of adjacent entorhinal cortex (EC) (Simic et al. 2005). Although a few neurofibrillary tangles (NFT) occur in normal aging brains, largely in the EC and sector CA1 of the HC (Corder et al. 2000), argyrophilic grains (AG) and ballooned neurons (BN) frequently accumulate in the HC, especially in brains of more extreme age (Pham et al. 2009). Hence, age-related pathology in HC and associated gyri could be one factor responsible for the decline in episodic and working memory observed in the elderly.

More serious memory deficits and dementia, however, are characteristic of a number of neurodegenerative diseases in which significant HC pathology is evident. Hence, a substantial reduction in HC volume occurs early in Alzheimer's disease (AD) and in other dementias (de Leon et al. 1997; Jack et al. 1997; et al. 1998; Head et al. 2005, Whitwell et al 2007) accompanied by the development of 'signature' pathological lesions including β-amyloid (Aβ) deposits (Glenner and Wong 1984) and neuronal cytoplasmic inclusions (NCI) such as NFT (Armstrong et al. 2008). As a result, variation in the density and distribution of pathology in the HC and adjacent gyri could be a factor influencing the course of dementia in different disorders and ultimately explain differences in cognitive domains such as memory.

The objective of this study was to compare the density and distribution of the 'signature' pathological lesions in the HC and adjacent regions of twelve neurodegenerative disorders using a standard quantitative method. The disorders included two amyloid diseases, three tauopathies, three synucleinopathies, two prion diseases, and two disorders with tau and α-synuclein-negative inclusions, viz. frontotemporal dementia with transactive response (TAR) DNA-binding protein of 43kDa (FTLD-TDP) and FTLD with fused in sarcoma (FUS)-immunoreactive inclusions (FTLD-FUS), e.g. neuronal intermediate filament inclusion disease

(NIFID). The specific objectives were to compare: (1) regions of the HC and adjacent gyri most affected by the pathology, (2) the anatomical pathways compromised, and therefore, (3) aspects of information processing likely to be affected by the developing pathology.

Materials and methods

Cases

Demographic details, signature pathological lesions, associated pathologies, and diagnostic criteria for the 12 disorders are shown in Table 1. Case material of AD, Down's syndrome (DS), dementia with Lewy bodies (DLB), Pick's disease (PiD) (FTLD-tau), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and sporadic Creutzfeldt-Jakob disease (sCJD) was obtained from the Brain Bank, Deptartment of Neuropathology, Institute of Psychiatry, King's College, London, UK. Variant Creutzfeldt-Jakob disease (vCJD) cases (Will et al. 1996; Ironside et al. 2000) were obtained from the National CJD Surveillance Unit, Western General Hospital, Edinburgh, UK. Parkinson's disease dementia (PD-Dem) cases were obtained from the Movement Disorders Center at Washington University School of Medicine in St. Louis, MO, USA (Kotzbauer et al. 2012; Armstrong et al. 2014). Sporadic frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions (FTLD-TDP) cases were obtained from Harvard Brain Tissue Resource Centre, Belmont, MA, USA, Vancouver General Hospital, Vancouver, Canada, University of Pittsburgh, Pittsburgh PA, USA, Washington University, St Louis, MO, USA, and the University of California, Davis, CA, USA (Armstrong et al. 2010). Neuronal intermediate filament inclusion disease (NIFID) cases were obtained from Vancouver General Hospital, Department of Neuropathology, Newcastle General Hospital, Newcastle-upon-Tyne, UK., Laboratoire de Neuropathologie, Hôpital de la Salpêtrière, Paris, France, Institute of Neurological and Gerontological Sciences, International University of Catalonia, Barcelona, Spain, Department of Pathology, Rikshospitalet, Oslo, Norway, Department of Pathology, Northwestern University Medical School, Chicago, Illinois, U.S.A, and Department of Pathology, Gunma University School of Medicine,

Maebashi, Japan (Cairns et al. 2004a; 2004b; 2004c; Armstrong et al. 2006). All cases were selected to reveal the end-stages of the various disorders.

Histological methods

A block of medial temporal lobe was taken at a standard location for neuropathological assessment of the HC, i.e., at the level of the lateral geniculate body (LGB). Tissue was fixed in 10% buffered formal saline and embedded in paraffin wax. Immunohistochemistry (IHC) was performed on 6 – 8 µm sections using appropriate antibodies to identify the signature pathological lesions (Table 1). Sections were also stained with haematoxylin.

Morphometric methods

The HC and adjacent gyri were divided into eight separate regions based on the scheme proposed by Nauta and Feirtag (1986). Hence, densities were measured throughout the PHG, subiculum, each CA sector of the HC (sector CA1 to CA4 inclusive), and the granule and molecular layers of the DG. The boundaries between these regions were identified histologically as follows: (1) the PHG/subiculum boundary where there was distinct 'bulge' of gray matter, (2) the subiculum/CA1 boundary where the neuronal cell layer exhibited an abrupt narrowing, (3) the CA1/CA2 boundary by the presence of clusters of large pyramidal neurons, (4) the CA2/CA3 boundary where large pyramidal neurons became more tightly packed, and (5) CA4 as the sector enclosed by the DG granule cell layer (Nauta and Feirtag 1986).

Protein deposits or inclusions were counted in 1000 x 200 µm sample fields arranged contiguously parallel with the tissue boundary (Armstrong 2003). First, to sample the PHG and subiculum, the short dimension of the sample field was aligned with the surface of the pia mater. The sample field included laminae I, II, and most of lamina III, the region containing the highest densities of pathological features in the majority of disorders (Armstrong 1996; Armstrong et al. 1999; 2000; 2005). In PD-Dem (Armstrong et al. 2014) and DLB (Armstrong et al. 1997), however, Lewy body (LB) density was greatest in lower cortical laminae and the sample field was aligned with the edge of the white matter encompassing most of laminae V and VI. A micrometer

with grid lines at intervals of 10 µm was used as the sample field and 32-128 contiguous sample fields were required to completely sample each PHG and subiculum. Second, in the HC, the sample fields were aligned with the alveus to sample sectors CA1 to CA3. Sampling was then continued into sector CA4 using a guideline marked on the slide and which ceased approximately 400 µm from the DG granule cell layer. Third, in the DG, the short edge of the sample field was aligned with the upper edge of the granule cell layer to study protein deposits in the molecular layer and then with the upper edge of the granule cell layer to study inclusions in granule cells.

Data analysis

Data analysis was carried out using STATISTICA software (Statsoft Inc., 2300 East 14th St, Tulsa, Ok, 74104, USA). First, within each disorder, a two-way (brain regions and cases) analysis of variance (ANOVA) was used to compare differences in density of signature lesions among brain regions (Armstrong and Hilton 2011), Fisher's 'protected least significant difference' (PLSD) being used as a *post-hoc* procedure. Second, to compare HC pathology among disorders, the data were analysed using principal components analysis (PCA) (Armstrong et al. 2010). The result is a scatter plot of the twelve disorders in relation to axes of maximum variance (PC), in which distance between disorders reflects their degree of similarity or dissimilarity. Such a plot can identify groupings of disorders with similar HC pathology and the neuropathological variables most important in determining variation among disorders (Armstrong et al. 2010). To correlate the location of a disorder on a PC axis with a specific pathology, correlations (Pearson's 'r') were calculated between the density of each feature and the factor loadings of the disorder on PC1 and PC2. A significant correlation with PC1, for example, would identify that feature as particularly important in determining the separation of disorders along PC1 (Armstrong et al. 2010).

Results

The distribution of Aβ deposits and NFT in AD and Aβ deposits in DS is shown in Fig 1. In AD, there was a significant difference in density of Aβ deposits among

regions ($F = 12.85$, $P < 0.001$), densities being greatest in PHG, greater in the subiculum than CA2/CA3, and greater in CA1 than in CA2 and CA3. The distribution of Aβ deposits in DS was similar to AD ($F = 14.233$, $P < 0.001$) with the exceptions that densities in the subiculum were greater than in CA2 and the molecular layer of the DG, and greater in CA1 compared with CA2, CA3, and CA4. By contrast, NFT in AD had a different distribution than the Aβ deposits ($F = 6.66$, $P < 0.001$), densities being greatest in CA1 and the subiculum, in CA1 compared with PHG, and in CA1 compared with CA4.

The distribution of NCI in the three tauopathies is shown in Fig 2. In PiD, there was a significant difference in density of Pick bodies (PB) among regions ($F = 7.50$, $P < 0.001$), largely attributable to the high density in DG granule cells, all remaining regions having similar densities. In both CBD ($F = 0.96$, $P > 0.05$) and PSP ($F = 1.22$, $P > 0.05$), by contrast, densities of NCI were significantly lower and there were no statistically significant differences among regions.

The distribution of the cellular inclusions in the three synucleinopathies is shown in Fig 3. In PD-Dem, there was a significant difference in density of LB between regions ($F = 4.57$, $P < 0.001$, densities in CA2, CA3, and CA4 being greater than in the subiculum, CA1, and DG. In DLB, no LB were observed in DG granule cells and there was a significant difference in density of LB between regions ($F = 4.92$, $P < 0.001$), densities of LB in the PHG being greater than in the subiculum and CA1, in CA3 compared with the subiculum, in CA2/CA3 compared with CA1, and in CA3 compared with CA4. By contrast in MSA, density of the glial cytoplasmic inclusions (GCI) was low, with a more restricted distribution, being present in CA1, CA2, and CA3, no significant differences being observed among these regions ($F = 3.25$, $P > 0.05$).

The distribution of NCI in sporadic FTLD-TDP and in NIFID is shown in Fig 4. In FTLD-TDP, there were no overall differences in density of TDP-43-immunoreactive inclusions among regions ($F = 1.68$, $P > 0.05$), *post-hoc* tests, however, suggesting that densities were greater in DG granule cells. In NIFID, the density of FUS-immunoreactive inclusions varied among regions ($F = 5.26$, $P < 0.001$), densities in

the DG being significantly greater than in other regions, and densities greater in CA1 and CA2 than all other regions with the exception of the DG.

The distribution of the PrP^{sc} deposits in the HC in sCJD and vCJD is shown in Fig 5. In sCJD, no PrP^{sc} deposits were observed in CA4 or in the molecular layer of the DG, but there were significant differences among remaining regions ($F = 3.49$, $P < 0.05$), densities being greater in PHG than all remaining regions. By contrast in vCJD, there was a significant difference in both diffuse ($F = 7.60$, $P < 0.001$) and florid PrP^{sc} deposits ($F = 13.01$, $P < 0.001$) among regions. Diffuse deposits were present at greatest density in the PHG and there were significantly greater densities in the subiculum compared with CA1, CA3, and CA4. By contrast, florid deposits were present in greater density in the subiculum compared with other regions.

A PCA of the 12 disorders resulted in the extraction of two PC's accounting in total for 69% of the total variance (PC1 = 39%, PC2 = 30%). A plot of the 12 disorders in relation to PC1 and PC2 is shown in Fig 6. The data suggested disorders could be divided in three groups: (1) AD, DS, sCJD, and vCJD, located at the upper left of the plot, (2) PiD, FTLD-TDP, and NIFID, the most distinctive group, located at upper right and (3) the remaining cases, viz., PD-Dem, DLB, PSP, CBD, and MSA, a miscellaneous group overlapping to some extent with the first group. In addition: (1) PC1 was positively correlated with the density of pathology in DG granule cells ($r = 0.63$, $P < 0.05$) and (2) PC2 was positively correlated with the density of pathology in CA1 ($r = -0.39$, $P < 0.05$).

Discussion

Based on the density and distribution of 'signature' pathological lesions, the PCA suggested three groups of disorders: (1) those in which lesions occurred throughout the HC and PHG, and with particularly high densities of Aβ or PrP^{sc} deposits in the PHG and subiculum, viz. AD, DS, sCJD, and vCJD, (2) those in which density of NCI was high in DG granule cells relative to other regions, viz., FTLD-TDP, NIFID, and PiD, and (3) a miscellaneous group in which the density of cellular inclusions was significantly lower, viz., PD-Dem, DLB, MSA, PSP, and CBD. Hence, there are

considerable differences in the anatomical distribution of the pathology and therefore, in the pathways likely to be affected in different disorders.

Considerable similarities were observed in the distribution of pathology in disorders characterised by the deposition of Aβ or PrP^{sc}, viz., AD, DS, and CJD. The distribution of the pathology in AD is similar to previous reports confirming the PHG and CA1 as particularly affected (Meencke et al. 1983; Saper et al. 1987; Armstrong 1992; Armstrong et al. 1992; Bancher and Jellinger 1994), the DG being less involved (Hoesen and Solodkin 1993). Observation of further sections taken more anteriorly than the LGN suggested similar pathology affecting the EC in AD. Hence, this pathology may affect the input pathway from EC to DG and the output pathways via CA1 and the subiculum. However in AD, NFT were also recorded in CA2 and CA3, and together with Aβ deposition in these regions, could affect information processing within the HC, thus contributing to memory disruption and poor performance on spatial tasks (Lee et al. 2007; Guillozet et al. 2003). Although some overall differences in Aβ pathology between AD and DS have been reported (Egensperger et al. 1999; Hof et al. 1995), there are considerable parallels with regard to the HC (Armstrong 1994; Armstrong and Smith 1995; Hyman et al. 1995), which could explain similarities in cognitive domains such as memory in the two disorders (Dalton and McLachlan 1984). In addition, the distribution of PrP^{sc} deposits in the HC in sCJD and vCJD were similar to those of Aβ deposits in AD and DS (Armstrong et al. 1992), i.e., high densities of deposits occur in the PHG. Nevertheless, there were also some differences between CJD and AD, i.e., in AD high densities of NFT are observed in CA1 while the CA sectors and DG were relatively spared by prion pathology (Masullo and Macchi 1997). Hence, processing of information within the HC and the output pathway appear to be less affected in CJD, especially vCJD than AD. These results are consistent with neuroimaging studies which suggest significant atrophy of the HC in AD (Schmidt 1992; De Leon et al. 1997; Jack et al. 1997; 1998; Head et al. 2005). In addition, [F-18] fluoro-2-deoxyge-D glycine (FDG) PET in sCJD show decreased glucose in bilateral parietal lobes, and in the frontal and occipital lobe but the medial temporal lobe and HC are less affected (Kim et al. 2012). Nevertheless, MRI studies suggest some atrophy of the HC in some variants of CJD (Poon et al. 2001).

FTLD-TDP, NIFID and PiD all share the common feature that densities of cellular inclusions were higher in the DG relative to other regions studied, a distribution most marked in PiD. This pathology could significantly affect the initial processing of information in the DG before being transported to the HC circuit via CA3/CA4 (Jackson and Lowe 1994; Hof et al. 1994). HC pathways in PiD may be particularly vulnerable to tau pathology (Garcia-Sierra et al. 2000) but occasional α- and β-synuclein-immunoreactive PB have also been observed in the DG in this disorder (Mori et al. 2002). A similar distribution of pathology is present in sporadic FTLD-TDP, although to a lesser extent (Yang et al. 2001; Woulfe et al. 2001; Rosso et al. 2001; Arai et al. 2003, Kovari et al. 2004; Yaguchi et al. 2004; Mackenzie et al. 2006), including cases with hippocampal sclerosis (HS) (Probst et al. 2007), the latter often exhibiting neuronal loss in the subiculum and CA1 (Josephs and Dickson 2007). TDP-43 immunoreactive dendrites have also been observed in HC neurons in the form of RNA granules co-localised with the post-synaptic protein PDS-95 (Wang et al. 2008). However, in many FTLD cases with visuo-spatial cognitive dysfunction there is widespread cortical pathology but the HC and DG are spared (Filey et al. 1994; Meiner et al. 2005). In addition, some studies suggest significantly less frequent NCI in the DG in familial cases caused by progranulin (*GRN*) and valosin-containing protein (VCP) mutations (Forman et al. 2006; Davison et al. 2007). Hence, in many FTD cases there is preservation of memory function compared with AD (Chow et al. 2006), at least until the later stages of the disease when memory impairment and visuo-spatial deficits become more apparent (Shinagawa et al. 2008) and severe neuronal loss has been recorded in CA1 (Kersaitis et al. 2004). In other FTD cases, there is a greater episodic memory deficit compared with AD which may be attributable to the greater DG pathology (Lindau et al. 2003). The DG is thought to contribute specifically to the formation of new episodic memories and to the exploration of novel environments (Saab et al. 2009). Imaging studies suggest atrophy of frontal and anterior temporal lobes on MRI which may spare the majority of the HC (Galimberti and Scarpini 2015). NCI in NIFID were widely distributed throughout the HC which could affect several pathways, initial processing within the DG being the most compromised. Hence, HC pathology may play a particularly significant role in the development of clinical dementia in NIFID (Cairns et al. 2004a;

2004b). Consistent with this conclusion, CT/MRI studies suggest significant temporal lobe atrophy in a significant number of cases of NIFID (Cairns et al. 2004c).

The remaining disorders, viz., PD-Dem, DLB, MSA, PSP, and CBD have a less dense pathology in the PHG and HC but also exhibit some differences. The PCA identified the density of pathology in CA1 as a major factor accounting for variation among disorders. In PD-Dem and DLB, cellular inclusions affect CA2, CA3, and CA4 more significantly than CA1, whereas in the tauopathies CBD and PSP, CA1 appears more vulnerable. In DLB, pathology in the PHG is greater than most areas of the HC, a result also reported by Gomez-Tortosa et al. (1999). In addition, atypical cases of DLB may have LB in the DG with abundant dystrophic neurites (DN) in the molecular layer of DG, CA1 and subiculum (Reyes et al. 1993; Wakabayashi et al. 1996). Hence, in DLB and PD-Dem, processing of information within the HC could be affected whereas the output pathway is more unaffected. In CBD, pathology may affect the input of information to the HC, but initial processing in the DG appears to be less affected. Nevertheless, there is evidence that the output pathway from CA1 to the subiculum could be compromised in CBD. In PSP, low densities of NFT were present in the PHG (Braak and Braak. 1992; Braak et al. 1992), while the presence of NFT in CA1 and to a lesser extent CA2 suggests that HC processing and the output pathway could be vulnerable. In some cases of PSP, NFT may be confined to the HC and especially the DG (Hof et al. 1992; Wakabayashi et al. 1996) and in others TDP-43 immunoreactive inclusions may be present in HC and DG (Yokata et al. 2010). Degeneration of the cholinergic pathway from medial septal area to CA3 and the subiculum has also been observed in PSP (Shinotoh et al. 1999), CA1 neurons being affected via their connections with these regions. Pathology has also been reported in the alveus in PSP (Armstrong et al. 2009) which could be a response to degeneration of CA1 and the subiculum. Relatively little pathology was observed in the HC and adjacent regions in MSA, with the possible exception of CA1 (Armstrong et al. 2004), and these patients are the least likely of those studied to develop dementia. In some studies of MSA, however, α-synuclein-immunoreactive NCI have been observed in the DG (Takeda et al. 1997; Wakabayashi et al. 1998). Consistent with these conclusions, imaging studies suggest significantly less atrophy of the temporal lobe and HC in CBD (Markus et al. 1995; Seritan et al. 2004), DLB (Barber et al. 2001), PD (Rektorovia et al. 2014; Lee et al. 2013), PSP (Saini et al. 2013), and MSA

(Mazere et al. 2013). However, in PD-Dem, using MRI source-based morphometry, atrophy of temporal lobes and HC has been observed in some cases (Rektorova et al. 2014).

Differences in HC pathology among disorders could be attributable to either differential vulnerability of neurons to various molecular pathologies or variation in the extent to which pathology may spread into the HC from adjacent regions (Goedert et al. 2010; Steiner et al. 2011). In AD, there is a preferential loss of neurons expressing 75KD neurotrophic receptor p75NIr (Yaar et al. 1997), Aβ binding specifically to this receptor. In addition, HC neurons immunoreactive to the calcium-binding protein calretinin are more resistant to Aβ (Pike and Cotman 1995). There may also be a lysosomal dysfunction in the HC resulting in the accumulation of fragments of amyloid precursor protein (APP) and loss of synaptic function (Bahr et al. 1994). In addition, astrocytes appear to be regionally vulnerable to reaction with Aβ (Hoke et al. 1994). Hence, Aβ applied to HC neurons and glial cells activates NADP resulting in a progressive loss of mitochondrial membrane potential in astrocytes followed by oxidative stress and cell death (Abeti et al. 2011). HC neurons are also more vulnerable to tau and α-synuclein pathology (Higashi et al. 2002). In CJD, there is selective vulnerability of HC γ-amino-butyric acid (GABA) neurons, i.e., parvalbumin-immunoreactive cells are depleted while calbindin-immunoreactive cells are preserved (Guentchev et al. 1997). These observations suggest that HC neurons are differentially vulnerable especially to the formation of protein deposits and therefore, the abundance and distribution of deposits in AD, DS, and CJD may reflect this vulnerability.

In normal aging, few NFT are present in the EC/PHG and CA1 while in AD, NFT occur in the subiculum and in older dementia cases, and develop extensively in these regions (Corder et al. 2000). In addition, three years before the onset of AD, there is a loss of gray matter in the HC and EC which within a year spreads to the posterior HC (Davis et al. 1999). Moreover, in elderly control cases (Armstrong 1995), Aβ deposits were present in the temporal lobe in the majority, but only in cortical gyri, e.g., PHG and lateral occipito-temporal gyrus (LOT), no deposits being observed in the subiculum, CA sectors of HC, or the DG. Hence in AD, spread of Aβ pathology into

the HC may have occurred from adjacent regions ultimately disconnecting the HC from the rest of the brain (Braak and Braak 1992; Braak et al. 1992; Armstrong 1992). The HC makes relatively few anatomical connections with the rest of the brain and is therefore especially susceptible to this spread. Hence, variation in the anatomical pathways and rate of spread could be factors explaining heterogeneity in HC pathology among disorders.

In conclusion, this comparative study of 12 disorders uses a standard quantitative method to provide estimates of absolute density of signature pathological regions in eight defined regions of HC and adjacent gyri. The data analysis enables statistically significant differences among regions to be identified in each disorder as well as similarities and differences among disorders. Limitations of the analysis include sampling at only a single level of the HC for comparative purposes and omission of the additional pathologies that could be present such as BN, glial pathology, and DN, all of which may contribute to HC damage within each disorder. The study confirms the importance of the medial temporal lobe region as a site of pathology in many disorders especially AD, CJD, DS, PiD, FTLD-TDP, and NIFID. Variations among disorders could reflect differential vulnerability of HC neurons to specific molecular pathologies and/or variation in the extent to which pathology may spread to involve the HC as the disease develops. Information regarding the distribution of pathology in the HC could ultimately help to explain variations in different cognitive domains, such as memory, observed in the various disorders.

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Compliance with ethical standards

Informed consent was given for the removal of all brain tissue subject to local ethical committee approval and the 1996 Declaration of Helsinki (as modified Edinburgh 2000). The authors report no conflicts of interest.

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Table 1. Summary of demographic details, signature pathology, associated pathology, and diagnostic criteria in the disorders studied.

Disorder	N	Mean age (SD)	M:F	Signature lesion	Additional pathology	Diagnostic criteria
AD	20	76 (13.0)	5:15	Aβ deposits NFT	EN, GVC	NINCDS/ ADRDA/ CERAD
sCJD	11	67 (8.5)	6:6	PrP^{sc} deposits	Vacuolation	Budka et al (1995)
vCJD	11	29 (9.1)	5:6	PrP^{sc} deposits	Vacuolation	Ironside et al (2000)
DS	12	51 (9.7)	6:6	Aβ deposits	NFT	By karyotype
PD-Dem	15	75 (5.0)	12:3	LB	LN, LG	UKPDSBB
PiD	10	65.3 (11.3)	7:3	PB	NFT, PC	Cairns et al (2007)
CBD	12	64.7 (9.07)	8:4	NCI	AP, GI, EN	NIH-ORD
PSP	8	73.4 (7.4)	4:4	NFT	TA,GI,NP	NINDS-SPSP
DLB	12	73.8 (7.2)	12:0	LB	DN	CDLB

MSA	10	66.5 (8.51)	7:3	GCI	NCI	MCC
NIFID	10	45.3 (12.1)	7:3	NCI	GI, DN	Cairns et al (2007)
FTLD-TDP	15	69.6 (8.50)	7:2	NCI	NII, DN, GI	Cairns et al (2007)

Abbreviations: *Disorders*: Alzheimer's disease (AD), Down's syndrome (DS), Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), neuronal intermediate filament inclusion disease (NIFID), frontotemporal lobar degeneration with TDP-43 proteinopathy (FTLD-TDP); Parkinson's disease dementia (PD-Dem), sporadic Creutzfeldt-Jakob disease (sCJD), Variant Creutzfeldt-Jakob disease (vCJD); *Neuropathology*: AP = Astrocytic plaques, DN = Dystrophic neurites, EN = Enlarged neurons, GI = Glial inclusions, GVC = Granulovacuolar change, LG = Lewy grains, LN = Lewy neurites, NCI = Neuronal cytoplasmic inclusions, NFT = Neurofibrillary tangles, NII = Neuronal internuclear inclusion, PC = Pick cells; *Diagnostic criteria*: 'National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association' (NINCDS/ADRDA) (Tierney et al 1988), 'Consortium to Establish a Registry of Alzheimer Disease' (CERAD) criteria (Mirra et al 1991); United Kingdom Parkinson Disease Society Brain Bank clinical diagnostic criteria (UKPDSBB); National Institute of Health-Office of rare disorders (NIH-ORD); National Institute of Neurological Disorders and Stroke (NINDS) and the Society of PSP (SPSP) (NINDS-SPSP) (Hauw et al 1994, Litvan et al 1996a, 1996b); 'Consortium on Dementia with Lewy bodies' (CDLB)' (McKeith et al 1996); 'Minneapolis Consensus Criteria (MCC) (Gilman et al 1998); Diagnostic criteria for PiD, NIFID (FTLD-FUS) and FTLD-TDP according to Cairns et al (2007). *Other abbreviations*: N = Number of cases studied, M = Male, F = Female, SD = Standard deviation

Legends to figures

Fig 1. Densities of β-amyloid (Aβ) deposits and neurofibrillary tangles (NFT) in the parahippocampal gyrus (PHG) and regions of the hippocampus (Sub = subiculum, CA = Cornu ammonis, DG = Dentate gyrus) in Alzheimer's disease (AD) and Down's syndrome (DS). Immunohistochemistry (IHC) is indicated at top corner (Abeta = β-amyloid). Analysis of variance (ANOVA): two-way with Fisher's PLSD: AD Aβ deposits $F = 12.85$ ($P < 0.001$) (*post-hoc*: PHG > all regions, Sub > CA2,CA3, CA1 > CA2, CA3; NFT $F = 6.66$ ($P < 0.001$) (*post-hoc*: CA1/Sub > all regions, PHG < CA1 > CA4; DS $F = 14.23$ ($P < 0.001$) (*post hoc*: PHG > all regions, Sub > CA2/DG, CA1 > CA2/CA3/CA4

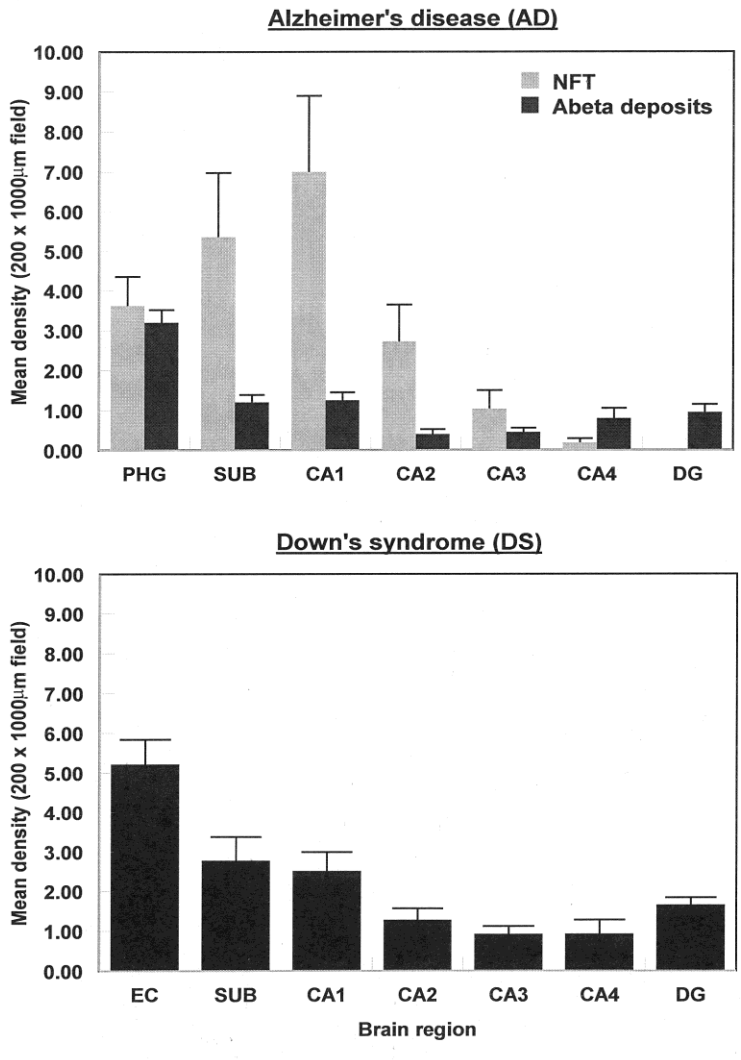

Fig 2. Densities of cellular inclusions in the parahippocampal gyrus (PHG) and regions of the hippocampus (Sub = subiculum, CA = Cornu ammonis, DG = Dentate gyrus) in three tauopathies, viz. Pick's disease (PiD), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP Immunohistochemistry (IHC) is indicated at top corner. Analysis of variance (ANOVA): two-way with Fisher's PLSD: PiD F = 7.50 (P < 0.001) (*post-hoc*: DG > all regions, CBD F = 0.96 (P > 0.05); PSP F = 1.22 (P > 0.05)

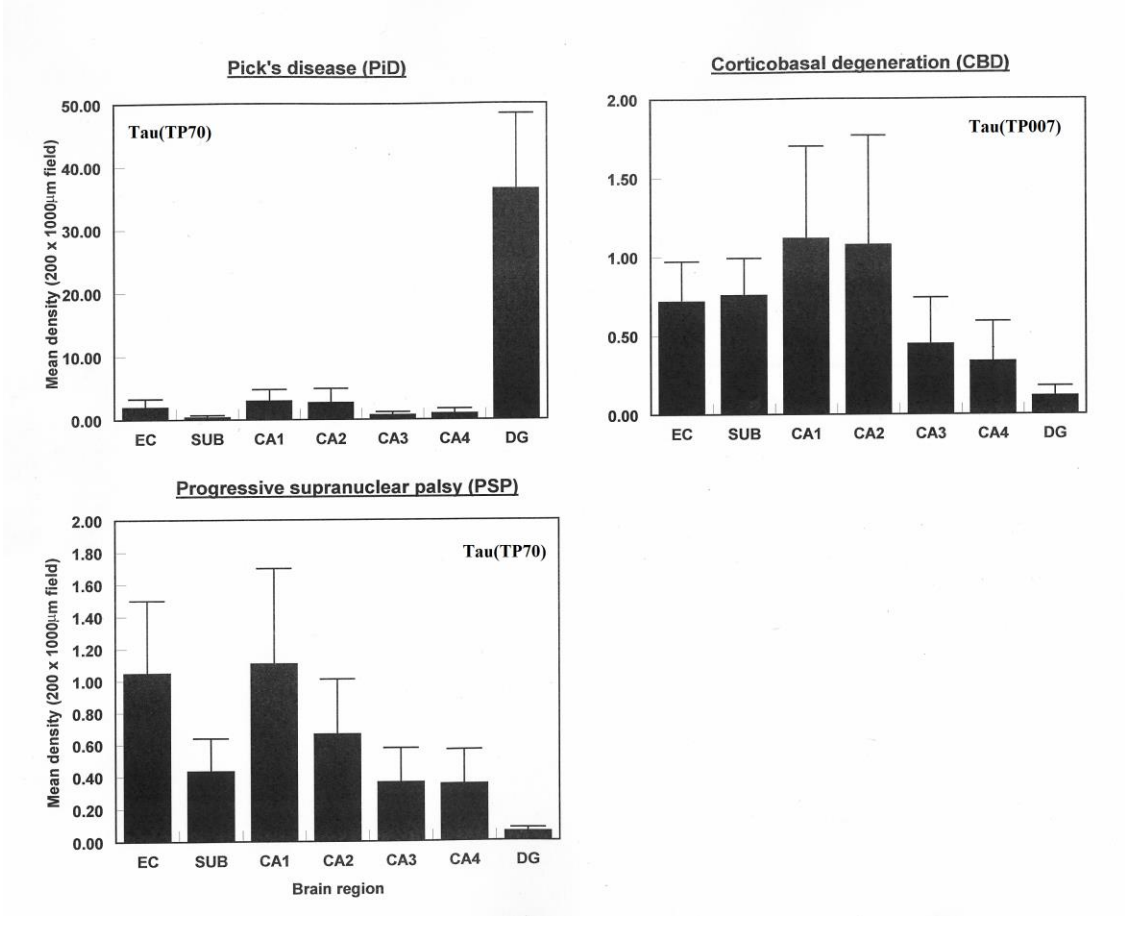

Fig 3. Densities of cellular inclusions in the parahippocampal gyrus (PHG) and regions of the hippocampus (Sub = subiculum, CA = Cornu ammonis, DG = Dentate gyrus) in three synucleinopathies, viz. dementia associated with Parkinson's disease (PD-Dem), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Immunohistochemistry (IHC) is indicated at top corner (Alpha-syn = α-synuclein, 'p' = phosphorylated). Analysis of variance (ANOVA): two-way with Fisher's PLSD: PD-Dem F = 4.57 (P < 0.001) (*post-hoc*: Sub < CA2/CA3/CA4, CA1 < CA2/CA3/CA4, CA2/CA3/CA4 > DG); DLB F = 4.92 (P < 0.001) (*post-hoc*: PHG > Sub/CA1, CA3 > Sub, CA2/CA3 > CA1, CA3 > CA4; MSA F = 3.25 (P > 0.05)

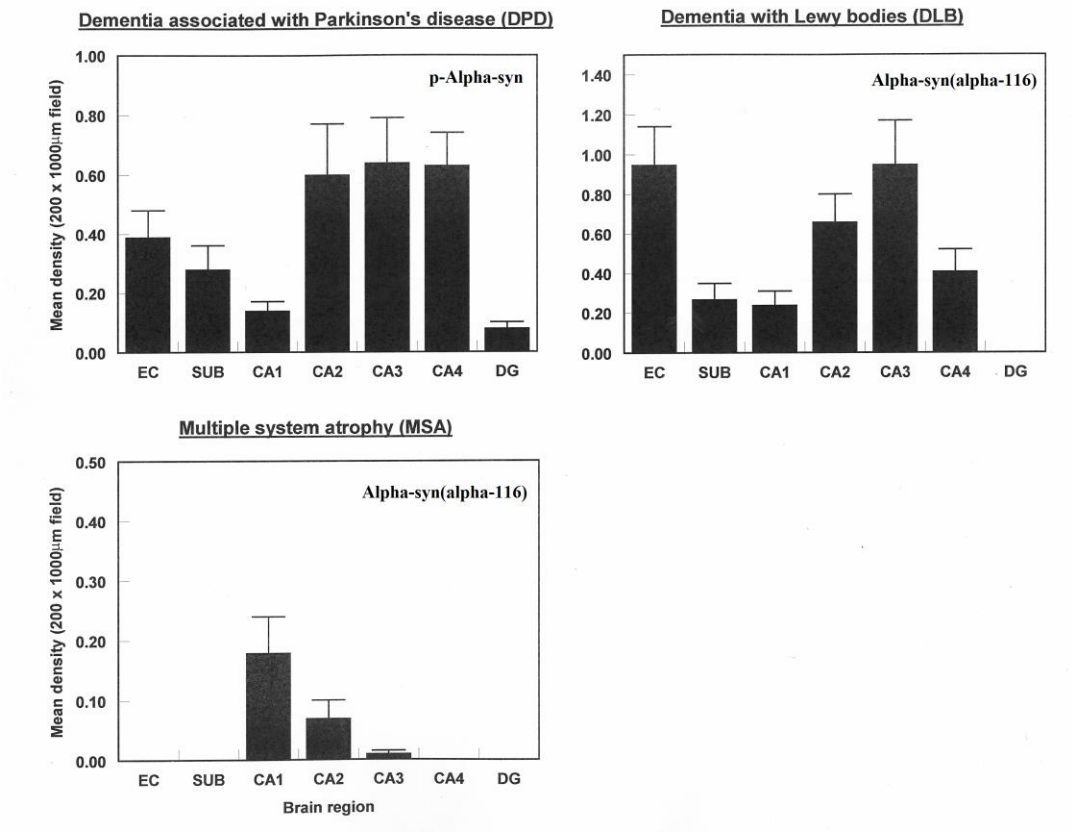

Fig 4. Densities of cellular inclusions in the parahippocampal gyrus (PHG) and regions of the hippocampus (Sub = subiculum, CA = Cornu ammonis, DG = Dentate gyrus) in frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions (FTLD-TDP) and neuronal intermediate filament inclusion disease (NIFID). Immunohistochemistry (IHC) is indicated at top corner (pTDP-43 = phosphorylated transactive response (TAR) DNA-binding protein, FUS = Fused in sarcoma). Analysis of variance (ANOVA): two-way with Fisher's PLSD: FTLD-TDP $F = 1.68$ ($P > 0.05$) NIFID $F = 5.26$ ($P < 0.001$) (*post-hoc*: DG > all regions)

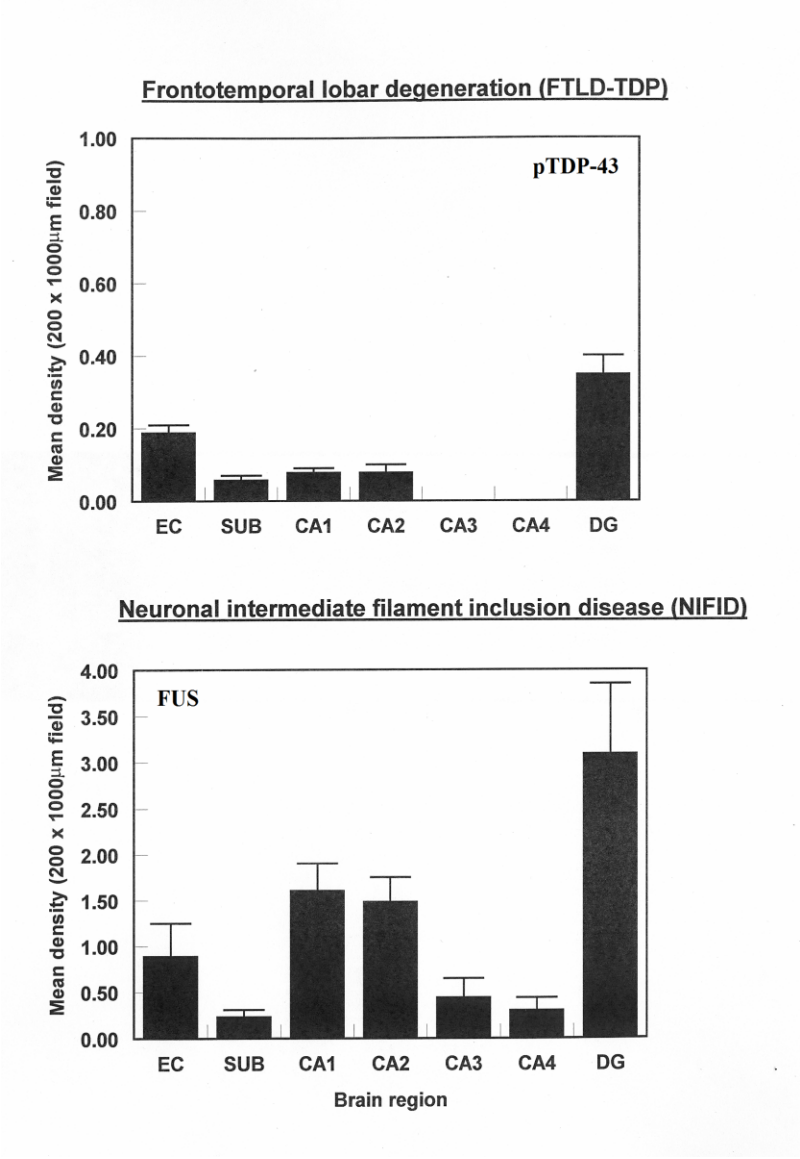

Fig 5. Densities of prion protein (PrP^{sc}) deposits in the parahippocampal gyrus (PHG) and regions of the hippocampus (Sub = subiculum, CA = Cornu ammonis, DG = Dentate gyrus) in sporadic (sCJD) and variant Creutzfeldt-Jakob disease (vCJD). Immunohistochemistry (IHC) is indicated at top corner. Analysis of variance (ANOVA): two-way with Fisher's PLSD: sCJD Aβ deposits $F = 3.49$ ($P < 0.05$) (*post-hoc*: PHG > Sub, CA1/CA2/CA3); vCJD diffuse deposits $F = 7.60$ ($P < 0.001$) (*post-hoc*: PHG > all regions, Sub > CA1/CA3/CA4); Florid deposits $F = 13.01$ ($P < 0.001$) (*post hoc*: Sub > all regions)

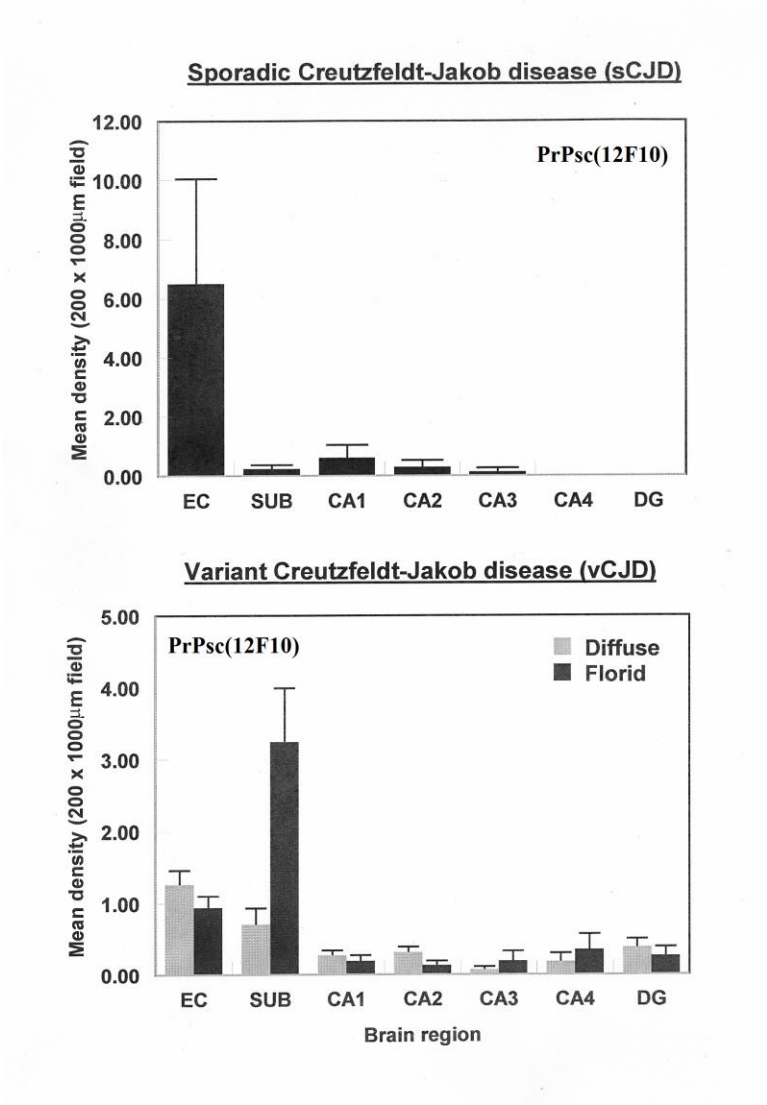

Fig 6. Principal components analysis (PCA) of the twelve disorders based on the densities of pathology in parahippocampal gyrus (PHG), subiculum, hippocampus (HC) CA sectors, and dentate gyrus (DG). A plot of disorders in relation to PC1 and PC2. Abbreviations: Alzheimer's disease (AD), Down's syndrome (DS), Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), neuronal intermediate filament inclusion disease (NIFID), frontotemporal lobar degeneration with TDP-43 proteinopathy (FTLD-TDP); Parkinson's disease dementia (PD-Dem), sporadic Creutzfeldt-Jakob disease (sC), Variant Creutzfeldt-Jakob disease (vC)