In vivo quantitative imaging of hippocampal inflammation in autoimmune neuroinflammatory conditions: a systematic review

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Title:
In vivo Quantitative Imaging of Hippocampal Inflammation in Autoimmune Neuroinflammatory Conditions: A Systematic Review.
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Short title
Imaging of hippocampal neuroinflammation

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Abbreviations:
ALD: Alzheimer’s disease
AD: Axial diffusivity
ADC: Apparent diffusion coefficient
AE: Autoimmune Encephalitis
ANAM: Automated Neuropsychological Assessment Metrics
BBB: Blood brain barrier
CA: Cornus Ammonis
CIS: Clinical Isolated Syndrome

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CLVT: California Verbal Learning Test
CNS: Central Nervous System
CSF: Cerebro-Spinal Fluid
DCE: Dynamic Contrast Enhanced
DG: Dentate Gyrus
DT: Diffusor Tensor
DW: Diffusion-Weighted
DVR: Distribution Volume Ratio
EAE: Experimental Autoimmune Encephalitis
EPI: Echo-planar imaging
FLAIR: Fluid-Attenuated Inversion Recovery
FSL: FMRIB software library
HPA: Hypothalamic-Pituitary-Adrenal
IQT: Image Quality Transfer
LTP: Long-Term Potentiation
MD: Mean diffusivity
ML: Molecular Layer
MRI: Magnetic Resonance Imaging
MRS: Magnetic Resonance Spectroscopy
MS: Multiple Sclerosis
MTLE: Mesial temporal lobe epilepsy
MTR: magnetization transfer ratio
NODDI: neurite orientation dispersion and density imaging
PET: Positron Emission Tomography
PBR: Peripheral Benzodiazepine Receptors
RAVLT: Ray Auditory Verbal Learning Test
ROCF: Rey–Osterrieth Complex Figure
RRMS: Relapsing Remitting Multiple Sclerosis
SDMT: Symbol Digit Modalities Test
SLE: Systemic Lupus Erythematosus
SLM: Stratum Lacunosum Moleculare
SR: Stratum Radiatum
SUV: Standardizez Uptake Values
SPMS: Secondary Progressive Multiple Sclerosis
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Abstract
The hippocampus is a morphologically complex region of the brain limbic system centrally involved in important cognitive, affective, and behavioural regulatory roles. It has exquisite vulnerability to neuroinflammatory processes, with some of its subregions found to be specific sites of neuroinflammatory pathology in ex-vivo studies. Optimising neuroimaging correlates of hippocampal neuroinflammation would enable direct study of functional consequences of hippocampal neuroinflammatory pathology, as well as the definition of therapeutic end points for treatments targeting neuroinflammation, and their related affective or cognitive sequelae. However, in vivo traditional imaging of the hippocampus and its subregions is fraught with difficulties, due to methodological challenges deriving from its unique anatomical characteristics. The main objective of this review is to provide a current update on the characterisation of quantitative neuroimaging correlates of hippocampal neuroinflammation, by focusing on three prototypical autoimmune neuro-inflammatory conditions [Multiple Sclerosis (MS), Systemic Lupus Erythematosus- (SLE), Autoimmune Encephalitis (AE)]. We focused on studies employing TSPO-targeting Positron Emission Tomography (PET), and Quantitative Magnetic Resonance Imaging (MRI) and Spectroscopy techniques assumed to be sensitive to neuroinflammatory tissue changes. We found 18 eligible studies (14, 2 and 2 studies in MS, AE and SLE respectively). Across conditions, the largest effect was seen in TSPO PET and diffusion weighted MRI studies. No study examined neuroinflammation-related changes at hippocampal subfields level. Overall, results were largely inconsistent due to heterogeneous imaging methods, small sample sizes and different population studies. We discuss how these data could inform future study design and conclude by suggesting further methodological directions aimed at improving precision and sensitivity of neuroimaging techniques to characterise hippocampal neuroinflammatory pathology in the human brain.

Summary
The hippocampus is a complex brain region crucially involved in neuroinflammation. We systematically reviewed quantitative imaging studies focusing on hippocampal pathology in...
autoimmune neuroinflammatory conditions and identified unmet research needs and future methodological directions.

1. Introduction

The hippocampus is a complex limbic structure anatomically embedded in each medial temporal lobe of the cerebral cortex. The functional role of the hippocampus has been well characterised and includes critical roles in learning, memory processes, spatial navigation, regulation of Hypothalamic-Pituitary-Adrenal (HPA) axis function and modulation of emotional behaviour. Several notable connections in and around the hippocampus are central to these functions. Polysynaptic pathways effectively regulate the learning/memory loop, and reciprocal and direct projections to the hypothalamus and amygdala, via a ventral striatal loop are elemental in influencing motor and emotional behaviour, as well as the release of adrenocorticotropic hormones (1).

The hippocampus is implicated in the orchestration of numerous critically important allostatic processes that facilitate neurodevelopment through the life span, adaptation to challenging environments and response to stress, as well as insults and injury. These processes include neurogenesis and synaptic plasticity (Long-Term Potentiation, LTP); excitation/inhibition balance and neuronal excitability, and a tight and dynamic feedback regulation of HPA axis function. The functional consequences of hippocampal neurodegeneration, the most obvious being seen in neuropsychiatric conditions such as Alzheimer’s disease (ALD), have enormous clinical relevance and impact in terms of general functional impairment and disability, reflecting the central role to the above-mentioned critical processes and systems. Hippocampal pathology has been the subject of extensive preclinical mechanistic characterisation. A large body of experimental animal and histopathological research established that the hippocampus is subject to neuroinflammatory pathology [(2), (3)] and that hippocampal neuroinflammation can have direct impact on its main roles and functions, culminating in alterations in neurogenesis such as reduction in synaptic density, (4) and alterations in synaptic plasticity (5), indicating plausible mechanisms that underlie cognitive and affective sequelae of neuroinflammatory pathology.

This exquisite vulnerability of hippocampus to neuroinflammation is related to several converging factors, including its plasticity and involvement in neuroimmune cross-talks [(6), (7)]. The hippocampal proximity to the choroid plexus for instance is presumed to facilitate,
via alterations in CSF composition and CNS inflammatory immune signal processing, activated lymphocytic cell entry during neuroinflammatory pathology [(8), (9), (10)]. The hippocampus also contains a very high density of interleukin 1 receptors (IL1) which mediate inflammatory processes (11), with the highest expression of IL1 receptors located in the granule layer of the dentate gyrus and pyramidal cell layer (CA1-4) of the hippocampus. Microglia in the hippocampal neuronal system of adult mice have a higher proliferative capability against LPS-induced inflammatory stimulation, relative to other brain regions examined (12).

More so, immune signalling molecules such as cytokines and chemokines, produced within the hippocampus in response to any perturbations of CNS homeostasis, are implicated in normal hippocampal neurogenesis processes (13). Adult neurogenesis is defined as a process whereby adult neural precursors in the CNS produce functional neurons (14). Recognised as a continuing process, hippocampal neurogenesis is characterised by the introduction of new neurons in the memory processing circuits and is a vital determinant of cognitive reserve (15). Impact of adult hippocampal neurogenesis has consistently been linked to the development of depression and anxiety (16). Neurogenesis in the subgranular zone of the dentate gyrus (DG) in particular appears to be readily impaired in a transgenic mouse model of neuroinflammation secondary to IL6 overexpression (17). In a mouse model of Experimental Autoimmune Encephalitis (EAE), these impairments of neurogenesis and neuroplasticity could be linked to specific microstructural modifications in the molecular layer (ML) of the DG, such as alterations in the dendritic tree and decreases in dendritic length, which manifest in diffusion-weighted MRI as reductions in axial diffusivity (AD, ie water diffusion along tracts) and mean diffusivity (MD). Interestingly, the reductions were only visible to the ML of DG, and not in other subfields (18), implying subregional variability to neuroinflammatory mechanisms, with potential relevance to the definition of specific anatomical neuroimaging endpoints.

The hippocampus also has high metabolic vulnerability due to limited perfusion reserve. In the presence of cerebral small vessel pathology, the already miniature arterial supply (posterior cerebral and anterior choroidal vessels), especially when only independently supplied (by the posterior cerebral artery) are compromised, leading to hypoxic injury in the hippocampal region (19). Indeed, when compared to the neocortex, experimental studies indicate notable reductions in blood flow, blood oxygenation and neurovascular coupling in
the hippocampus as a consequence of distinct alterations in endothelial cell function and vascular network, such as lower capillary density and marginal pericyte contractile morphology (20). Accordingly, there are observed varying individual subfield vulnerabilities with respect to hypoxic/ischaemic injury. Specifically, CA1 pyramidal neurons are found to be more vulnerable to ischemic effects, due in part to reduced metabolic capabilities and excess glutamate release, compared to other hippocampal subfields (21) (22). These findings are paralleled by the notion of an extremely high metabolic requirement of a specific subgroup of hippocampal interneurons functioning at near limit of their mitochondrial metabolic capacity to continuously provide fine-tuning of the neuronal excitatory-inhibitory balance of hippocampal circuits (23). Considering the increased neurometabolic demands generally associated with neuroinflammatory processes, the sensitivity of hippocampus to inflammation and its limited oxygen supply reserve, it would be expected that the hippocampal metabolic vulnerability would be further exaggerated and amplified in neuroinflammatory pathology.

Although abundant animal research provided full characterisation of inflammatory pathology of the hippocampus, there has been comparatively less research on the pathological characteristics of human hippocampal neuroinflammation. A few post-mortem studies provide evidence of neuroinflammatory demyelination of human hippocampus in the prototypical neuroinflammatory condition, multiple sclerosis (MS) [(2);(24); (4)]. However, no study so far has directly correlated post-mortem pathological findings to neuroimaging, to enable in vivo characterisation of hippocampal neuroinflammation. The ability to identify neuroimaging biomarkers of hippocampal inflammation in vivo would be crucial to characterise its pathology, but also would help in the identification of endpoints for clinical trials with therapeutics targeting neuroinflammatory processes.

Over the past two decades, there have been promising advances in the field of quantitative neuroimaging, in terms of sensitivity to detect neuroinflammation. For example, PET targeting 18 kDa translocator protein (TSPO) as well as novel MRI approaches claim to have good sensitivity and some degree of specificity for measuring brain inflammatory processes [(25); (26); (27), (28)(29)]. However, various methodological aspects complicate the characterisation of the hippocampus with neuroimaging. For instance, the complex sub structural organization of the hippocampal formation, which comprise subfields, have individual vulnerability to physiological and pathological processes. Pereira et al (30) observed a correlation between ageing, diffusion tensor imaging measures and volumes of

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varying subfields. Zheng et al (31) also observed volume alterations of differing hippocampal subfields at different ages with positive correlations to delayed and immediate recall measures. Specifically, CA1-4, DG are impacted upon. Indeed, some studies have emphasized distinct links between biological ageing, elevated inflammatory markers and chronic inflammation, a phenomenon known as inflammageing or accelerated aging (32), (33).

Given the above evidence of aging-related processes impacting differentially on hippocampal subfields, it is plausible to expect similar subfields-specific vulnerability to neuroinflammatory processes. In particular, and as highlighted above; such mechanisms may comprise the interplay between glial activation and the rate of neurogenesis in DG, and under perfusion induced metabolic modifications made more prominent in CA1.

The unique anatomical location of the hippocampus also makes it vulnerable to partial volume artefacts (when more than one tissue type is present in a voxel, invalidating the quantitative accuracy). Use of segmentation techniques employing automated co-registration of quantitative maps on high-resolution anatomical images might therefore be suboptimal. Further, separation of subfields is difficult due to low resolution of imaging techniques. Conventional MRI approaches have also failed to accurately discriminate between varying subfield layers.

Despite these challenges associated in general to hippocampal neuroimaging methods, there has been an increasing number of applications of novel quantitative approaches to study neuroinflammation in the hippocampus. In the present overview, we will provide details on how these quantitative techniques might inform on various aspects of neuroinflammatory pathology. We also aim to summarise the state of the art on hippocampal imaging of neuroinflammation by systematically reviewing studies that employed quantitative imaging techniques to assess hippocampal neuroinflammatory processes. We will focus on MS, systemic lupus erythematosus (SLE), and autoimmune encephalitis (AE) as prototypical examples of autoimmune neuroinflammatory diseases that might involve the hippocampus.

We include studies that used imaging techniques targeting neuroinflammation-specific pathological processes, namely:

1) the activation of resident immunocompetent cells (TSPO PET; MRS (Lactate, Myo-inositol, Choline);
2) BBB disruption/permeability (dynamic contrast enhanced or DCE MRI);
3) Interstitial modifications consequent to neuroinflammation, such as oedema and modifications to the relative size of the extra-cellular water compartment, which can

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be detected using diffusion-weighted (DW) MRI, magnetization transfer ratio (MTR), or magnetic resonance spectroscopy (MRS) by quantifying metabolites such as Lactate, Choline, and Lipids.

Furthermore, we will also separately report findings from quantitative neuroimaging studies that assessed hippocampal morphology differentially across hippocampal subfields. These studies will be useful to reveal the sequelae of neuro-inflammation such as neuronal loss / neurodegeneration.

2. Overview of relevant imaging techniques

The most frequently used imaging tool in routine clinical settings to identify in vivo biomarkers in neuroinflammatory conditions such as MS, is MRI. For example, MRI is established as gold standard in the diagnosis of MS and is used to investigate the natural course of the disease and monitor treatment effects in clinical trials. MRI “lesions” appear as hyperintensities on T2-weighted images and, in the relapsing-remitting phase of MS (RRMS), the effect of a treatment on MRI lesions and its effect on the frequency of relapses are strongly correlated, supporting the use of MRI parameters as surrogates for clinical endpoints (34). However, conventional MRI measures are limited by lack of neuropathological specificity, and for example, non-specifically reflects demyelination, oedema, or gliosis (35). Furthermore, as disability progresses in the secondary progressive phase of MS (SPMS), the strength of the relationship between T2-hyperintensities and clinical severity becomes weaker. Importantly, conventional MRI measures, including T2-weighted FLAIR, is only able to detect a minority of cortical or sub-cortical grey matter lesions. This may be due to the different pathophysiology of cortical grey matter lesions, compared to those in the white matter, with less inflammatory cell infiltration and absent blood–brain barrier damage (36). All these factors impact the value and utility of conventional MRI measures for the assessment of hippocampal neuroinflammation. We have therefore focused our review on alternative molecular imaging techniques that provide higher, although not absolute, specificity to the pathological processes that are relevant for hippocampal neuroinflammation. Here we provide a brief description of the imaging techniques used in the studies we reviewed.

POSITRON EMISSION TOMOGRAPHY

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Positron Emission Tomography imaging, based on the in vivo administration of radiolabelled ligands that bind selectively to a target of interest, offers the potential of high specificity for molecular markers of cellular and metabolic processes. The high selectivity of PET allows microdosing of the radiotracer, ensuring high safety and tolerability for the subjects who undergo the procedure. Although for over two decades there have been intense research in the identification of suitable PET targets for neuroinflammation imaging, only a limited number of targets have been investigated in living patients to date, and the only extensively characterised target in clinical populations is the 18 KDa Translocator Protein (TSPO). TSPO, formerly known as the peripheral benzodiazepine receptor (PBR), is a protein primarily (but not exclusively) localized on cells outer mitochondrial membrane. In normal conditions TSPO is highly expressed in peripheral tissues, particularly where steroids are synthesized, consistent with its role in steroidogenesis (37). In the normal human brain, the expression of TSPO is low. TSPO expression is observed in macrophages and microglia, astrocytes, oligodendrocytes, endothelial cells and smooth muscle cells, platelets, subpial and subependymal glia, meninges (vessels, macrophages and sometimes, arachnoid cells), ependymal cells, and choroid plexus. Furthermore, recent evidence confirmed TSPO is also expressed in neurons (38) (39). Autoradiography studies using radiolabelled TSPO ligands demonstrate that the expression of TSPO is dramatically enhanced in response to microglia proliferation or activation, in the case of a disrupted blood brain barrier, on invading cells of mononuclear-phagocyte lineage (40) (41) (42) (43)]. The precise role of TSPO in the inflammatory processes of microglia during such disease states remains unclear, with accumulating evidence suggesting an allostatic role of TSPO in the orchestration of bioenergetic, and more specifically, redox responses that accompany neuroinflammatory processes.

In neuroinflammation, the areas of focal tissue damage and demyelination, such as for example in active or chronic active MS lesions, are characterized by dramatically increased microglia density, therefore TSPO represents an attractive target for imaging focal lesional neuroinflammatory pathological processes. However, TSPO PET also enables assessment of neuroinflammation in non-lesional areas providing clinically relevant information that is not available with conventional routine MRI approaches (26). An important caveat to consider relates to the notion that the specificity of TSPO to each cellular type is not uninform across species, brain regions and disease processes [(42); (43); (37); (39)]. Therefore, the application
of TSPO PET imaging should be informed by histopathological studies that reveal, for each specific target and application, which cellular types, and immunopathological processes are contributing the greatest proportion of TSPO signal. In parallel to developments in the TSPO PET field, we note promising results from first-in-human applications of other emerging PET radiotracers targeting neuroinflammatory processes, such as for example the COX-1 targeting $^{[11}C]PS13 which displays exquisitely high hippocampal uptake (44). Furthermore, promising data are emerging from novel human applications of $^{[11}C$]-deuterium-L-deprenyl ($^{[11}C$]-DED) (45) and $[^{11}C]^{-BU99008}$ (46), which bind respectively to Monoamine Oxidase B, and the non-adrenergic imidazoline-2 binding site, both of which are overexpressed in reactive astrocytes.

MAGNETIC RESONANCE SPECTROSCOPY

MRS aims to quantify the concentration of tissue metabolites, by exploiting a phenomenon known as chemical shift. In molecules more complex than water, the negatively charged electrons can oppose the external static magnetic field resulting in a small shift of the resonance frequency of each metabolite. As these molecules are fairly mobile, their signal results in relatively narrow peaks in frequency, which can be easily identified. By measuring the area under each peak, it is possible to estimate their concentration. The main metabolites visible in the brain are N-acetyl aspartate (NAA), only present in neurons, and often regarded as a neuronal marker; choline (Cho), a marker of membrane turnover, which resides in glial cells and neurons; and creatine (Cr), a marker of cellular energetics, often used as a reference for other peaks. Other metabolites of interests, which are, however, more difficult to measure, are glutamate (Glu), glutamine (Gln), myo-inositol (mI), and lactate (Lac). The last two are of interest in the context of neuroinflammation, as mI is only present in glial cells, while Lac is virtually invisible in healthy brain but increases in conditions of hypoxia, poor perfusion and other pathologies. More details can be found in (47).

DYNAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING

The aim of DCE MRI is to assess the integrity of the blood brain barrier (BBB) by measuring the distribution of a paramagnetic contrast agent (typically, gadolinium chelates) injected intra-venously. When the BBB is intact, the contrast agent stays in the vasculature, while in the presence of increased permeability, it leaks in the tissue altering the MRI signal.
Alterations to the BBB are known to occur in the presence of neuroinflammation, for example in acute MS lesions (48). More subtle increases in permeability have also been reported in conditions such as dementia (49), and have been linked to the presence of underlying chronic inflammation. The transfer constant $K_{\text{trans}}$ can be estimated by fitting analytical models of tissue compartmentalisation to serial T1-weighted acquired after the injection. $K_{\text{trans}}$ tends to increase with increased BBB permeability. Please see [(50); (51)] for more information.

DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING

Diffusion refers to the microscopic random motion of small particles immersed in a fluid. Water molecules experience self-diffusion, i.e. diffusion within the water itself. In biological tissue, water self-diffusion is affected by the microstructure, i.e. membranes and organelles that hinder the diffusion of molecules, thus providing information about microstructure and integrity of the tissue itself. Diffusion-weighted (DW) MRI uses magnetic field gradients to enhance the natural sensitivity of MRI to motion, and enables the estimation of tissue apparent diffusion coefficient (ADC) (52). When it became obvious that diffusion is anisotropic in the white matter, i.e., that it depends on the direction along which it is measured, diffusion tensor (DT) MRI was introduced (53), enabling the estimation of diffusion fractional anisotropy (FA), as well as of the local tissue orientation. The concept of ADC was replaced by the mean diffusivity (MD), a directional average of the diffusion coefficient. MD tends to increase whenever there is an increase in free water content (or loss of tissue), while FA tends to reduce under similar circumstances. Radial (RD) and axial (AD) diffusivities are sometimes used to map diffusion across and along fibre bundles, which have supposedly better specificity to myelin and axon integrity, respectively (54). Although DT MRI is still extremely popular in clinical applications, more refined models of diffusion MRI, accounting for multiple water compartments, have been introduced. These methods typically require longer acquisition times, which makes them less suited for clinical studies. A good compromise between complexity and acceptable scan time is neurite orientation dispersion and density imaging (NODDI) (55), which provides estimate of the intra-neurite and the isotropic volume fractions. Although non-specific to inflammation, changes to diffusion parameters such as the mean diffusivity can be the consequence of increased water (oedema), and therefore reflect inflammation.

MAGNETIZATION TRANSFER IMAGING & MAGNETIZATION TRANSFER RATIO
MRI is only sensitive to the signal from small, mobile hydrogen-containing molecules, as the signal from larger ones (lipids, proteins) decays too fast to be probed. Nevertheless, hydrogen protons in differing chemical environments can exchange magnetization, thus enabling the indirect probing of macromolecular protons through an MRI measurement. This forms the basis of magnetization transfer (MT) imaging. MT uses radiofrequency pulses far from the resonance frequency of water to saturate macromolecular protons without affecting water protons directly. Thanks to the exchange of magnetization between the two, such saturation is transferred to the water protons and results in a signal attenuation, which depends on the local density of macromolecules. Early attempt to quantify these effects led to the development of the MT ratio (MTR), a percentage difference between the signal measured with and without MT saturation. Larger MTRs typically indicate tissue rich in protein and lipids (including myelin), while reduced MTR values suggest either a reduction in macromolecular content, or an increase in the extracellular water compartment. The interested reader is referred to (56). In the rodent, MT imaging has demonstrated sensitivity to the effects of peripheral inflammation on the brain (57) and sciatic nerve (58), primarily through its sensitivity to increased water content.

MESH MODELLING
Three-dimensional renderings of brain structures also known as mesh models can be obtained from structural MRI data via finite element modelling. These digital 3D-renderings are obtained by combining simple elements (typically tetrahedral or hexahedral ones). The advantage of mesh models is that they enable relevant properties of the brain, such as cortical folding and structural shape, to be captured better than using standard image volumes. Several image analysis packages include similar options, and are typically used to compare morphological structures within or between groups (59). In the context of hippocampal inflammation, mesh modelling can be used to compare the hippocampal shape and volumes, as well as those of its subfields.

3. Methods
A systematic review was conducted following PRISMA guidelines (See Supplementary Figure 1) (60).

Study Selection
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Prior to the review, we defined our search terms and data to be extracted as highlighted in Supplementary Tables 1 and 2. We employed the free search engine pubmed.ncbi.nlm.nih.gov to search the literature from June 1988 to July 2021. Start year was selected based on when selected articles began to meet relevant criteria as per PubMed search. We also manually searched the references of relevant and related articles. In terms of target clinical populations, we decided to focus our search of studies on quantitative neuroimaging measures of hippocampal neuroinflammation with a focus on three prototypical neuroinflammatory autoimmune conditions for which post-mortem pathology reports clearly confirm hippocampal involvement namely MS; AE; SLE [(2); (61), (62); (63)]. Eligible studies were then further split in two categories; the first group (15 studies in total) comprised studies that used imaging techniques to target primary neuroinflammatory processes, and the second group (3 studies in total) included studies of morphological alterations of hippocampal subfields reflecting neuroinflammatory sequelae, such as neuronal loss/neurodegeneration. We did not include studies focused on conditions such as temporal lobe epilepsy (TLE) and Alzheimer’s disease (ALD) with well characterised hippocampal involvement but whose primary pathology is non-neuroinflammatory. From the selected studies, we reported on each ability to differentiate between patients and normal brain.

**Article Selection**
All articles included are original research papers and are all in English language. The study designs of selected articles comprised longitudinal studies, case controls and cross-sectional studies. Primary search was conducted by PN, and reviewed by AC and MC. Only studies, which were eligible, based on inclusion and exclusion criteria were selected.

**Data Extraction**
Data was extracted by PN and later reviewed by AC and MC. Key data included clinical population, imaging methods, outcome measures and effect sizes. Effect sizes were estimated by calculating the Cohen’s $d$, which was determined by calculating the mean difference between two groups (affected participants and controls), and dividing obtained result by the standard deviation. Cohen’s $d = (M_2 - M_1)/SD$. Complete table of data information is available in Supplementary Table 2.

**Quality Assessment**
The quality of each study included, was independently assessed by AC and MC.

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4. Results
During the initial search, we came up with 621 articles (See Prisma flow diagram in Fig 2). We excluded conference extracts, non-human studies and non-English language articles. Case reports, case series and reviews were also removed. A further 551 articles were excluded upon review of their titles and abstracts. The remaining 29 articles were further screened by three reviewers (PN, AC and MC): 4 articles were excluded due to imaging methodology not meeting eligibility criteria and a further 7 were excluded because their target disease was not primary neuroinflammatory pathology. A total of 18 studies met the criteria for inclusion. Fifteen of these used imaging techniques directly examining neuroinflammatory pathology, whilst three applied imaging techniques measuring morphological changes in separate hippocampal subfields, reflecting neurodegenerative changes such as neuronal loss secondary to neuroinflammation.

Of the 18 studies included in the systematic review, 14, 2, and 2 studies focused on MS, AE and SLE respectively. The overall study cohorts included 729 MS, 16 SLE and 166 patients with autoimmune encephalitis, giving a total number of 911 patients. Healthy controls were 497 in total. Ages ranged from 28-66 years and SD between 4 and 13. Female to male ratio was 467/262 for MS patients, and 101/65 for AE patients. The gender of participants was unspecified in the SLE studies. Comprehensive details of demographics and results can be found in Tables 1 and 2. In our review of studies (n=15) targeting primarily neuroinflammatory processes, 4 studies used TSPO PET, 8 studies used DW MRI, whilst one study used DCE, MRS, MTR respectively. There was high heterogeneity in terms of techniques and specific imaging methodology employed, and virtually no study replicated exactly the same methodology within the same condition, with the exception of five studies in MS that all used DW MRI. The three PET studies in MS used three different 2nd generation TSPO radiotracers and reported different outcome measures (SUV<sub>R</sub>; V<sub>T</sub>; DVR)

All neuroinflammation – targeting studies revealed at least one significant signal change in the hippocampus, relative to the control group. The effects sizes varied greatly across studies (range 0.1 to 1.6). Across conditions, the largest effect sizes were seen with TSPO PET and DW MRI, indicating respectively increases in hippocampal TSPO binding and in the Diffusion based MD parameter; and a reduction in diffusion-based FA. These changes appeared consistent across MS studies and were evident in various MS sub-types, although increase in TSPO PET signal [(64), (26)], as well as changes in diffusion FA and MTR appeared more prominent in progressive forms of MS relative to relapsing-remitting, and
even more to CIS [(65), (66), (67)]. Increases in MD were reported in the two studies on AE (68) (69), which were consistent with findings in MS. In contrast, the two studies in SLE revealed TSPO binding changes opposite to those seen in MS, and alterations in BBB permeability that no other studies had examined. Only two studies (both DW MRI studies on AE) separately examined individual hippocampal subfields [(68), (69)]. No other studies reported regional subfield analysis.

In MS, increased TSPO binding and elevations in mean diffusivity parameter (MD) correlated with neurological disability and impaired cognitive performance. For instance, Symbol Digit Modalities Test (SDMT) z-scores negatively correlated with TSPO uptake in the hippocampus (64). Increase in diffusion-based MD parameter also negatively correlated with SDMT and California Verbal Learning Test (CVLT) scores in MS and CIS respectively and was also able to effectively discriminate between memory impaired and memory preserved patients with CIS. In contrast, a decrease in the FA parameter had positive correlations with SDMT (66). Negative correlations were observed with the following: BBB parameters in SLE and elevated MD in AE correlated with varying neuropsychological assessment scores (Automated Neuropsychological Assessment Metrics (ANAM); Ray Auditory Verbal Learning Test (RAVLT) and Rey–Osterrieth Complex Figure (ROCF) respectively) [(51), (68), (69)]. There were also correlations observed with imaging measures and scores on the affective scales in MS and SLE patients. TSPO hippocampal distribution volume ratio in MS and BBB parameters in SLE were positively correlated with BDI scores [(26), (51)]. Decrease FA parameter correlated with HAMD scores (70).

In the second group of studies examining separate hippocampal subfields and reporting neurodegenerative changes due to neuroinflammation, we included 3 studies using MESH modelling. Regional changes were detected between subfields. In MS patients there was surface expansion of the hippocampal dentate gyrus (DG) as measured by radial distance (RD) enlargement (71). This was also observed in the study by Cacciaguera et al (72), looking at serial regional measurements, with surface expansion more pronounced in later months. In contrast, there was a reduction in RD in the CA1 subfield after 3 months progressing to the subiculum. Across MS and AE, deformation overlap corresponded to damage within the CA1 subfield (73).

**DISCUSSION**

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Our systematic review of the literature focused on imaging measures of hippocampal neuroinflammation in 3 prototypical autoimmune neuroinflammatory conditions. It revealed the largest and most consistent significant differences between cases and controls in MS patients, particularly those with the more progressive forms, as shown by studies using TSPO PET and DW MRI. Preliminary results from studies employing other techniques, such as susceptibility, MTR, DCE, appeared promising but require replication in larger samples. All studies reported global hippocampal imaging measures, and no information specifically related to immunocompetent cells density (e.g. TSPO) or microstructural integrity (e.g. DWI) was reported for separate hippocampal subfields. Although two studies in AE depicted individual sub regional atrophy in CA1, CA2/CA3, CA4/DG and in the subicula regions of the hippocampus, diffusion changes were only reported in the hippocampus as a whole. Our separate analysis looking at effect on morphological changes, resulting from neurodegeneration, in neuroinflammatory conditions confirmed our predicted differential vulnerability of subfields to inflammation. For instance, there were specific contrasting measurements in radial distance observed between DG and CA1.

The value of correlations to functional deficits and clinical manifestation were limited by small samples but overall provided preliminary evidence that signs of hippocampal neuroinflammation, capable of causing functional alterations such as in processing speed, semantic organisation, attention, concentration, visuospatial constructional ability, depression and anxiety, might be detected using quantitative imaging markers[(74); (75) and (67) (26)]. Although these correlational data suggest that these quantitative imaging measures are potentially related to clinical phenomena, the lack of specific correspondence between imaging signals and underlying histopathology limit their precise interpretability. For instance, although a large proportion of the TSPO PET signal increases observed in the acute phase of inflammation in MS can be attributed to an increased density of TSPO expressing macrophages/microglia resulting from their infiltration, proliferation and activation [(42), (43)]; it is possible that as time progresses, astrocytes contribute to an increasingly substantial proportion of observed hippocampal signal (76). The discrepancy between findings in MS relative to SLE studies might reflect unique and disease-specific changes in constitutive binding to TSPO expressed by non-inflammatory cells (including for example platelets, endothelia, or other TSPO expressing peripheral cell types), which might be particularly relevant to conditions with systemic and generalised inflammatory responses such as SLE. Furthermore, TSPO PET presents challenges to quantification of the specific radiotracer binding which become particularly difficult to address in presence of systemic inflammatory
responses (77), and might contribute to variability of results between studies due to inconsistencies in methodological approaches.

DW MRI was frequently utilized especially in MS. The specificity of its applications and the extent to which it captures and quantifies hippocampal microstructural alterations in neuroinflammatory pathology have been frequently investigated using pre-clinical and experimental models. Göbel-Guéniot and coworkers (78) observed CA1 pyramidal cell degeneration and granular cell layer dispersions correlated significantly with alterations in tissue diffusivity parameters in murine models of Mesial temporal lobe epilepsy (MTLE), a common type of epilepsy affecting inner aspects of the temporal lobes, which can present in the hippocampus. The findings support the capability of high resolution DW MRI in measuring quantitative changes in epileptic hippocampal tissue consistent with histopathological features in MTLE. Crombe (18) assessed two diffusion-related imaging measures (DTI and NODDI) in terms of their sensitivity to effectively delineate, compute and quantify microstructural alterations in specific hippocampal layers in mice with EAE, a murine experimental model of RRMS. NODDI employs a multishell tissue modality in the characterisation of tissue microstructure while DTI is a simpler approach that assumes a single water compartment characterised by anisotropic diffusion. Both modalities were equally effective in delineating specific hippocampal layers and the quantification of diffusivity parameters presented with differences within 3 specific layers (Stratum Radiatum (SR), Stratum Lacunosum Moleculare (SLM), Molecular Layer (ML)). DTI showed more prospects with regards to quantification. The same study assessed histopathological correlations between EAE pathology and DW-imaging measures and identified a reduction in AD and MD in the molecular layer of the hippocampus of mouse model of EAE, corresponding histologically to microglial activation and a reduction in dendritic density, consistent with early neuroinflammatory and neurodegenerative processes respectively. This interestingly contrasts with findings of the studies we reviewed here, where both MS and AE were associated with increased hippocampal MD across studies. A logical explanation here may indeed be due to progression from the MD reduction, reflecting the early neuroinflammatory and neurodegenerative disease processes characteristic of EAE, to more sustained and progressive neurodegenerative pathology seen in MS patients where the expansion of extracellular fluid and microscopic barrier disruptions become progressively more prominent (68). Similar distinctive observations were a sole reduction in FA in Clinically isolated syndrome (CIS), considered the first neurological onset of potential MS, and an additional increase in MD seen in MS patients (66). However, the impact of partial
volume effects with CSF should not be excluded, as human MRI data are typically acquired with much lower resolution. Due to indirect measures between tissue architecture and DW parameters, DW MRI does lack levels of specificity in neuroinflammatory pathology (18). Both MD and FA are sensitive to increases in extracellular water, reduction in myelin, changes in microstructure and changes in cell density. It is therefore difficult to associate the observed changes with a specific pathological substrate. More so, human applications have also revealed considerable limitations in acquisition due to low resolution protocols specifically designed for whole brain (79). To mitigate against these effects and limitations, Treit developed a simple DTI protocol which employed standard single-shot 2D Echo-planar imaging (EPI) at 3T, to obtain high spatial resolution images (1x1x1mm³) of the human hippocampus. In order to compensate for the SNR loss induced by the small voxels, they proposed to use relatively low b-value (thus reducing the amount of diffusion weighting), at the price of limiting the sensitivity to microscopic water environment. This may potentially decrease or limit the certainty in identifying vital micro-image details in neuroinflamatory pathology, in an already complex structure such as the hippocampus.

There are other notable methodological concerns in processing hippocampal neuroinflammatory imaging data, which may arise post MRI acquisition such as proposed methods of segmentation, risk of poor precision in co-registration of DW maps if segmentation is done on T1 and resolution limits that can effectively distinguish hippocampal subfields or layers. DW MRI is typically acquired using echo-planar imaging (80), a pulse sequence insensitive to bulk motion, but characterised by geometric distortions induced by magnetic susceptibility (81). As a consequence, the anatomy on DW EPI does not match the corresponding T1-weighted scans, making image coregistration between the 2 modalities challenging.

Even if perfect coregistration could be achieved, due to the morphological complexities and extremely small structural sizes of the hippocampal compartments, segmenting the subregions of the hippocampus is indeed fraught with difficulties and immense challenges in the analysis of MRI images (82). Hippocampal segmentation might be obtained by either automated or manual methods: most of the studies included in our review have utilized automated methods, such as FSL and Free Surfer. Only the studies by Rocca et al (71) and Cacciaguerra et al (72) employed manual tracing for hippocampal segmentation. While manual segmentation by adequately trained human raters is generally regarded as the gold standard (83), semi-automated and more automatic methods appear to be gaining traction.
with a view to reducing workload, increasing reproducibility and avoiding inter/intra rater variability which is also common with manual methods of segmentation. Automated methods are however not without limitations, which range from a lack of public availability, being subject to error in significant disease states and requiring parameter tuning (84).

Taking resolution into consideration, a future approach could be computational imaging techniques, which enhances contrast and resolution of lower resolution images. One such application is the Image Quality Transfer (IQT) approach, which mitigates the challenges resulting from spatial resolution, lengthy acquisition protocols, slow translation, interpolation and complex processing pipelines. IQT technique adapts clinically low-quality mappings to experimental high-quality images applying the likeness of images across scales, modalities, regions and subjects (85). With the avoidance of artefacts comprising hot-spots and blurring, and the reduction of partial volume effects, finer details are recovered which were lost at low resolution, hence, allowing for easier identification of hippocampal architecture including morphology, digitations, landmarks, boarders and separation of sub regional layers. Zooming into desired region (Medial Temporal Lobe for instance) allows for adequate manual segmentation directly on diffusion images, with subsequent computation of desirable diffusion parameters. The need for co-registration to anatomical or histological images is hence diminished.

The poor specificity of diffusion MRI is caused by its sensitivity to all water compartments (intra and extra cellular). A way to overcome this limitation is by combining the sensitivity to microstructure offered by diffusion MRI with the cell-specificity of MRS. Diffusion-weighted MRS (DW-MRS) offers a promising and cheaper alternative for non-invasively characterising the effects of inflammation in the brain (29). In De Marco's study, DW-MRS was able to provide cell specific information about cellular morphology and equally, was found sensitive to systemic inflammation induced glial cytomorphological changes in grey matter (29). It should be re-iterated, however, that the hippocampus is an exceptionally challenging region to capture with this technique, which is inherently characterised by very poor spatial resolution.

**CONCLUSION**

In our review, we explained why the hippocampus is an important site of neuroinflammation and highlighted possible reasons underlying its vulnerability, which differentially affects hippocampal subfields. We also reported challenges associated to the application of hippocampal imaging of neuroinflammation using both conventional and novel imaging

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Our review did provide confirmatory evidence that a few imaging markers that reflect neuroinflammatory tissues changes, such as DW-MRI and TSPO PET, were able to detect signal alterations in the hippocampus in prototypical neuroinflammatory conditions. However, no study as yet has examined hippocampal subfields separately. We propose that this could be addressed by use of higher resolution acquisitions, or alternatively the adoption of particular post-processing techniques, which represent promising approaches to gain better insight into neuroinflammatory pathology in vivo, ultimately enabling more precise and sensitive characterisation of hippocampal pathophysiology.

### Tables

| Authors; year | Clinical population | Imaging Methods | Outcome Measures | Findings |
|---------------|---------------------|----------------|-----------------|----------|
| (Colasanti et al. 2016) (26) | MS | TSPO PET \[^{18}F\]PBR 111 | BDI-II | MS: \[^{18}F\]PBR111 DVR: 0.8 (p=0.024) |
| | HC: n=22; 49(10) yrs; 14F | Automated (CIC Atlas) | | Whole MS cohort: \[^{18}F\]PBR28 SUVR (p=0.05) neg correl to SDMT |
| | RRMS: n=12; 43(10) yrs; 10F | \[^{11}C\]PBR28 SUVR; | SDMT; TMT-A & B; CVLT-II; BMVT-R; WCST | RRMS: \[^{11}C\]PBR28 SUVR;: 1.1 (p=NS) \[^{11}C\]PBR28 DVR: 0.8 (p=NS) |
| | SPMS: n=15; 52 (7) yrs; 11 F | Automated (First/FSL) | | SPMS \[^{11}C\]PBR28 SUVR;: 1.6 (p<0.003) \[^{11}C\]PBR28 DVR: 1.2 (p<0.005) |
| | HC: n=14; 48 (13) yrs; 6 F | \[^{18}F\]PBR06 SUV; | | MS cohort: \[^{18}F\]PBR111 DVR (p=0.037) pos correl to BDI |
| (Herranz et al. 2016) (64) | MS | TSPO PET \[^{11}C\]PBR 28 | \[^{18}F\]PBR111 DVR (p=NS) | |
| | RRMS: n=7; 33(7) yrs; 5 F | Automated (PNEURO) | | |
| | SPMS: n=5; 35(4) yrs; 3F | \[^{18}F\]PBR06 SUV; | | |

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| Study                  | Group | MRI Type | Task | No. of Subjects | Results |
|-----------------------|-------|----------|------|----------------|---------|
| (Cappellani et al. 2014) (65) | HC: n=5; 38 yrs; 3F | DW-MRI | Automated (First/FSL) | 46 | FA, MD, RD, AD |
|                       | HC: n=110; 47 yrs; 76 F |                  |                              | 24 | NA |
| (Geurts et al. 2006) (75) | MS: n=33; 48 yrs; 16 F | MRS | NS | 30 | Ins |
|                       | HC: n=10; 43 yrs; 7 F |                  |                              | 20 | BRB-N |
| (Planche et al. 2017) (66) | MS: n=37; 37 yrs; 29F | DW-MRI | Automated (First/FSL) | 41 | MD, FA |
|                       | MS: n=32; 41 yrs; 23 F |                  |                              | 22 | MD |
|                       | HC: n=36; 38 yrs; 10 F |                  |                              | 21 | NA |
| (Roosendaal et al. 2010) (87) | MS: n=25; 39 yrs; 17 F | DW-MRI | Automated (First/FSL) | 40 | FA |
|                       | HC: n=30; 41 yrs; 20 F |                  |                              | 21 | HAMD |
| (Shen et al. 2014) (70) | MS: n=15; 38 yrs; 11 F | DW-MRI | Automated (First/FSL) | 42 | FA |
|                       | HC: n=15; 37 yrs; 11 F |                  |                              | 22 | HAMD |
| (Vrenken et al. 2007) (67) | MS: n=35; 39 yrs; 24 F | MRI-MTR | Automated (First/FSL) | 36 | MTR |
|                       | PPMS: n=12; 58 yrs 5 F |                  |                              | 15 | PASAT |
|                       | SPMS: n=19; 44 yrs; 11 F |                  |                              | 21 | RRMS: MTR 0.1(p=NS) |
|                       | HC: n=23; 31 yrs; 11 F |                  |                              | 21 | MTR 0.7(p=NS) |
| (Yin et al. 2018) (88) | MS: n=22; 32 yrs; 13 F | DW-MRI | Automated (FreeSurfer) | 33 | FA, ADC |
|                       | HC: n=22; 32 yrs; 13 F |                  |                              | 22 | NA |
| (Filip et al. 2020) (74) | MS: n=10; 47 yrs; 8 F | DW-MRI and susceptibility | Automated (FreeSurfer) | 50 | RAFF4, T1p, T2, FA, MD, AD, RD |
|                       | HC: n=10; 46 yrs; 8 F |                  |                              | 20 | SDMT CES-D |

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| Study Reference | Condition | Control | Age/Clinical Details | Neuroimaging | Cogn | Neuroinflammation Tests | Neuroinflammation Results |
|-----------------|-----------|---------|----------------------|--------------|------|-------------------------|--------------------------|
| Chi et al. 2019  | SLE | n=6, 38(13) yrs; (NS) F | HC: n=5; 34(11) yrs; (NS) F | DCE-MRI | No | No | K<sub>trans</sub>, Ve, CBF | SLE: K<sub>trans</sub>: 0.9 (p=0.04) Ve: 0.9 (p=0.04) CBF: 1.1 (p=0.013) |
| Wang et al. 2017 | SLE | n=10; 41(9) yrs; (NS) F | HC: n=11; 39 (11); (NS) F | TSPO PET | Automated (FreeSurfer) | No | [11C]DPA -713 VT | SLE: [11C]DPA-713 VT: 0.8 (p<0.05) |
| Finke et al. 2016 | Anti-NMDAR Encephalitis | anti-NMDAR encephalitis (n=40; 28(12) yrs; 36 F HC: n=25; 28 (11) yrs; 23 F | DW-MRI | Automated (First/FSL) | Yes | MD | RAVLT, ROCF | Anti-NMDAR Encephalitis: LH MD 0.09 (p=0.004) RH MD 0.7 (p=0.019) RAVLT LH MD r= -0.524 (p=0.001) RH MD r= -0.470 (p=0.004) ROCF LH MD r= -0.45 (p=0.008) RH MD r= -0.44 (p=0.009) |
| Finke et al. 2017 | Anti-LGI1 Encephalitis | anti-LGI1 encephalitis (n=30; 66(12) yrs; 11 F HC: n=27; 64 (2) yrs; 9 F | DW-MRI | Automated (FreeSurfer) | Yes | MD | RAVLT, ROCF | Anti-LGI1 Encephalitis: LH MD 1.1 (p=0.001) RH MD 1 (p=0.001) RAVLT LH MD r= -0.41 (p=0.04) RH MD r= 0.57 (p=0.03) |

Table 1: Summary of Neuroimaging studies reporting neuroinflammatory changes in the hippocampus
| Authors; year | Clinical population | Imaging Methods | Outcome Measures | Findings |
|--------------|---------------------|----------------|-----------------|---------|
| Disease | n cases; mean age (SD); gender | Imaging type | Segmentation method | Subfields analysis | Imaging | Affective / Cognitive | Difference Cases vs controls effect size (ES); p value | Correlations to cognitive / affective measures |
| (Heine et al. 2020) (73) | MS | RRMS (n=30; .43 (6) yrs (SD); 18 F HC (n=30; .42 (8); .18 F anti-NMDAR encephalitis (n=30; 28 (8) yrs (SD); 26 F HC (n=30; .29 (8); .26 F anti-LGI1 encephalitis (n=30; 66 (9) yrs (SD); 9 F HC (n=30; .63 (10); .9 F) | MRI | Automated (First/FSL) | Mesh Modelling | Post MRI: Surface based analysis; Scalar values | NMDA/ LG1 ; RAVLT, RWFT | NMDA | RAVLT Scalar r= 0.335 (p=0.035) RWFT Scalar r= - 0.033 (p=0.432) BDI-II Scalar r= - 0.100 (p=0.356) |
| (Rocca et al. 2015) (71) | MS | BMS (n=26; .44 (7) yrs (SD); 18 F RRMS (n=28; .40 (11) yrs (SD); 20 F SPMS (n=34; .46 (11) yrs (SD); 24 F HC (n=28; .45 (11); .18 F) | MRI | Manual Tracing (MNI) Space | Mesh Modelling | Post MRI: Vertex based analysis; Radial Dist. (DG) | WL test, SS test | BMS | WL Lt DG Rad Dist r= -0.43 (p=NS) |
| (Cacciaguerre et al. 2019) (72) | MS | CIS (n=36; 31 (7) yrs (SD); 29 F HC (n=14; 34 (8) yrs (SD); 10 F) | MRI | Manual Tracing (MNI) Space | Mesh Modelling | Post MRI: Radial mapping analysis; Radial Dist. HSRV (CA1, Presubiculum, CA4, DG) | PASAT | CIS (M3) Rt CA1 HSRV 0.2 (p=0.009) Rt mol layer HSRV 0.1 (p=0.003) Rt gran layer DG HSRV 0.2 (p=0.002) Rt Presubiculum HSRV 0.3 (p=0.026) Rt CA4 HSRV 0.3 (p=0.007) | No correlation with PASAT |

**Table 2: Neurodegenerative changes associated with inflammation in Hippocampal subfields**
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Data Availability Statement
Since this is a systematic review article of the available literature, data sharing is not applicable to this article as no new data were created or analysed in this study.

Competing interests
Dr Prince Nwaubani has no conflict of interest or competing interests to disclose.
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Author contributions
Data was extracted by Dr Nwaubani and later reviewed by Dr Colasanti and Prof Cercignani.
The quality of each study included, was independently assessed by Dr Colasanti and Prof Cercignani. Write up of article was done by all three authors.
**Title and Legends to Figures**

**Figure 1: Immunopathology of BBB disruption in SLE.**
Diagrammatic representation showing rationale for Dynamic Contrast Enhanced MRI of Neuropsychiatric lupus pathology with impact on the Hippocampus. Neuronal damage within the Hippocampus is induced following breach of the blood-brain barrier (BBB) and access of SLE Auto-Antibodies. Accumulation of gadolinium based contrast agent, as measured by increasing capillary permeability ($K_{trans}$), and accumulation in the extravascular space ($V_e$) have been reported (51). Significant decrease in TSPO distribution in the Hippocampus has also been reported using PET (89).

**Figure 2. Immunopathological and Neuroimaging features of hippocampal neuroinflammation across neuroinflammatory diseases.**

**A,B, C: Multiple Sclerosis (MS):** reduced density of ramified Microglia (HLA class II staining) in a lesion center with increased density of activated microglia and macrophages in the lesion edge (A); Pattern of hippocampal demyelination in the DG of a MS patient (B) (from Papadopolous et al, 2009 (2)). Reduced Hippocampal volume in patient with MS (C) (unpublished data).

**D, E, F: Systemic Lupus Erythemateous (SLE):** Lymphocytes infiltrates in the Choroid Plexus (D). Evidence of neuronal loss in DG (E) (from Ballok et al., 2004). Hippocampal atrophy in SLE patient (F) (from Appenzeller, S et al., 2006 (90).

**G, H, J: Autoimmune Enkephalitis (AE):** Hippocampal microglial activation (HLA class II staining)(G) and reduced NMDAR-expression (H) in a patient with NMDAR encephalitis (from Zrzavy et al., 2021 (91)). FLAIR MR image showing hyperintense swelling of the left hippocampus (J) (from Dekeyzer, S et al., 2017 (92)).