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Mechanobiology of the brain in ageing and Alzheimer's disease

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Abstract

Just as the epigenome, the proteome and the electrophysiological properties of a cell influence its function, so too do its intrinsic mechanical properties and its extrinsic mechanical environment. This is especially true for neurons of the central nervous system (CNS) as long-term maintenance of synaptic connections relies on efficient axonal transport machinery and structural stability of the cytoskeleton. Recent reports suggest that profound physical changes occur in the CNS microenvironment with advancing age which, in turn, will impact highly mechanoresponsive neurons and glial cells. Here, we discuss the complex and inhomogeneous mechanical structure of CNS tissue, as revealed by recent mechanical measurements on the brain and spinal cord, using techniques such as magnetic resonance elastography and atomic force microscopy. Moreover, ageing, traumatic brain injury, demyelination and neurodegeneration can perturb the mechanical properties of brain tissue and trigger mechanobiological signalling pathways in neurons, glia and cerebral vasculature. It is, therefore, very likely that significant changes in cell and tissue mechanics contribute to age-related cognitive decline and deficits in memory formation which are accelerated and magnified in neurodegenerative states, such as Alzheimer's disease. Importantly, we are now beginning to understand how neuronal and glial cell mechanics and brain tissue mechanobiology are intimately linked with neurophysiology and cognition.

KEYWORDS

Alzheimer's disease, atomic force microscopy, hippocampus, magnetic resonance elastography, mechanotransduction

Abbreviations: AD, Alzheimer's disease; AFM, atomic force microscopy; ARTAG, ageing-related tau astrogliopathy; ATP, adenosine triphosphate; BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; CSPG, chondroitin sulphate proteoglycan; CTE, chronic traumatic encephalopathy; DRG, dorsal root ganglion; ECM, extracellular matrix; ERK2, extracellular signal-regulated kinase 2; FAK, focal adhesion kinase; GFAP, glial fibrillary acidic protein; GM, grey matter; HA, hyaluronan; HAPLN, hyaluronan and proteoglycan link protein; Has1, hyaluronan synthase 1; HD, Huntington's disease; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; MLCK, myosin light chain kinase; MRE, magnetic resonance elastography; OPC, oligodendrocyte progenitor cells; PART, primary age-related tauopathy; PD, Parkinson's disease; PNN, perineuronal net; PSD, postsynaptic density; S1P, sphingosine 1-phosphate; SAC, stretch-activated channel; SC, spinal cord; TAZ, transcriptional coactivator with PDZ-binding motif; TBI, traumatic brain injury; TFM, traction force microscopy; WM, white matter; YAP, Yes-associated protein.

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1 | INTRODUCTION

Mechanobiology, an emerging field at the interface of biology, engineering and physics, is a rapidly expanding discipline in neuroscientific research (Jansen et al., 2015; Smith, Cho, & Discher, 2018; Xia, Pfeifer, Cho, Discher, & Irianto, 2018). The mechanical properties of cells, and the external and internal forces acting on them, can regulate important cellular functions and behaviours, such as migration, growth and differentiation (Calvo et al., 2013; Wozniak & Chen, 2009), cell division and programmed cell death (Kunda et al., 2012; Zhu, Gan, Fan, & Yu, 2015), and can also influence cellular regeneration or pathogenesis (Bertalan et al., 2020; Schlüßler et al., 2018). The brain is one of the softest organs in the mammalian body and is encased within a much harder skull for protection (Tagge et al., 2018). However, the brain and the cells that comprise it experience various physical forces (see Box 1) during development, maturation and ageing that affect their underlying biology and neurochemistry (Budday, Steinmann, & Kuhl, 2015). Importantly, neurons and glial cells possess membrane-bound mechanosensors that translate physical forces into biochemical signals in a process termed mechanotransduction. Therefore, perturbations to the external mechanical environment of a cell can influence its biology and can even trigger pathological signalling processes (Jaalouk & Lammerding, 2009). To understand and measure the mechanical properties of neurons and glia, and the forces that they experience and exert during physiological processes, engineers and biophysicists are teaming up with neurophysiologists to develop interdisciplinary approaches and techniques to advance the field (Jorba et al., 2017; Magdesian et al., 2016; Robinson, Valente, & Willerth, 2019). Such collaborations have been important for detailing the mechanical properties of different brain regions, such as the hippocampus, which is important for memory formation. Here, we will discuss how techniques such as atomic force microscopy (AFM), magnetic resonance elastography (MRE) and traction force microscopy (TFM) have revolutionised our understanding of how neuronal and glial cell mechanics are impacted by ageing, traumatic brain injury (TBI) and neurodegeneration (Pogoda & Janmey, 2018). We also highlight some areas of controversy in the field that require clarification. Finally, we argue how a deeper understanding of the mechanics of CNS pathologies, such as Alzheimer's disease (AD), could help to elucidate the underlying mechanisms of neurodegeneration (e.g. excess synapse loss), as well as accelerate the discovery of novel drug targets and therapeutic interventions aimed at enhancing axonal and myelin repair.

2 | MECHANOSENSATION IN THE CENTRAL NERVOUS SYSTEM

2.1 | Axonal growth cones

Pioneering research in developmental neurobiology has led to the identification of gradients of chemoattractant (e.g. netrins) and chemorepellent (e.g. slits and semaphorins) molecules that guide migrating axons (Atkinson-Leadbeater et al., 2010; Campbell et al., 2001; Piper et al., 2006; Plump et al., 2002) and facilitate the precise wiring of neural networks in the brain and spinal cord (Tessier-Lavigne, Placzek, Lumsden, Dodd, & Jessell, 1988). However, evidence from experiments performed in the optic tract of the frog (*Xenopus laevis*) suggests that axon guidance may also rely, in part, on mechanical cues that steer axonal growth towards the optic tectum (Koser et al., 2016; Thompson et al., 2019). As such, retinal ganglion cell axons appear to migrate along local stiffness gradients, with growth cones becoming more exploratory and terminating in softer optic tectum brain tissue (Koser et al., 2016). The stiffness of cell culture substratum also influences the migration velocities of neurons and glial cells in vitro. Neurons preferentially grow and extend processes on soft materials of ~700 Pa (Georges, Miller, Meaney, Sawyer, & Janmey, 2006). However, when substratum is too soft (~300 Pa) neurite extension is retarded. Knocking down Piezo1 also disrupts developmental axon guidance (Koser et al., 2016), suggesting that growth cone migration is partly regulated by mechanosensitive ion channel activity. Similarly, the peptide GsMTx4, a negative allosteric modulator of several mechanoreceptors (Bae, Sachs, & Gottlieb, 2011), can influence neurite growth. However, GsMTx4 has been reported to both enhance and inhibit neurite extension (Jacques-Fricke, Seow, Gottlieb, Sachs, & Gomez, 2006; Koser et al., 2016). Because mechanoreceptors influence axonal regeneration and the functional recovery of synaptic contacts after CNS injury (Song et al., 2019), it will be important to further investigate how mechanical cues regulate growth cone behaviour (Kayal, Moeendarbary, Shipley, & Phillips, 2019). An understanding of growth cone mechanics is also important for the ageing and neurodegeneration research fields. For example, extensive somatodendritic sprouting of filopodium-like structures (that resemble developmental growth cones) (Ihara, 1988; Jørgensen, Hansen, Hoffman, Fülöp, & Stein, 1997) occurs in Alzheimer's disease, which likely reflects attempted synaptic remodelling in response to presynaptic or axonal damage (Scott, 1993). Therefore, the perturbed mechanical properties of AD brain tissue (discussed below) may hinder the regeneration of meaningful numbers of new functional synaptic contacts and contribute to the gradual impairment of cognition (Hiscox et al., 2020; Levy Nogueira et al., 2016; Murphy et al., 2011, 2016).

BOX 1 Glossary of terms

Mechanical properties can be measured by applying tensile, compression and shear forces. They describe the internal resistance of a material to distortion by an external force.

Elasticity: The time-independent property of a solid material which regains its original shape and size upon removal of a tensile or compression load.

Young's elastic modulus (E): The elasticity of a material is characterised by Young's elastic modulus (E) which is the ratio of applied tensile stress to concomitant tensile strain.

Viscosity: A property of fluids that describes resistance to flow. The viscosity is measured as the ratio of applied shear stress to concomitant shear strain rate.

Viscoelasticity: When deformed or loaded, most biological materials exhibit both elastic and viscous properties, and the degree of their fluid- or solid-like response depends on the time scale of the applied load or deformation.

Stress: The ratio of the force to the area it is applied to.

Strain: The change in length divided by the initial length of the material under stress.

Stiffness: Stiffness is a degree of material's resistance to deformation under application of force. Similar to elastic modulus, it has a unit of Pascal (Pa) which is force per unit area. Stiffness can be derived from the slope of the load–displacement curve.

Tensile strain: The ratio of change in length to the original length of a material in the loading direction.

Tensile stress: The amount of force per unit area required to stretch the material and induce tensile strain.

Shear strain: Application of force parallel to a plane creates shear strain which is the length of deformation in the direction of applied force divided by the length of deformation perpendicular to the force direction.

Shear stress: The amount of force per unit area that induces deformation of material along the parallel plane of the imposed force.

Shear modulus (G): Describes the elasticity of a material when exposed to transverse/shear deformations. It is defined as the ratio of shear stress to the concomitant shear strain and has the unit of Pa. Young's elastic modulus (E) and G are related through $E = 2G(1 + \nu)$, where ν is the Poisson's ratio which is a measure of material's degree of compressibility.

Shear waves: Shear waves create a transverse movement of material components that propagates in the direction of the wavefront. As the shear wave passes through material, it induces shear strain, and therefore, the shear modulus can be estimated by calculating the velocity of shear wave propagation.

Damping ratio: It is a measure of dissipation of the shear waves. High values of damping ratio indicate that oscillations attenuate more rapidly, suggesting a more fluid-like viscous behaviour whereas low values are an indicator of solid-like elastic behaviour.

Oscillatory rotational shear test: A shear test performed on a sample positioned between two parallel plates. The bottom plate remains stationary and the top plate rotates via application of torque to create oscillations with defined rotational speed/frequency.

Storage modulus (G'): It is a measure of elastic behaviour of a viscoelastic material and indicates the amount of energy that is elastically stored during oscillatory mechanical loading.

Loss modulus (G''): It is a measure of viscous behaviour of a viscoelastic material and indicates the amount of energy dissipation during oscillatory mechanical loading.

Dynamic modulus (G): It is the ratio of stress to strain when oscillatory mechanical loading is exerted on a viscoelastic material. It represents both elastic and viscous behaviour of a viscoelastic material and is related to the dynamic and loss moduli through $G^2 = (G')^2 + (G'')^2$.

Pascal (Pa): It is the SI unit of pressure used to quantify stress, Young's and shear moduli. It is unit force per unit area (one Newton per metre^2).

Poroelasticity and fluid-solid interactions: Soft hydrated tissues display poroelastic properties (Esteki et al., 2020; Malandrino & Moeendarbary, 2019) meaning that their mechanical behaviour can be understood by considering them as a sponge-like porous elastic matrix (comprised of the extracellular matrices and cells) bathed in an interstitial fluid (comprised of water and solutes). The mechanical behaviour of a poroelastic material depends on the interactions between its fluid and solid phases. Fluid and pressure distribution within different tissues, such as brain, have been modelled by poroelastic theory (Guo et al., 2018).

Mechanotransduction: The process whereby cells convert a mechanical stimulus into chemical signals.

2.2 | Mechanosensors

Neurons and glia in the brain express well-known mechanosensitive receptors (for a detailed review see Tyler, 2012). Integrins are transmembrane cell adhesion molecules that link the extracellular matrix (ECM) to the cytoskeleton and are highly sensitive to both external mechanical stimuli (e.g. matrix stiffness) and internal forces generated via actomyosin contractions or actin polymerisation (Schwartz, 2010). Clusters of ECM–integrin–actin filament complexes located on the outer cell membrane are known as focal adhesion sites and act as specialised mechanosensors that regulate cell motility and behaviour (Ciobanasu, Faivre, & Le Clainche, 2013; Kechagia, Ivaska, & Roca-Cusachs, 2019). Focal adhesion sites are coupled to intracellular signalling molecules, such as focal adhesion kinase (FAK), which integrates mechanical signals and regulates the activity of second messengers including Rho GTPases (RhoA, Rac and Cdc42), Src, extracellular signal-regulated kinase 2 (ERK2) and mitogen-activated protein kinase (MAPK), as well as other cadherin-mediated cell–cell contacts (Hood & Cheresh, 2002). FAK can also relay information to the nucleus via activation of Yes-associated protein (YAP) and the transcriptional coactivator with PDZ-binding motif (TAZ) (Kaushik & Persson, 2018; Lachowski et al., 2018; Rausch & Hansen, 2020). Moreover, mechanotransduction-associated phosphorylation of ERK2 and activation of myosin light chain kinase (MLCK) can modulate focal adhesion site dynamics and control cell motility (Mitra, Hanson, & Schlaepfer, 2005).

FA complexes are also rich in membrane-spanning ion channels that can open in response to membrane stretch (Chen et al., 2018; Jaalouk & Lammerding, 2009). Stretch-activated channels (SACs) include the non-selective cation channels, Piezo1 and Piezo2 (Coste et al., 2010), which open in response to forces generated either internally or external to the cell. For example, changes in membrane tension can originate from internal cytoskeleton-mediated force generation (e.g. cell traction forces; Li & Wang, 2010) or from the ECM microenvironment (Fletcher & Mullins, 2010). SACs conduct calcium (Ca^{2+}) ions and trigger a range of mechanotransduction signalling molecules (Jaalouk & Lammerding, 2009; Vollrath, Kwan, & Corey, 2007). Recent studies have shown that intracellular Ca^{2+} flickers, mediated by Piezo1 channels opening at FA sites, are generated by Myosin-II phosphorylation by MLCK (Ellefsen et al., 2019). If these discrete mechanotransduction episodes were to occur in the small and narrow filopodia located at the tips of growth cones (Song et al., 2019), they may facilitate fast and transient localised signalling events that fine-tune axonal pathfinding or cell migration, for example. SAC activation can also lead to inside-out signalling via neuromodulator release. Recent studies have shown that Piezo1 activation causes the release of adenosine triphosphate (ATP) (Cinar et al., 2015; Miyamoto et al., 2014; Mousawi et al., 2020), nitric oxide (Li et al., 2014) and endothelin-1 (Solis et al., 2019). Therefore, mechanosensors can also indirectly regulate a number of important cellular processes, such as vascular tone (Iring et al., 2019), inflammation (Albarrán-Juárez et al., 2018) and neurotransmitter release (Chen & Grinnell, 1995). Similarly, Piezo1-mediated Ca^{2+} influx can be modulated by several common signalling molecules released into the extracellular spaces, such as sphingosine 1-phosphate (S1P), which fine-tunes the sensitivity of Piezo1 channel gating (Kang et al., 2019). Interestingly, S1P and S1P receptor signalling are known to be involved in axon guidance in the frog optic nerve (Strochlic, Dwivedy, van Horck, Falk, & Holt, 2008). Neurons and glia also express other mechanosensitive channels that open in response to direct forces, such as TRPV4 (upregulated in astrocytes following hypoxic/ischaemic injury) (Butenko et al., 2012), TRPA1 (expressed in layer V pyramidal neurons in the somatosensory cortex) (Kheradpezhouh, Choy, Daria, & Arabzadeh, 2017), TRPC1 (knockout of which abolishes environmental enrichment-induced neurogenesis in the dentate gyrus) (Du et al., 2017), NMDA receptor (channel gating is modulated by hydrostatic and osmotic pressures and deformations in the cell membrane) (Kloda, Martinac, & Adams, 2007; Paoletti & Ascher, 1994) and Ca^{2+}-activated potassium (BK) channels (expressed in the outer layers of the cortex and the perforant path fibres projecting to the hippocampus) (Li et al., 2019; Wanner et al., 1999). Table 1 describes some of the receptors and signalling cascades that may be important in CNS mechanosensation.

Neuronally expressed mechanosensitive ion channels may play fundamental roles in important cognitive processes (Jerusalem et al., 2019). For example, long-term potentiation (LTP) and depression (LTD) of synaptic transmission, the cellular and electrophysiological correlates of memory formation, are dependent on fast (minutes to hours) and long-term (days to years) changes in synapse morphology which are driven by modulation of actin dynamics and cytoskeletal re-arrangements at the level of individual dendritic spines (Bramham et al., 2010; Huang, Chotiner, & Steward, 2007; Lüscher & Malenka, 2012). It is currently unknown whether LTP-mediated changes in dendritic spine morphology or membrane tension/curvature of the synapse are functionally relevant modulators of the mechanosensitivity of the NMDA receptor (Figure 1), which itself is tethered to actin cytoskeletal proteins and neuronal intermediate filaments via the postsynaptic density (PSD) network of anchoring and scaffolding proteins, for example PSD-95, Shank and Homer (Kilinc, 2018; Levy, Omar, & Koleske, 2014; Lüscher & Malenka, 2012). As the brain ages and the lipid composition of the neuronal membrane changes (Ledesma, Martin, & Dotti, 2012), this may alter the mechano-gating

TABLE 1 Mechanosensitive ion channels expressed in the brain

Mechanosensitive receptor	Areas expressed in the brain	Signalling cascades activated	Potential physiological or pathological functions	References
Piezo1	Cortical neurons	Calpain activation	Neuronal apoptosis	Wang, Zhang, et al. (2019)
	Retinal ganglion cells	Ca^{2+} signalling	Axon guidance	Koser et al. (2016)
	Reactive astrocytes	Ca^{2+} signalling	Inhibition of cytokine release	Velasco-Estevez, Rolle, et al. (2020)
	Oligodendrocyte precursor cells	Ca^{2+} signalling	Inhibition of OPC differentiation into mature myelinating oligodendrocytes	Segel et al. (2019)
Piezo2	Cortical and hippocampal pyramidal neurons, cerebellar Purkinje cells and olfactory mitral cells	???	Synchronisation of neural networks by transducing intracranial pressure pulses	Wang and Hamill (2020*pre-print*)
	Astrocytes in the optic nerve head	???	Traumatic injury	Choi, Sun, and Jakobs (2015)
TRPV4	Cortical neurons	Ca^{2+} signalling	Epileptic seizures and neuronal apoptosis	Chen et al. (2016)
	Hippocampal CA1 and CA3 astrocytes and microglia	NLRP3, apoptosis-related spotted protein (ASC) and caspase-1 IL-1β, TNF-α and IL-6 release	Activation enhances neuroinflammation and cell death in pilocarpine-induced model of epilepsy	Wang, Zhou, et al. (2019)
TRPC1	Hippocampal CA1 and CA3 pyramidal neurons	Ca^{2+} signalling and activation of Egr-1, an immediate early gene	LTP and LTD maintenance Spatial working memory	Lepannetier et al. (2018)
TRPA1	Layer V pyramidal cortical neurons	Ca^{2+} signalling	Neuronal depolarisation	Kheradpezhouh et al. (2017)
	Hippocampal astrocytes (upregulated in AD mice)	Ca^{2+} signalling, NF-kB and NFAT transcription	Enhances $A\beta_{42}$-induced neuroinflammation and amyloid plaque deposition	Lee et al. (2016)
NMDA receptor	Hippocampal neurons	Ca^{2+} signalling and activation of Calpain and Caspase-3	TBI and stretch-induced apoptosis	DeRidder et al. (2006)

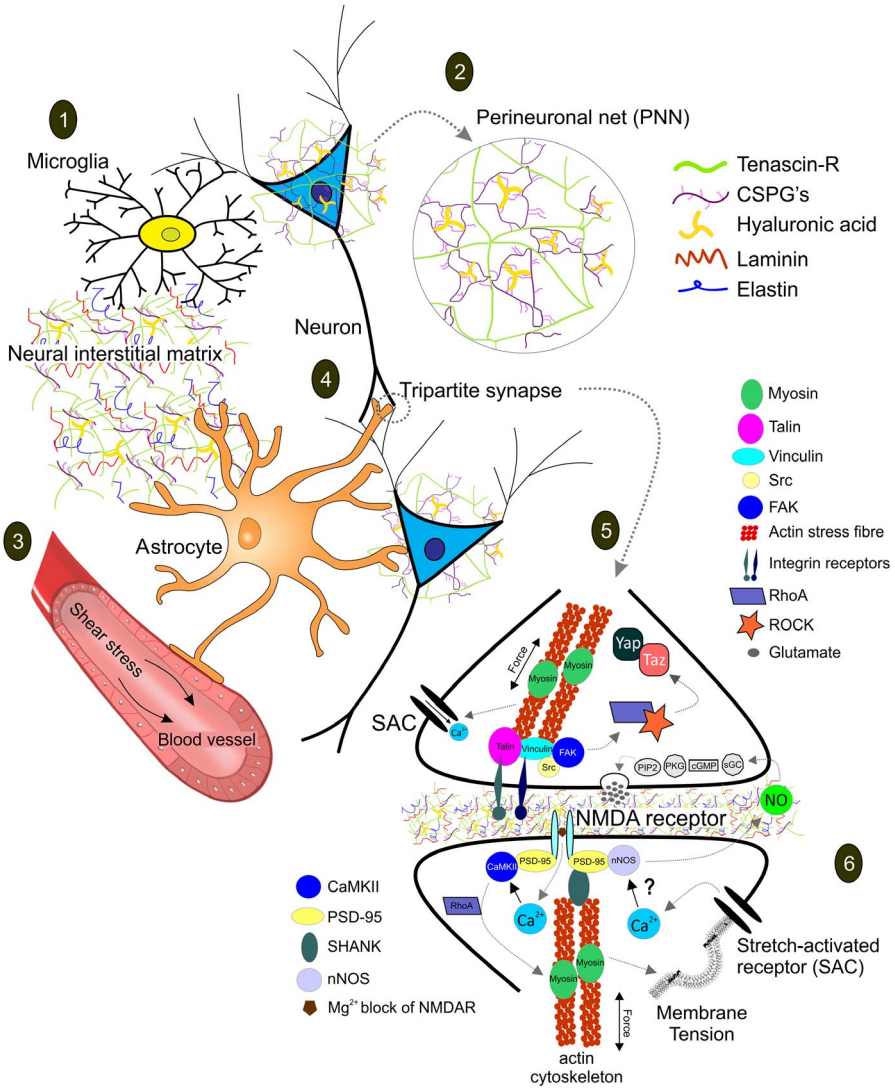
Note: This table gives a brief overview of several ion channels that are expressed in neurons and glia in the brain and have been shown to possess mechanosensitive gating properties. Those listed are mainly cation channels (permeable to Ca^{2+} and Na^{+} ions) and play functional roles in both health and disease/trauma.

of channels, such as the NMDA receptor (Johnson, Battle, & Martinac, 2019).

2.3 | Mechanotransduction and electrophysiology

Interestingly, several studies have shown that the intrinsic electrical properties of neurons can change in response to different mechanical environments (Wen et al., 2018; Zhang et al., 2015). Mouse hippocampal neurons cultured on stiff substrata displayed enhanced voltage-gated Ca^{2+} channel currents compared to neurons on softer substrata (Wen et al., 2018; Zhang et al., 2015). As mechanically gated ion channels, such as Piezo1, conduct calcium and sodium ions (Coste et al., 2012; Nilius, Vriens, Prenen, Droogmans, & Voets, 2004), and channel expression can be altered by substratum stiffness (Chen et al., 2018), it is possible that the mechanical properties of brain tissue could modulate cellular Ca^{2+} levels and tune the electrophysiological properties of neurons (Jerusalem et al., 2019). If so, then altered tissue mechanics may contribute to calcium dysregulations in the ageing or AD brain (Chandran et al., 2019; Kawamoto, Vivar, & Camandola, 2012).

The composition of ECM can also alter neuronal electrophysiology. Mouse hippocampal neurons grown on laminin-coated stiff substratum display larger Ca^{2+} currents than those grown on a fibronectin coating (Wen et al., 2018). It is worth noting that most in vitro neuronal preparations also contain glial cells, and so it is possible that glia also actively sense the mechanical properties of their underlying substrata and relay this information to neurons (Zhang et al., 2015).



In vitro studies consistently report that astrocytes possess a more organised F-actin cytoskeleton and display a flat extended morphology on stiffer materials. In contrast, they exhibit lower adhesion to softer materials and become more spherical in shape (Georges et al., 2006). Ageing also influences astrocyte morphology, and they display larger soma and thicker shorter processes in the brains of elderly humans (Jyothi et al., 2015). Future mechanobiology experiments in the CNS should aim to elucidate the role of astrocytes and other glial cells in communicating mechanobiological information to local neural networks (Blumenthal, Hermanson, Heimrich, & Shastri, 2014).

The studies described above provide some mechanistic insight into how cell and tissue mechanics can influence brain development (Barnes, Przybyla, & Weaver, 2017; Farge, 2011; Guo et al., 2019; Heisenberg & Bellaïche, 2013; Koser et al., 2016; Wozniak & Chen, 2009). In contrast, our current understanding of how the brain's mechanical properties change in old age or in response to neuropathologies like Alzheimer's disease is somewhat limited (Wu, Fannin, Rice, Wang, & Blough, 2011). This is due to some experimental and technical hurdles, for example: (a) the difficulty in modelling the full complexity of human brain ageing or neurodegeneration using animal models that generally do not recapitulate the full range of cellular pathologies observed in human brain disorders (Dawson, Golde, & Lagier-Tourenne, 2018), and (b) the requirement for contact indentation methods when investigating microscale mechanical changes which is currently only possible with in vitro human tissue (Bouchonville et al., 2016), although AFM has been performed in vivo in the embryonic *Xenopus laevis* brain (Thompson et al., 2019). Therefore, we are still a long way from obtaining high-resolution in vivo AFM maps of the mechanical changes that occur in human brain structures during the normal ageing process versus neurodegenerative disease (for a more detailed discussion of AFM studies, see Box 2). Once achieved, the next goal will be to investigate whether age- or disease-related mechanical disturbances impact mechanosensation or mechanotransduction in neurons or glial cells in different brain regions. In the following sections, we summarise what

BOX 2 Atomic Force Microscopy (AFM)

AFM has the ability to measure small, but significant, differences in the mechanical properties of neurons and glial cell types. For example, bipolar and amacrine retinal neurons and hippocampal pyramidal neurons (measured between 480 and 970 Pa) are all twice as stiff as glial cells (Lu et al., 2006). Cortical neurons are slightly softer at ~200 Pa (Spedden, White, Naumova, Kaplan, & Staii, 2012), whilst oligodendrocytes, which form CNS myelin, are ~150 Pa (Jagielska et al., 2012). This has led some to propose that glial cells, in addition to their many other supportive functions, may provide a compliant "shock-absorbing" environment which protects neurons against compressive trauma (Lu et al., 2006). However, the functional implications of these slight differences in cellular mechanics are an area of intensive research. Recent advances in generating high-resolution AFM mechanical maps of distinct subregions of the brain are advancing our understanding of how relative changes in tissue stiffness (in response to ageing, brain trauma and neurodegenerative disease) can impact neuronal and glial cell physiology. To date, however, it has not been possible to conduct AFM indentation tests on humans in vivo as it requires direct physical contact between the indenter and the tissue. However, AFM experiments can extract high-resolution mechanical maps of CNS tissue ex vivo (Figure 2a). For example, in rat hippocampal slices the CA3 stratum radiatum appears to be significantly stiffer than the CA1 and dentate gyrus (Elkin, Azeloglu, Costa, & Morrison, 2007). A variation of the AFM technique, called ferrule-top dynamic indentation, measured cell body-dense regions, such as the granule cell layer of the hippocampal dentate gyrus, as softer than regions with a lower density of cell bodies, such as the stratum radiatum of the CA3 and CA1 and the stratum lacunosum-moleculare (Antonovaite, Beekmans, Hol, Wadman, & Iannuzzi, 2018). Moreover, the surrounding entorhinal cortex was stiffer than hippocampal regions. Therefore, AFM has revolutionised our ability to map relatively small changes in cell and tissue stiffness in different brain regions at the micron-scale, providing a basis for understanding how changes in mechanics and mechanosensitivity can regulate fundamental CNS processes.

FIGURE 1 Schematic diagram showing the key mechanical components of the extracellular matrix (ECM) which surrounds neurons in the brain. (1) The neural interstitial matrix differs from that of the rest of the body and is formed of hyaluronic acid, CSPGs, tenascin-R, elastin and laminin. There is very little collagen in healthy brain ECM (Suttkus et al., 2016), and, when present, it is mostly localised to the basement membrane which surrounds vasculature (Novak & Kaye, 2000). Upon injury or disease, ECM composition can change which is detected by mechanosensitive microglia, astrocytes and neurons. (2) There are specialised regions of ECM in the brain, called perineuronal nets, which form a barrier around certain types of neurons. These are composed of chains of hyaluronic acid and proteoglycans and cross-linked with tenascin-R. There is evidence to suggest that perineuronal nets protect neurons from neurodegeneration (Baig et al., 2005; Miyata et al., 2007; Morawski et al., 2010). (3) Astrocyte endfeet contact blood vessels and can sense blood flow and shear stress (Mishra, 2017). Astrocyte processes also wrap around neuronal synapses and release gliotransmitters that can modulate neurotransmission and synaptic plasticity (Paixão & Klein, 2010). Therefore, changes in astrocytic function due to mechanical perturbations in the brain may impact key neuronal processes (De Luca, Colangelo, Virtuoso, Alberghina, & Papa, 2020). (4) Cell mechanics is also important at the level of individual synapses. F-actin and neurofilaments that compose the cytoskeleton regulate synapse morphology (Konietzny, Bär, & Mikhaylova, 2017). (5) Cytoskeletal filaments are also connected to the ECM via integrin receptors (Shi & Ethell, 2006). Integrins are known regulators of synaptic plasticity and can activate signalling molecules such as FAK, Src and the RhoA/ROCK pathway (Lilja & Ivaska, 2018) which can modulate the activity and nuclear localisation of mechanoresponsive transcriptional co-activators, such as Yap1 (Nardone et al., 2017; Rojek et al., 2019). Integrin-mediated modulation of cytoskeletal processes may also modulate the gating of presynaptic stretch-activated ion channels (SACs) (which facilitate Ca^{2+} influx). This, in turn, could regulate neurotransmitter (e.g. glutamate) release (Hu, An, & Chen, 2015; Kneussel & Wagner, 2013). (6) Neurotransmission and synaptic plasticity can also modulate postsynaptic mechanics through influx of Ca^{2+}, activation of CaMKII and actin remodelling (Khan, Downing, & Molloy, 2019). This may lead to changes in membrane tension and altered mechanosensitivity of NMDA receptors (e.g. unblocking the channel pore of Mg^{2+} ions) or opening of other SACs leading to further Ca^{2+} influx (Kloda, Lua, Hall, Adams, & Martinac, 2007; Kloda, Martinac, et al., 2007). SAC-mediated activation of nNOS and production of nitric oxide (NO) could, in theory, lead to modulation of neurotransmission (Garthwaite, 2008; Song et al., 2019) via presynaptic activation of soluble guanylate cyclase (sGC), production of cyclic GMP, activation of protein kinase G (PKG) and upregulation of phosphatidylinositol 4,5-bisphosphate (PIP2), which ultimately regulates neurotransmitter release probability (Hardingham, Dachtler, & Fox, 2013). This theoretical model which integrates SACs into known plasticity pathways needs confirmation. However, what is known is that both neuronal cell mechanics and pre- and postsynaptic function are intimately linked with the ECM and cell adhesion molecules, as well as signalling molecules that associate with membrane-bound scaffolds and functionally connect the ECM to the cytoskeleton (Lilja & Ivaska, 2018)

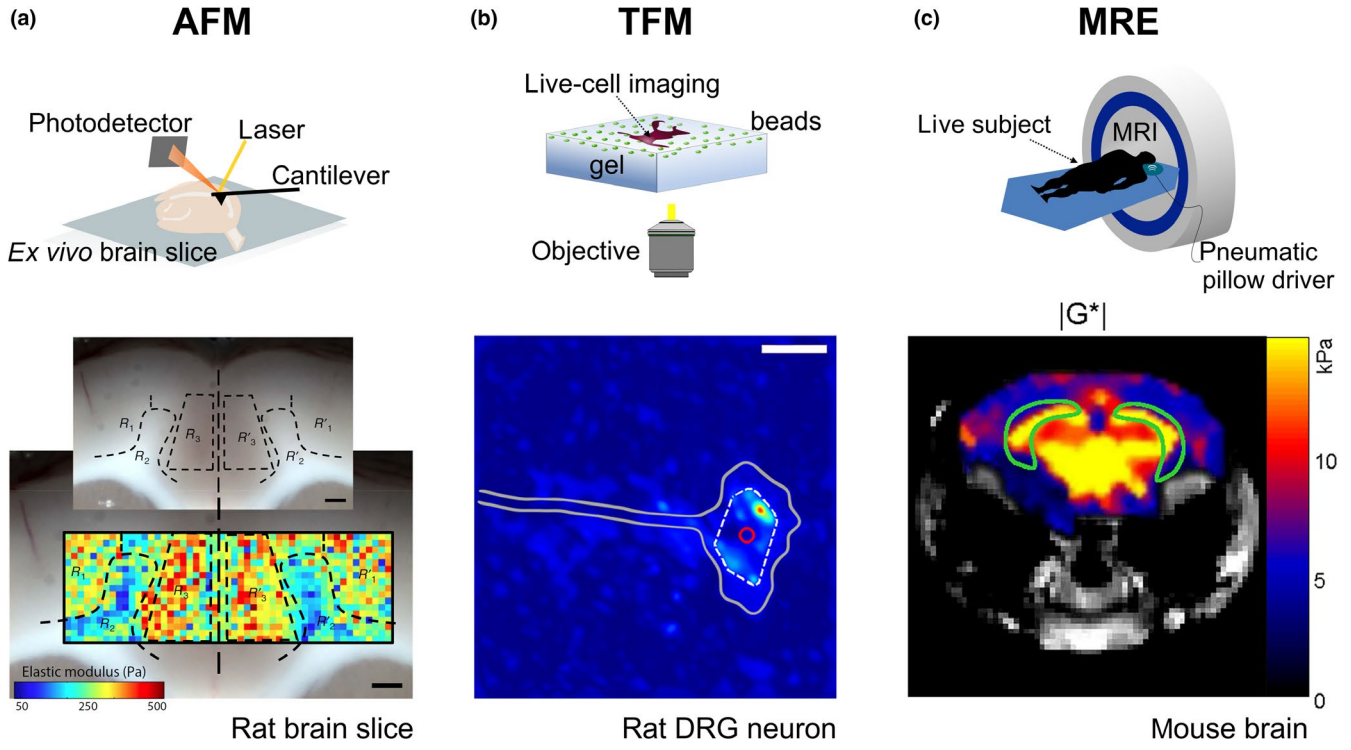


FIGURE 2 Schematic diagram of three different techniques for measuring the mechanical properties of tissue and cells. (a) Stiffness map of the rat cerebral cortex obtained using atomic force microscopy (AFM), image adapted from Moeendarbary et al. (2017). (b) Traction stress field of a primary rat dorsal root ganglion (DRG) growth cone cultured on a soft polyacrylamide hydrogel. Image was obtained using traction force microscopy and adapted from Polackwich, Koch, McAllister, Geller, and Urbach (2015). (c) Elastogram depicting viscoelastic dynamic modulus obtained using magnetic resonance elastography (MRE), image adapted from Klein et al. (2014)

is currently known regarding the mechanobiology of the ageing brain.

3 | THE EXTRACELLULAR MATRIX

3.1 | The ageing ECM

The brain's ECM is composed of perineuronal nets (PNNs) which envelop neurons, the basement membrane which surrounds blood vessels, and the interstitial matrix, as illustrated in Figure 1. In contrast to other connective tissues, the brain's ECM is not abundant in collagen and, when present, collagen is mostly limited to the cerebral vasculature and meninges (Rutka, Apodaca, Stern, & Rosenblum, 1988). Instead, brain ECM is mainly composed of glycosaminoglycans, which can be unbound in the form of hyaluronan (HA), or bound to proteins forming proteoglycans such as chondroitin sulphate proteoglycans (CSPGs) (Ruoslahti, 1996). The basement membrane does contain collagen and is also composed of fibronectin and proteoglycans. PNNs are formed of HA, tenascin-R (a glycoprotein) and CSPGs. The functions of PNNs include the regulation of ion homeostasis, stabilisation of synapses, control of synaptic plasticity and neuroprotection (Suttkus, Morawski, & Arendt, 2016). The cytoskeletons of neurons and glia are connected to the ECM at focal adhesion complexes via transmembrane integrin receptors, which transmit forces (mechanotransduction) from the ECM to the cell's interior and vice versa (Holle et al., 2018). As discussed above, mechanosensitive and Ca^{2+} permeable channels, such as Piezo1, cluster around focal adhesion sites and open in response to traction forces generated by the cytoskeleton of cells (Ellefsen et al., 2019).

The composition, structure and stiffness of brain ECM can regulate neuronal and glial function. Moreover, growth cone mechanosensing, traction force generation (see Box 3), axon guidance, stem cell differentiation and synapse maintenance are regulated by the mechanical properties of the extracellular environment (Betz, Koch, Lu, Franze, & Käs, 2011; Heisenberg & Bellaïche, 2013; Koser et al., 2016). Therefore, changes in the composition and stiffness of the ECM with ageing and neuropathology alter the mechanosensitivity of neurons and glial cells and may contribute to the progression of neurodegenerative disease. Matrix metalloproteinases are increased in neurodegenerative disorders and cause the degradation of ECM proteins, the remodelling of cerebral vasculature, and increase the permeability of the blood–brain barrier (BBB) (Raffetto & Khalil, 2008; Rosenberg, 2009). The BBB is a specialised layer of endothelial cells and

BOX 3 Traction Force Microscopy (TFM)

TFM can be used to measure small (piconewton level) forces exerted by adhered or moving cells and growth cones. This method involves growing and monitoring cells plated on soft gels (ideally elastic hydrogels such as polyacrylamide) with fluorescent microbeads embedded inside (see Figure 2b). By tracking the displacement of each bead, it is possible to calculate the cell-generated force field (Colin-York et al., 2019; Ferrari, 2019). Using this technique, it has been shown that microglia exert higher forces on stiffer substrata and tend to migrate towards regions of higher stiffness (durotaxis) on stiffness gradient gels (Bollmann et al., 2015). TFM also revealed that neuronal growth cones exert stresses in the order of ~30 Pa (where 1 Pa = 1 pN/μm^2) (Betz et al., 2011). Most TFM measurements to date have been obtained via 2D cell culture. We know, however, that cells function very differently in vivo and in 3D cell culture matrices (Watson, Kavanagh, Allenby, & Vassey, 2017). The morphology of astrocytes, for example, is much more "star-like" in 3D cell culture versus the flat and stretched "fried egg" morphology often observed on stiff glass and hard 2D substrata. As cell morphology and function are intimately linked, recent advances that combine live super-resolution microscopy (Colin-York et al., 2019) with 3D TFM (Steinwachs et al., 2016) in native hydrogels will allow us to more precisely approximate how trauma or disease can alter the force-generating capabilities of different types of brain cells in more native 3D microenvironments.

basement membrane that separates the cerebrospinal fluid (CSF) of the brain from the main blood circulatory system. In vitro models of the BBB estimate its stiffness to be ~5 kPa, which presents a significant mechanical barrier to the brain (Reinhart-King, Dembo, & Hammer, 2005; Schrot, Weidenfeller, Schäffer, Robenek, & Galla, 2005). However, the BBB is leaky in Alzheimer's disease and vascular dementia (Erickson & Banks, 2013) and, therefore, it is likely that the mechanical properties of the BBB are also significantly altered by ageing and neurodegeneration.

Extracellular matrix components also play key functional roles in the healthy ageing brain. HA degradation in the hippocampus affects neurogenesis and synapse formation, suggesting a functional link between ECM structure and learning and memory (Yoshino et al., 2018). Healthy ageing does not appear to cause drastic changes in the ECM, but increased expression of HA in the cortex and cerebellum was seen in aged 24-month-old mice compared to young 4-month-old mice (Reed et al., 2018). HA is the major component of PNNs, along with glycoprotein, tenascin-R and CSPGs. Glycosaminoglycan chains sulphated in position 6, which are permissive to axon growth, are decreased in 18-month-old versus 3-month-old rats. This suggests that PNNs in 18-month-old rats are more inhibitory to axon growth than PNNs in 3-month old rats, which may explain why synaptic plasticity is attenuated in the ageing brain (Foscarin, Raha-Chowdhury, Fawcett, & Kwok, 2017).

3.2 | The neurogenic niche

The stiffness of brain ECM also modulates stem cell plasticity. The hippocampal dentate gyrus is a mechanically heterogeneous brain structure. The granule cell layer is approximately twice as stiff as the subgranular zone and hilus (Luque, Kang, Schaffer, & Kumar, 2016). This is noteworthy, as the subgranular zone (neurogenic niche) is highly populated by newborn and immature granule neurons (whilst the hilus is formed of mossy cell types). Interestingly, adult-born neurons mature more slowly in the aged brain versus younger dentate tissue. Is it possible that the speed of neuronal maturation is related to the stiffness of the neurogenic niche? Recent studies have shown that neuronal differentiation, oligodendrocyte maturation and myelin formation are enhanced on soft (<1 kPa) substrata (Leipzig & Shoichet, 2009). Interestingly, the mechanical properties of ECM in the rat cortex, in which oligodendrocyte progenitor cells (OPCs) reside, stiffen with age (Segel et al., 2019). This inhibits OPC proliferation and differentiation (Leipzig & Shoichet, 2009). This is reversible by transplanting aged OPCs into the prefrontal cortex of neonatal rats that possess softer brain tissue or by plating aged OPCs on decellularised neonatal ECM or soft hydrogels in vitro. It is also possible to increase the differentiation and proliferation of aged OPCs by reducing Piezo1 channel expression using short interfering RNA (siRNA) (Segel et al., 2019). This has potential implications for the optimisation of stem cell therapies for the treatment of a range of CNS injuries and demyelinating pathologies. However, a more recent study showed that the neurogenic niche of the subependymal zone of the lateral ventricles is stiffer than non-neurogenic cortical and striatal tissue, with values measured in the range of 50–400 Pa (Kjell et al., 2020). Does this suggest that stem cell migration from the subependymal zone to the olfactory bulb may, in part, be regulated by mechanical cues (durotaxis)? Alternatively, perhaps differentiation of neural stem cells into neurons requires slightly stiffer ECM and astrocytic or OPC maturation may be favoured in softer neonatal ECM (Pathak et al., 2014). We still have much to learn about how the mechanical properties of ECM regulate neural stem cell differentiation into neurons, astrocytes or myelinating oligodendrocytes.

3.3 | The ECM in Alzheimer's disease

In Alzheimer's disease, certain glycosaminoglycans are upregulated around amyloid plaques and neurofibrillary tangles and downregulated in blood vessels in affected brain regions (Bonneh-Barkay & Wiley, 2009). CSPGs are also upregulated around amyloid plaques and neurofibrillary tangles in Alzheimer's disease (DeWitt, Silver, Canning, & Perry, 1993). Expression levels of collagen IV, perlecan (a proteoglycan) and fibronectin are enhanced in the brain as amyloid deposition increases in subclinical AD and AD patients (Lepelletier, Mann, Robinson, Pinteaux, & Boutin, 2017). The plasma concentration of high-molecular-weight fibronectin is also usually greater in AD patients than controls (Lemańska-Perek, Leszek, Krzyzanowska-Gołab, Radzik, & Katnik-Prastowska, 2009), suggesting that fibronectin may be a by-product of the disease. Moreover, the PNNs that surround neurons (e.g. GABAergic parvalbumin-positive neurons) and astrocytic processes are thought to be neuroprotective (Miyata, Nishimura, & Nakashima, 2007; Morawski, Brückner, Jäger, Seeger, & Arendt, 2010). In AD patients, there is a significant reduction in PNNs surrounding GABAergic parvalbumin-positive neurons in the cortex (Baig, Wilcock, & Love, 2005) and a distinct absence of colocalisation between PNNs and phosphorylated tau (Miyata et al., 2007; Morawski et al., 2010). Notably, dopaminergic neurons in the substantia nigra pars compacta, which degenerate in Parkinson's disease, are not ensheathed by PNNs (Brückner, Morawski, & Arendt, 2008). In vitro, primary neurons ensheathed by PNNs were protected from Aβ toxicity, whilst neurons without PNNs were susceptible to degeneration (Miyata et al., 2007). Tau distribution is more widespread in organotypic slice cultures prepared from knockout mice deficient in the PNN components, tenascin-R and the hyaluronan and proteoglycan link protein (HAPLN1) (Suttkus et al., 2016). Moreover, in the early stages of tau hyperphosphorylation and microtubule breakdown, there is a redistribution of hyaluronan synthase 1 (Has1) from axons to cell bodies (Li, Li, Jin, Wang, & Zhao, 2017). Taken together, age- and AD-associated changes in the composition of ECM, and loss of protective PNNs surrounding neurons, may exacerbate neuronal loss and alter brain tissue mechanics.

4 | MECHANOBIOLOGY OF THE BRAIN

4.1 | MRE measurements of the ageing brain

Oscillatory rotational shear tests on different regions of post-mortem human brain tissue indicate that the adult brain is 3–4 times stiffer than infant brain tissue (Chatelin, Vappou, Roth, Raul, & Willinger, 2012). However, studies that investigate the mechanical properties of the aged brain are hampered by the fact that ex vivo tissue is no longer perfused with blood and CSF (Goriely et al., 2015; Guo et al., 2018). Ageing has detrimental effects on the glymphatic system, and the exchange of CSF and interstitial fluid is impaired in old mice. Moreover, disrupted interstitial solute clearance impacts glial cell functioning and BBB integrity and exacerbates neurovascular disease (Kress et al., 2014; Simon & Iliff, 2016). Characterisation of the mechanical properties of the brain of healthy aged volunteers in vivo using MRE (see Box 4) revealed that the viscoelasticity of brain tissue decreases ~0.75% per year and brain volume decreases at a rate of ~0.23% per year (Sack et al., 2009). Therefore, tissue atrophy may contribute to age-related decreases in brain stiffness (Sack, Streitberger, Krefting, Paul, & Braun, 2011). Moreover, as the viscoelastic modulus decreases with age, but the geometry and structure of brain tissue remains relatively constant, the softening appears to be caused by a solid–fluid phase transition, termed "tissue liquefaction" (Sack et al., 2009). MRE on adults aged 56–89 years, who showed no signs of elevated amyloid burden, suggests that the stiffness of the cerebrum decreases by 11 Pa per year (Arani et al., 2015). Age-related softening is region-dependent, with sub-cortical brain structures softening more rapidly than the cerebral cortex (Sack et al., 2011). In adolescents, however, all sub-cortical structures, except for the hippocampus, are significantly stiffer than the cerebrum (McIlvain, Schwarb, Cohen, Telzer, & Johnson, 2018). Correcting for the volume of each region of interest, the stiffness of the total cerebrum, including all sub-cortical structures (with the exception of the hippocampus), decreases with age (Hiscox et al., 2018). This suggests that the hippocampus displays a higher resistance to mechanical changes compared to the other brain regions.

Regional heterogeneity in brain tissue stiffness may be explained by differences in cytoarchitecture and the ratio of white matter to grey matter (Johnson et al., 2013). MRE studies have found that white matter-rich areas of the brain are stiffer than grey matter (Kruse et al., 2008; McCracken, Manduca, Felmlee, & Ehman, 2005), although some studies find no statistically significant differences (Zhang, Green, Sinkus, & Bilston, 2011) or the inverse relationship (Green, Bilston, & Sinkus, 2008). The elasticity values reported for MRE are, however, well outside the range measured using AFM and are likely subject to strain differences (Franze, Janmey, & Guck, 2013). The elastic moduli values of white matter versus grey matter measured in different studies are displayed in the semi-log plot in Figure 3. The variation in stiffness measurements is likely due to different length and time scales associated with each measurement technique, variations in the size and type of probe used, different methods of sample preparation, the animal

BOX 4 Magnetic resonance elastography (MRE)

MRE is a non-invasive and non-contact method to measure the viscoelasticity of brain tissue in live human volunteers and has been extremely useful in advancing our limited knowledge of the mechanical properties of the human brain (Mariappan, Glaser, & Ehman, 2010). Briefly, MRE involves generating shear waves of specific frequencies that travel through brain tissue whilst the subject lies inside a magnetic resonance imaging (MRI) scanner (Figure 2c). Whilst the brain is exposed to oscillatory shear waves, MRI images are captured and converted to elastograms which display the viscoelastic properties of the distinct brain regions. A major limiting factor of MRE elastograms is their spatial resolution (1–2 mm), as shear waves must propagate through an entire plane of the brain (Fehlner et al., 2017). The brain has a complex inhomogenous cytoarchitecture, and factors such as cell body density (Thompson et al., 2019), myelination, axonal orientation (Koser, Moeendarbary, Hanne, Kuerten, & Franze, 2015) and ECM composition (Kjell et al., 2020) contribute to the mechanical heterogeneity of different brain regions. Therefore, the direction of shear wave propagation through brain tissue and the spatial resolution of MRI could significantly influence the stiffness values estimated by MRE. If inhomogeneity of brain tissue is factored in, the elastogram calculations require accurate modelling of boundary conditions (Yin, Romano, Manduca, Ehman, & Huston, 2018). Therefore, measuring the stiffness of small or sub-cortical brain regions, such as the hippocampus or thalamus, has been difficult until more recently. The incorporation of high spatial resolution MRE with corrections to accurately define sub-cortical regions has shown variations in damping ratio and shear modulus of sub-cortical grey matter regions in healthy human adults (Hiscox et al., 2018; Johnson et al., 2016). This suggests that even regions with similar cell compositions display different mechanical properties. Experiments combined with computational simulations that consider the compression-tension asymmetry of the human brain, using a modified Ogden model, calculate shear modulus values ranging between 300 and 700 Pa (Budday et al., 2017). This is within the range measured by AFM of ex vivo mammalian brain slices, suggesting that the Ogden model may be a better fit for MRE experiments.

species being investigated and whether measurements were performed in vivo or ex vivo. This range of experimental variables is illustrated in Figure 4, with further details provided in Table S1. Recent developments in the field may help to standardise protocols and ensure that results are repeatable between laboratories using different measurement tools (Budday, Ovaert, Holzapfel, Steinmann, & Kuhl, 2019).

4.2 | AFM indentation measurements

To limit the effects of cell death on ex vivo tissue elasticity calculations, human brain samples should be measured quickly (1–2 hr) after excision (Chatelin et al., 2012). However, there may be some flexibility if tissue is kept under optimal physiological conditions as AFM experiments performed on mammalian brain slices show no significant changes in tissue stiffness within 6 hr of death (Christ et al., 2010; Garo, Hrapko, van Dommelen, & Peters, 2007; Shulyakov, Fernando, Cenkowski, & Del Bigio, 2009). Moreover, AFM indentation studies on ex vivo brain tissue found no significant differences in the elasticity of the cortex or hippocampus of 18-month-old mice compared to 2-month-old mice (Jorba et al., 2017). However, the cerebellum of 2-month-old mice was measured as significantly softer than the cortex. This could be due to a higher white matter content or a larger proportion of small granule neurons in the cerebellum versus the cortex. Several other AFM studies have also reported stiffness heterogeneity within the CNS, the most notable observation being that grey matter is twice as stiff as white matter (Christ et al., 2010; Koser et al., 2015). For example, in SJL mouse spinal cord the apparent elastic modulus of grey matter and white matter was 159 ± 26 Pa and 60 ± 7 Pa, respectively (Koser, Moeendarbary, Kuerten, & Franze, 2018), which is similar to measurements in C57Bl/6 mice (123 ± 9 Pa for grey matter vs. 55 ± 9 Pa for white matter) (Koser et al., 2015). In contrast, bovine brain tissue stiffness positively correlates with myelin content. Macroscale indentation tests performed on fresh bovine brain slices recorded the stiffness of white matter as 1.33 ± 0.63 kPa, and grey matter was measured as 0.68 ± 0.2 kPa (Weickenmeier, De Rooij, Budday, Ovaert, & Kuhl, 2017). Interestingly, demyelination of embryonic chick spinal cord significantly reduces the stiffness and tensile stress of the spinal cord compared to myelinated (uninjured) neural tissue (Shreiber, Hao, & Elias, 2009). Given that different studies have found opposing results for grey and white matter tissue mechanics (Figure 3) (Bartlett, Choi, & Phillips, 2016), it will be important to try to resolve these discrepancies at various length scales (Ayad, Kaushik, & Weaver, 2019) and to develop models that can correlate AFM and MRE measurements. This will benefit clinicians interested in diagnosing

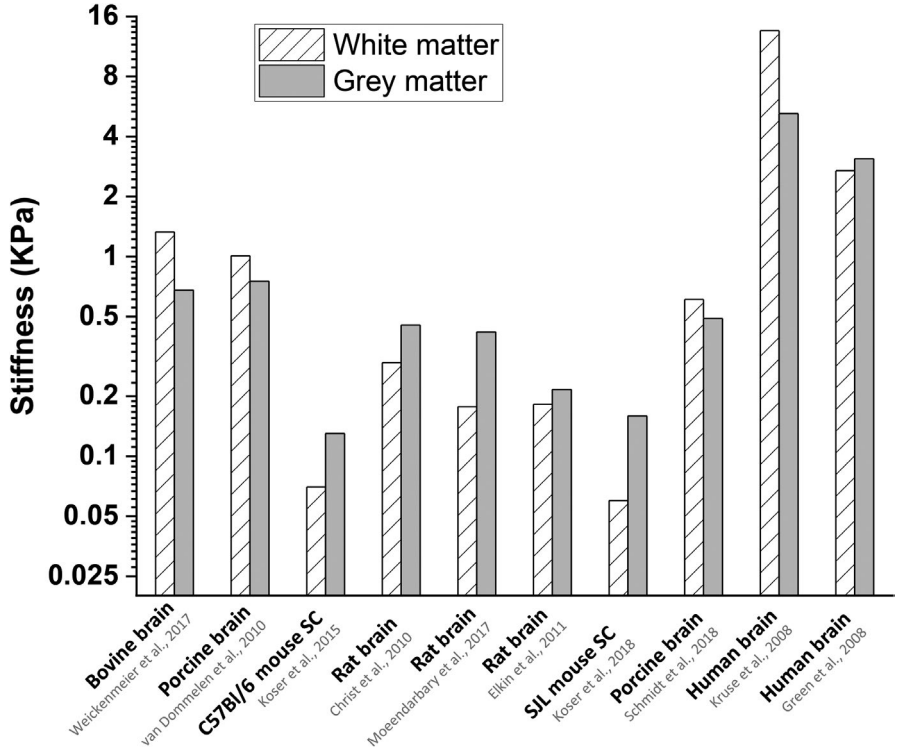


FIGURE 3 Graphed are the wide-ranging stiffness values obtained for CNS white matter (WM) and grey matter (GM) using various mechanical measurement techniques. Displayed are the stiffness measurements (in kPa) for brain or spinal cord (SC) WM and GM tissue obtained from experiments conducted in mouse, rat, human, cow or pig using a range of indentation or indirect elastography techniques. Most AFM studies find that white matter is softer than grey matter, whilst the MRE studies find the opposite relationship. These values are taken from the studies Weickenmeier et al., 2017; van Dommelen, van der Sande, Hrapko, & Peters, 2010; Koser et al., 2015; Christ et al., 2010; Moeendarbary et al., 2017; Elkin, Ilankovan, & Morrison, 2011; Koser et al., 2018; Schmidt et al., 2018; and Kruse et al., 2008. Further experimental details can be found in Table S1

and treating patients with various neurological disorders and neurophysiologists interested in understanding the functional and biological relevance of changes in brain tissue stiffness with age or disease.

4.3 | Cerebellar mechanics

Cerebellar pathology is often disregarded when attempting to clinically diagnose neurodegenerative conditions, especially in the absence of ataxia as a symptom (Liang & Carlson, 2019). One recent study aimed to identify cerebellar atrophy in seven different neurodegenerative conditions (i.e. Alzheimer's disease, Parkinson's disease, Huntington's disease, frontotemporal dementia, amyotrophic lateral sclerosis, multiple system atrophy and progressive supranuclear palsy) (Gellersen et al., 2017). Notably, their meta-analysis did not reveal consistent cerebellar atrophy in patients with Parkinson's disease (PD) or Huntington's disease (HD). They note that this may be due to the high clinical variability in PD and HD samples. The most affected cerebellar regions across all diseases were Crus I and Crus II, but overall, different patterns of atrophy were observed. This suggests that cerebellar grey matter loss is disease-specific and not due to regional susceptibility to neurodegeneration. There is limited evidence of cerebellar pathology in AD, and there is no clear link suggesting an age-dependent loss of integrity or function (Liang & Carlson, 2019). However, diseases such as frontotemporal dementia and chronic traumatic encephalopathy (CTE) do show age-dependent loss of tissue integrity and function in the cerebellum. The stiffness of the mouse cerebellum, measured using microindentation and AFM, is less than half that of the cerebral cortex (Jorba et al., 2017; MacManus, Pierrat, Murphy, & Gilchrist, 2015), potentially reflecting extensive myelination of Purkinje axons in the arbour vitae regions of the cerebellar lobules. MRE studies also reported the cerebellum to be significantly softer than that of the cerebrum (Arani et al., 2015; McIlvain et al., 2018; Millward et al., 2015; Zhang et al., 2011). Interestingly, cerebellar stiffness does not vary significantly with age (Arani et al., 2015). This is noteworthy, as further investigation into the mechanical properties and apparent resilience of the cerebellum may provide insight and uncover potential new drug targets for cortical or hippocampal degeneration.

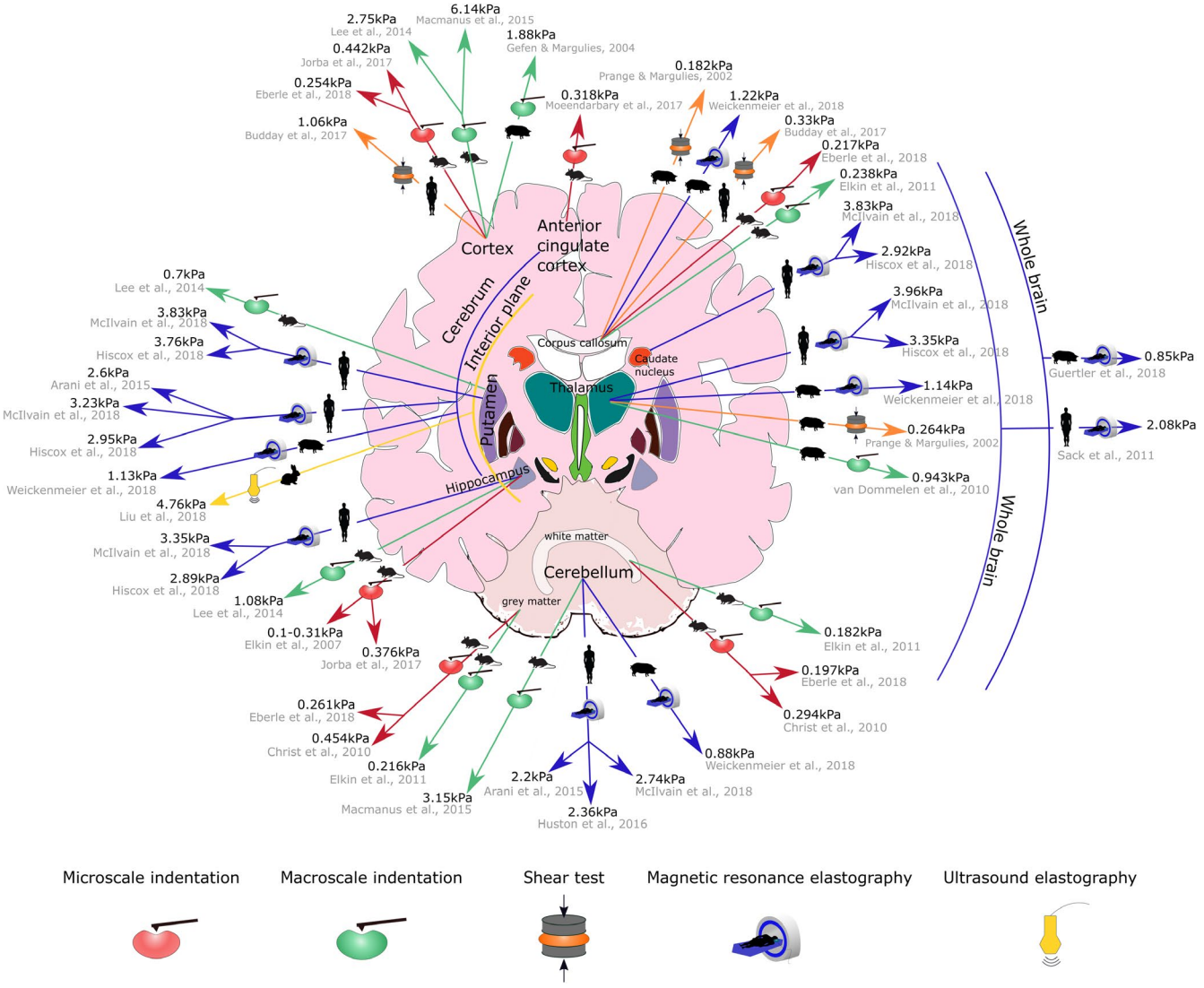


FIGURE 4 Schematic diagram showing stiffness measurements for various regions of the mammalian brain. All values are from experiments on living tissue (in vivo or ex vivo) and are expressed in kPa. The elastic modulus value is either the Young's modulus, shear modulus or storage modulus, that is the ratio of stress to strain of brain regions. Stiffness measurements from different healthy adult mammalian species (human, porcine, rabbit and rodent) are depicted by the black silhouette images. Arrows emanating from brain regions are colour-coded according to the method used to measure brain stiffness. Red, microindentation methods such as atomic force microscopy; green, macroindentation methods; orange, shear tests; blue, magnetic resonance elastography; and yellow, ultrasound elastography. A methods key is provided below, and the corresponding symbol is used for clarity. The data for this figure come from the studies Arani et al., 2015; Budday et al., 2017; Christ et al., 2010; Eberle et al., 2018; Elkin et al., 2007; Elkin et al., 2011; Gefen & Margulies, 2004; Guertler et al., 2018; Hiscox et al., 2018; Huston et al., 2016; Jorba et al., 2017; Lee et al., 2014; Liu et al., 2018; MacManus et al., 2015; McIlvain et al., 2018; Moeendarbary et al., 2017; Prange & Margulies, 2002; Sack et al., 2011; van Dommelen et al., 2010; and Weickenmeier et al., 2018. Additional experimental details can be found in Table S1. From this diagram, it is clear that measured stiffness values of adult mammalian brain vary considerably. Whilst some of this is undoubtedly due to differences in species and the experimental method used, there are occasions when studies using the same method on the same species still report different stiffness values. As discussed in the main text, standardising experimental protocols will perhaps increase the repeatability across studies

5 | TRAUMATIC BRAIN INJURY (TBI) AND CYTOSKELETAL MECHANICS

There is now strong evidence linking TBI to dementia, especially when the head trauma occurs in later life (Fann et al., 2018; Gardner et al., 2014, 2015, 2018). Severe and recurrent head injuries cause mechanical damage to brain cells and can trigger pathophysiological cascades that lead to CTE (McKee, Stein, Kiernan, & Alvarez, 2015). Several forms of dementia, including CTE, involve the gradual and chronic hyperphosphorylation, misfolding and missorting of

microtubule-associated protein, *tau*. When tau is phosphorylated, it detaches from microtubules at the axon initial segment and breaks down the barrier that normally prevents retrograde flow of axonal tau (Hatch, Wei, Xia, & Götz, 2017; Li et al., 2011). This may cause the neuron to become stiffer due to accumulation of tau in the somatodendritic compartment (Hagestedt, Lichtenberg, Wille, Mandelkow, & Mandelkow, 1989; Zempel et al., 2017). Therefore, hyperphosphorylation of tau causes intrinsic mechanical disturbances in damaged neurons.

Microtubules are a major component of the neuronal cytoskeleton. AFM studies in which the microtubules, microfilaments (F-actin) and neurofilaments had been pharmacologically disrupted found that microtubules are the largest contributor to axonal stiffness (Ouyang, Nauman, & Shi, 2013). They contribute to the intrinsic mechanical properties and structural integrity of the cell and influence its mechanical behaviour (Kapitein & Hoogenraad, 2015). The actin component of the cytoskeleton is also an important link between cell mechanics and neurophysiology (Kilinc, 2018). F-actin polymerisation increases with ageing and may lead to a decrease in membrane fluidity (i.e. increased membrane rigidity) which can modulate ion channel properties (Garcia & Miller, 2011; Phillip, Aifuwa, Walston, & Wirtz, 2015; Yuan, O'Connell, Jacob, Mason, & Treistman, 2007). Therefore, age- or trauma-related perturbations to the intrinsic mechanical properties of neurons or their surrounding ECM may trigger changes in parameters such as neuronal excitability, spontaneous firing rates, basal calcium levels or the frequency of spontaneous Ca^{2+} transients (Matute, 2010; Sheng, Leshchyns'ka, & Sytnyk, 2013; Sheridan, Moeendarbary, Pickering, O'Connor, & Murphy, 2014; Sohn et al., 2019; Yang et al., 2019; Yu, Chang, & Tan, 2009; Zhang et al., 2015). A better understanding of how cytoskeletal and lipid membrane mechanics are linked to the intrinsic electrophysiological properties of neurons will be key to fully comprehend the aetiology of cognitive decline and dementia in old age (Rizzo, Richman, & Puthanveettil, 2014).

In rats, tau phosphorylation decreases with healthy ageing (Watanabe et al., 1993), but increases with age in humans (Braak, Thal, Ghebremedhin, & Del Tredici, 2011). Primary age-related tauopathy (PART) is characterised by the accumulation of neurofibrillary tangles in the absence of amyloid plaque pathology (Crary et al., 2014). Aggregation of abnormally phosphorylated tau protein in astrocytes is also relatively common in older humans, a condition known as "ageing-related tau astrogliopathy" (ARTAG) (Kovacs et al., 2016). Interestingly, depending on the brain regions affected, individuals that present with either PART or ARTAG usually display only mild or undetectable cognitive impairment. This suggests that ageing neurons and glia may tolerate a certain degree of mechanical stress. However, more severe breakdown in axonal transport machinery occurs in neurodegenerative and neuroinflammatory disorders such as Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis (Li et al., 2011; Millecamps & Julien, 2013; Sorbara et al., 2014). Because axonal transport is dependent on a normal functioning cytoskeleton, marked changes in the stiffness of neurons may be a useful and novel biomarker of neurodegenerative disease (Nötzel et al., 2018). Moreover, a deeper comprehension of how distinct neuropathologies impact the intrinsic mechanical properties of neurons and glia will help to identify novel molecular targets for treating the symptoms of dementia in older individuals.

6 | MECHANOBIOLOGY OF ALZHEIMER'S DISEASE

6.1 | Amyloid plaques

Neurodegenerative disorders, such as Alzheimer's disease, are likely to cause more severe perturbations to brain mechanobiology than "normal" ageing. The major neuropathological hallmarks of AD include severe cortical and hippocampal atrophy, reduced glucose metabolism in temporoparietal regions, formation of neurofibrillary tangles of hyperphosphorylated tau and the deposition of extracellular amyloid plaques (Dubois et al., 2010; Fox et al., 1996). Amyloid plaques are formed of a dense core and surrounded by diffuse oligomeric fibrils (Dickson & Vickers, 2001). Interestingly, longer fibrils fold into a more disorganised plaque, allowing for more bending in response to indentation. Using a computational simulation, the contact moduli of plaques formed of 50, 100 and 200 nm amyloid fibrils are approximately 3.26 GPa (i.e. GPa = 10^9 Pascal), 1.88 and 0.67 GPa, respectively (Paparcone, Cranford, & Buehler, 2011). Other studies have used Brillouin microscopy, high-pressure X-ray diffraction and image analysis of electron micrographs and found that the Young's modulus of amyloid fibrils lies within the GPa range (Knowles & Buehler, 2011; Mattana, Caponi, Tamagnini, Fioretto, & Palombo, 2017). This indicates that amyloid plaques are far stiffer than surrounding brain tissue. On the oligomeric scale, AFM has been used to investigate the effects of $A\beta_{40}$ and $A\beta_{42}$ on neuronal membrane stiffness. Primary hippocampal neurons were stressed in vitro using cell culture medium lacking antioxidants and trophic factors, which resulted in "accelerated ageing" of the 21-day-old rat neurons (measured as an increase in lipofuscin levels) (Ungureanu et al., 2016). The Young's modulus of these neurons was significantly reduced after one-hour incubation with 10 μM $A\beta_{40}$ and $A\beta_{42}$. This was also true of 21-day in vitro (DIV) neurons cultured under standard conditions, but only after incubation with 10 μM $A\beta_{42}$. However, the opposite effect was observed in the mouse neuronal cell lines, N2a and

HT22; that is, $A\beta_{42}$ exposure increased membrane stiffness (Lulevich, Zimmer, Hong, Jin, & Liu, 2010). Whilst these discrepancies may reflect different cell sources (primary tissue versus cell lines), it is also possible that the higher forces used in the latter study led to strain-dependent stiffening effects. This occurs in nonlinear materials such as mammalian brain tissue, wherein higher forces cause more cross links in polymer chains and result in a higher measured stiffness.

The structure of $A\beta_{42}$ is similar to the fusion domain of the virus influenza hemagglutinin (Crescenzi et al., 2002). $A\beta_{42}$-mediated neurotoxicity may, in part, be explained by the formation of membrane pores (Ambroggio et al., 2005; Arispe, Pollard, & Rojas, 1993; Lee et al., 2017; Poojari, Kukol, & Strodel, 2013; Quist et al., 2005; Sciacca et al., 2012; Valincius et al., 2008), which could also explain how $A\beta_{42}$ reduces membrane stiffness so rapidly (Kim & Frangos, 2008). Non-amyloid peptides do not interact with membranes in this way (Quist et al., 2005). In addition, $A\beta_{42}$ causes dysregulations to calcium-mediated homeostatic processes, induces oxidative stress and alters the biophysical properties of cell membranes (for review see Yang, Askarova, & Lee, 2010). Therefore, novel methods to interfere with the physical interaction of $A\beta_{42}$ and neuronal and glial cell membranes could help to slow down its neurotoxic actions in Alzheimer's disease. We have recently shown in a transgenic rat model of AD that astrocytes surrounding amyloid plaques upregulate mechanosensitive Piezo1 cation channels (Velasco-Estevez et al., 2018). The function of this upregulation in mechanosensitive channels is as yet unknown. Our recent data suggest that Piezo1 may play a role in neuroinflammation as pharmacological activation of Piezo1 in reactive mouse astrocytes in vitro causes extracellular Ca^{2+} influx and Ca^{2+} release from internal stores and suppresses the secretion of pro-inflammatory cytokines (Velasco-Estevez, Rolle, Mampay, Dev, & Sheridan, 2020). Upregulation of astrocytic Piezo1 also suggests that glial cells may sense stiff plaques and adjust mechanotransduction-associated signalling cascades induced by changes in their surrounding mechanical microenvironment. Whether this re-tuning of cellular mechanosensation is harmful or beneficial in the AD brain is yet to be determined.

6.2 | Neurofibrillary tangles

Intracellular neurofibrillary tangles formed of hyperphosphorylated tau protein are also present in the Alzheimer's disease brain and are a better predictor of cognitive dysfunction than amyloid plaques (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Nagy et al., 1995; Wilcock & Esiri, 1982). Interestingly, tau protein becomes stiff upon phosphorylation (Hagestedt et al., 1989). Tangles disrupt the microtubule cytoskeleton of neurons, altering their morphology, connectivity and the intrinsic mechanical properties of axons which, in turn, likely contributes to the perturbed synaptic plasticity associated with Alzheimer's disease (Palop & Mucke, 2010; Shankar et al., 2008). Microtubules in the axon initial segment are highly dynamic in healthy neurons but become less so when exposed to amyloid-β. This results in reduced F-actin remodelling (Zempel et al., 2017) and tau missorting. Recently, a specific tau mutation observed in frontotemporal dementia was shown to impair activity-dependent plasticity of the cytoskeleton in the axon initial segment. This coincided with neuronal hyperactivity in response to chronic depolarisation (Sohn et al., 2019). This study elegantly shows how cytoskeletal perturbations, caused by disease, lead to altered neuronal function.

6.3 | Tissue mechanics in Alzheimer's disease

Despite microscopic structural changes caused by NFTs and amyloid plaques, there is no obvious direct relationship between amyloid load or neurofibrillary tangle density and the macroscale changes in brain tissue stiffness that occurs in Alzheimer's disease. However, there is a positive correlation between increasing amyloid load and reduced brain stiffness in mild cognitive impairment (Murphy et al., 2016). Overall, MRE measurements in AD patients show a decrease in brain stiffness compared to healthy controls (Hiscox et al., 2020; Levy Nogueira et al., 2016; Murphy et al., 2011, 2016). Moreover, intracranial pressure, resulting from fluid–solid interactions between cerebral microvasculature, brain parenchyma and the CSF, can be as much as 42% higher in Alzheimer's disease patients compared to healthy age-matched adults (Levy Nogueira et al., 2016). Factors such as a decrease in the neuron-to-glial cell ratio may also contribute to the overall softening of Alzheimer's disease brains, at least on the macroscale of MRE elastograms.

MRE in transgenic APP23 mice suggests that hippocampal viscosity, elasticity and cell numbers are reduced compared to controls (Munder et al., 2018). This supports the observation in the embryonic brain of frogs that cell body density positively correlates with tissue stiffness (Koser et al., 2016), although contrasts with a more recent study in the mouse hippocampus (Antonovaite et al., 2018). In a different transgenic AD mouse model, AFM measurements showed that cortical stiffness was also reduced compared to wild-type controls (Menal et al., 2018). The cell loss that occurs in neurodegenerative diseases may explain the global decreases in tissue stiffness measured. That said, the elasticity of the hippocampus increases with the number of Aβ-positive cells, but only in animals housed under environmentally enriched conditions (Munder et al., 2018). This suggests that internalisation of Aβ may enhance cellular elasticity and this

may be more noticeable in environmentally enriched animals due to the enhanced survival of both aged and adult-born hippocampal cells. Indeed, hippocampal viscoelasticity also positively correlates with aerobic fitness (Schwarb et al., 2017) and higher levels of exercise correlate with increased neurogenesis (Brown et al., 2003; Holmes, Galea, Mistlberger, & Kempermann, 2004). Therefore, moderate exercise and staying physically fit and active into old age, lifestyle interventions that are known to promote neurogenesis in the hippocampus, could potentially rescue at least some of the decreases in brain tissue stiffness that occur in old age and in people with dementia.

7 | GLIAL CELL MECHANICS

7.1 | Reactive astrocytes and glial scarring

The role of glia in the mechanobiological signature of specific disorders often seems contradictory, and several studies have now shown differences between acute injury, chronic scarring and inherited disturbances in glial morphology. A recent study that used a mouse model of Alexander disease in which the astrocytic gene, glial fibrillary acidic protein (GFAP), has a gain-of-function mutation, showed that there was enhanced F-actin formation and an approximate 30% increase in brain tissue stiffness (Wang etal.,2018). Moreover, at the cellular scale, Müller glial cells damaged by ischaemia–reperfusion injury show elevated expression of vimentin and GFAP and a corresponding increase in elastic modulus (Lu etal.,2011). We have shown, however, that gliosis markers such as vimentin and GFAP, in addition to the ECM components laminin and collagen IV, are positively correlated with softening of cerebral cortical tissue following a sterile stab injury (Moeendarbary etal.,2017). In this study, we mapped the mechanical properties of rat glial scar tissue using AFM indentation and showed it to be softer than healthy cortical brain tissue (Moeendarbary etal.,2017). Glial scars form gradually as a result of CNS injury and are composed of reactive astrocytes, microglia, basement membrane and blood-derived immune cells. The softening of CNS tissue may be detrimental to neuronal regeneration and repair, as axonal growth is faster and more directional on stiff (~10kPa) than very soft (~100Pa) substratum (Koser etal.,2016). However, the exact function of the glial scar in aiding or hindering axonal repair after damage is unknown. It is also possible that the soft mechanical nature of the glial scar is beneficial in promoting healing after injury, by creating a softer microenvironment which may promote neurogenesis, OPC differentiation and remyelination (Keung, Dong, Schaffer, & Kumar,2013; Saha etal.,2008; Teixeira etal.,2009). The glial scar may also encourage microglial activation, as microglia become more amoeboid on softer substrata (Bollmann etal.,2015) and, as a consequence, may be more effective in clearing debris (Neumann, Kotter, & Franklin,2009). Elegant studies have argued that the glial scar does not inhibit regeneration of neurons as ablation of the glial scar after tissue injury hinders axonal regeneration and, in fact, can worsen functional recovery (Anderson etal.,2016). Astrocytes and proteoglycans, key components of the glial scar (Rolls, Shechter, & Schwartz,2009), are also associated with neurogenesis (Gates etal.,1995; Ida etal.,2006; Ma, Ming, & Song,2005). However, evidence suggests that the chronic overexpression of molecules secreted by the glial scar inhibit differentiation and neuronal maturation, which would ultimately hinder functional recovery from injury (Fitch & Silver,2008; Sofroniew,2009).

7.2 | Demyelination

In addition to neuronal damage, recurrent head traumas are often accompanied by demyelination of axons (Mamere, Saraiva, Matos, Carneiro, & Santos, 2009). White matter damage reduces action potential conduction velocity and exacerbates neurodegeneration (Leviton & Gressens, 2007; Nashmi & Fehlings, 2001), thus increasing the likelihood of irreversible loss of neurons. However, the functional consequences of demyelination on neuronal cell mechanics are still largely unknown (Heredia, Bui, Suter, Young, & Schäffer, 2007). Myelination and different forms of myelin damage can exert a range of effects on CNS tissue mechanics; in some cases causing increased tissue stiffness and in others tissue softening (Eberle et al., 2018; Urbanski, Brendel, & Melendez-Vasquez, 2019; Weickenmeier et al., 2017). Traumatic CNS injury also induces changes in the extracellular matrix (e.g. CSPGs) which can inhibit remyelination of the injured area (Lau, Cua, Keough, Haylock-Jacobs, & Yong, 2013). Moreover, chemical (cuprizone) demyelination in mice leads to the accumulation of glycosaminoglycans, mucopolysaccharides and fibronectin in the brain, as well as a decrease in corpus callosum viscoelasticity measured by MRE (Schregel et al., 2012). Interestingly, recent AFM evidence also suggests that acute cuprizone-induced demyelination leads to corpus callosum tissue softening. However, this effect was not measured in the shiverer mouse model of inherited hypomyelination (Eberle et al., 2018). Shiverer mice possess an autosomal recessive loss-of-function mutation in the myelin basic protein gene. Acquired neuroinflammatory disorders in humans, such as multiple sclerosis, display an accumulation of laminin, hyaluronic acid and matrix metalloproteinase-19 within the core of demyelinating CNS lesions (Bonneh-Barkay & Wiley, 2009). Moreover, astrocytes in chronically demyelinated lesions secrete a high-molecular-weight HA which prevents the maturation of OPCs, thereby preventing remyelination (Back et al., 2005). We have recently shown

that demyelination of organotypic mouse brain slices (using the cytotoxic sphingolipid, psychosine) can be attenuated by inhibition of mechanosensitive ion channels with the blocking peptide, GsMTx4 (Velasco-Estevez, Gadalla, et al., 2020). In the absence of any cytotoxic chemicals, GsMTx4 also enhanced developmental myelination of these cerebellar slice cultures. Recent observations by others also suggest that OPC maturation is, in part, regulated by mechanosensitive Piezo1 channels (Segel et al., 2019). Interestingly, missense mutations in a gene known as TMEM63A, which encodes for a mechanosensitive ion channel that is highly expressed in oligodendrocytes, result in a transient infantile disorder in humans that resembles a hypomyelinating leukodystrophy, which somehow resolves within the first 4 years of life (Yan et al., 2019). These and other studies (Espinosa-Hoyos et al., 2018; Jagielska et al., 2017; Mei et al., 2014) point towards an important role for mechanosensation in developmental myelin formation in the brain.

8 | CONCLUSIONS AND FUTURE DIRECTIONS

Neuro-mechanobiology research is developing at an exciting and promising pace. In this review, we have identified several key questions that should help to advance the field (see Box 5). Answering some of these questions could ultimately lead to improved therapeutics for TBI or neurodegenerative disease. Firstly, it would be useful to confirm the relationship between cell body density, cell type and tissue stiffness in different brain regions. It is interesting that one of the most neuron-dense structures in the brain, the cerebellum, is relatively soft. Another important point to clarify is whether white matter is softer or stiffer than grey matter and the functional significance of these mechanical measurements in healthy and disease states. We also need to better understand how pathological proteins and peptides, such as $A\beta_{42}$ and hyperphosphorylated tau, alter the mechanical properties of neurons and glia and how the chronic neuroinflammation that they cause impacts tissue stiffness in different brain regions. Aberrant cell signalling is a hallmark of neurodegeneration, and, as such, it is important to discover what role, if any, neuronal mechanotransduction plays in ageing and disease-related cognitive decline, especially at the level of the synapse. To overcome some of the limitations of high-resolution indentation methods, such as AFM, and low-resolution non-invasive imaging techniques, such as MRE, emerging tools for mechanobiology research are continually being developed and refined. Brillouin microscopy, for example, is a non-contact imaging method that can be combined with Raman spectroscopy (Traverso et al., 2015) or fluorescence microscopy (Elsayad et al., 2016) to measure the mechanical properties of cells or tissues at high spatial resolution (Schlüßler et al., 2018). The introduction of novel high-resolution instruments for measuring mechanical forces is sure to spark many new and innovative collaborations between neuroscientists, bioengineers and clinicians and will help to answer some of the outstanding questions discussed above. However, it is also important to understand the limitations of material science techniques when they are applied to interrogate biological systems (Prevedel, Diz-Muñoz, Ruocco, & Antonacci, 2019; Wu et al., 2018). This will ensure that the functional significance of mechanical measurements of neuronal and glial cell stiffness can be fully integrated into biomedical hypotheses and experimental designs that aim to investigate how the healthy brain ages and how neurodegeneration begins and progresses. Combining such knowledge could be vital for developing novel therapeutics and interventions for cognitive decline in old age and for memory impairment in people living with Alzheimer's disease.

BOX 5 Outstanding questions in CNS mechanobiology

1) What is the relationship between cell body density, cell type and brain tissue stiffness?
2) What is the relationship between axonal orientation and brain tissue stiffness?
3) Is CNS white matter softer or stiffer than grey matter?
4) Does ageing impact the mechanical properties of white matter to a greater degree than neighbouring grey matter?
5) Does the stiffness of the neurogenic niche promote neurogenesis or stem cell migration?
6) How does altered mechanotransduction impact calcium homeostasis in neurons and glial cell types?
7) How do extracellular mechanical forces impact the intrinsic electrical properties of neurons?
8) How do ageing and neurodegenerative diseases affect neuronal and glial mechanotransduction?
9) How do tau tangles, amyloid plaques and other protein/ peptide aggregates alter the mechanical properties of the brain?
10) Does chronic neuroinflammation contribute to ECM remodelling and changes to brain tissue stiffness?
11) Does the stiffness of the glial scar affect neural regeneration?
12) Are mechanosensitive ion channels potential drug targets for CNS pathologies?

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CONFLICT OF INTEREST

The authors declare no conflicts of interest and no competing financial interests.

AUTHOR CONTRIBUTIONS

G.K.S. and E.M. conceived the review topic. All authors prepared the figures and contributed to the writing of the manuscript. All authors reviewed, edited and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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