ELSEVIER

Alzheimer's & Dementia ■ (2015) 1-10

Alzheimer's & Dementia

Featured Article

Mechanical stress related to brain atrophy in Alzheimer's disease

Marcel Levy Nogueira[a,b,c,*], Olivier Lafitte[d], Jean-Marc Steyaert[c], Hovagim Bakardjian[a,b], Bruno Dubois[a,b,e], Harald Hampel[a,e,f], Laurent Schwartz[c]

[a]*Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A), Département de Neurologie, Hôpital de la Pitié-Salpêtrière, AP-HP, Paris, France*
[b]*Institut des Neurosciences Translationnelles de Paris (IHU-A-ICM), Institut du Cerveau et de la Moelle Epinière (ICM), Paris, France*
[c]*Laboratoire d'informatique (LIX), UMR 7161, Ecole Polytechnique, Université Paris-Saclay, Palaiseau, France*
[d]*LAGA, UMR 7539, Université Paris 13, Sorbonne Paris Cité, Villetaneuse, France*
[e]*INSERM, CNRS, UMR-S975, Institut du Cerveau et de la Moelle Epinière (ICM), Paris, France*
[f]*AXA Research Fund & UPMC Chair, Sorbonne Universités, Université Pierre et Marie Curie, Paris, France*

Abstract

Background: The effects related to endogenous mechanical energy in Alzheimer's disease (AD) pathology have been widely overlooked. With the support of available data from literature and mathematical arguments, we hypothesize that brain atrophy in AD could be co-driven by the cumulative impact of the pressure within brain tissues.

Methods: Brain volumetric and physical data in AD and normal aging (NA) were extracted from the literature. Average brain shrinkage and axial deformations were evaluated mathematically. Mechanical stress equivalents related to brain shrinkage were calculated using a conservation law derived from fluid and solid mechanics.

Results: Pressure equivalents of 5.92 and 3.43 mm Hg were estimated in AD and in NA, respectively.

Conclusions: The calculated increments of brain mechanical stress in AD, which could be impacted by marked dampening of arterial pulse waves, may point to the need to expand the focus on the mechanical processes underpinning pathologic aging of the brain.

Keywords: Brain atrophy; Total brain volume; Alzheimer's disease; Mechanical stress; Fluid mechanics; Brain stiffness

1. Introduction

During evolution and through the external environment, all human body organs are constantly influenced by mechanical forces. In the brain, cellular process and tissue structures are continuously affected by mechanical stress, e.g., through gravity [1]. Fluid-solid mechanical interactions constantly occur between brain parenchyma and cerebral blood and cerebrospinal fluid (CSF) [2]. These intracranial pressures interacting with brain compartments are confined within the progressively rigid structure of the skull. A variety of brain diseases alter intracranial pressure dynamics that may, in turn, result in physical alterations in the brain. However, the extent to which mechanical dynamics influence brain structure still remains unclear.

Morphologic brain shrinkage is largely investigated using structural magnetic resonance imaging (MRI), which differentiates Alzheimer's disease (AD) from normal aging (NA) subjects on measures of global and regional brain volume, tissue morphology, and rate of atrophy [3]. By the time of diagnosis of the late-stage syndromal AD dementia, statistically significant atrophy is usually found throughout wide neocortical and subcortical regions with a relative sparing of primary sensory and motor cortices [4]. Chronically progressive neuronal and synaptic loss are the main pathologic substrates of brain atrophy [5].

Interestingly, beyond volume and neuronal depletion, brain atrophy has been correlated to alterations in brain mechanical properties, both in AD and NA. Magnetic resonance elastography (MRE) estimates the stiffness of

*Corresponding author. Tel.: +33-1-42-16-75-67; Fax: +33-1-42-16-75-04.
E-mail address: marcel.levy@psl.aphp.fr

http://dx.doi.org/10.1016/j.jalz.2015.03.005
1552-5260/

tissues by imaging their responses to sound (shear) waves propagated through the body. MRE is useful for characterizing and mapping brain viscoelastic properties and it has shown the reduction of brain stiffness in NA [6] and specially in AD [7]. As a result, it might indicate a role of the chronic impact of classical mechanics in brain shrinkage due to neurodegeneration and other pathophysiological molecular and cellular mechanisms.

In the past, the effects related to endogenous mechanical energy [1] in AD pathology have been widely overlooked in postulated hypotheses such as mono-linear, mono-system amyloidocentric molecular pathway models (the amyloid cascade theory [8] conceiving AD as a protein misfolding disorder) derived from reductionist transgenic animal mutation models that do not integrate principles of mechanics. The aim of this article was, therefore, to revisit an old hypothesis: the fact that mechanical principles play a key role in the pathogenesis of AD and dementia.

Applying principles of fluid and solid mechanics, the equivalents of mechanical stress associated with brain shrinkage in AD were estimated. Our hypothesis is that the biological cascade of neurodegeneration could be impacted and/or driven by cerebrovascular hemodynamic stress. This is an alternative or complementary hypothesis which is not aimed against other hypotheses but is rather integrative. Selecting AD as a primary model of a nonlinear dynamic, chronically progressive degenerative disease [9–11], equivalents of pressure related to brain atrophy were calculated using data from published studies that provide measures of volume and mechanical properties of the brain in AD, NA, and adulthood conditions. These results were compared with compatible measures of cerebrovascular hemodynamic stress. Assuming that these equivalents of pressure could be exerted by intracranial environment, we compared them with the measures of physiological intracranial dynamics attained from the literature.

2. Methods

2.1. Literature review and data retrieval

2.1.1. Brain volumetry

An overview of the methods used in this work is summarized in Fig. 1. As a first step, a review of the literature was performed to extract data of the total brain volume (BV) in AD, NA, and normal adulthood situations. We carried a MEDLINE/PubMed research of publications providing brain volumetric MRI data using the following keywords: "total brain volume," "brain volume," "Alzheimer," "aging," and "age." The actual number of studies including >50 participants and providing measures of total BV and total intracranial volumes (ICV) in AD, NA, and adulthood conditions were selected. Then, volumetric data attended from the literature search were compared with those from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort [12]. The ADNI population provides one of the largest groups of probable AD subjects with standardized imaging assessments, permitting numerous investigators to validate volumetric biomarkers using data from this highly referenced database. The clinical diagnosis of AD dementia in ADNI was based on the 1984 probable AD criteria [13] which were used to define AD in the studies selected for this analysis. As a result, the extreme diversity

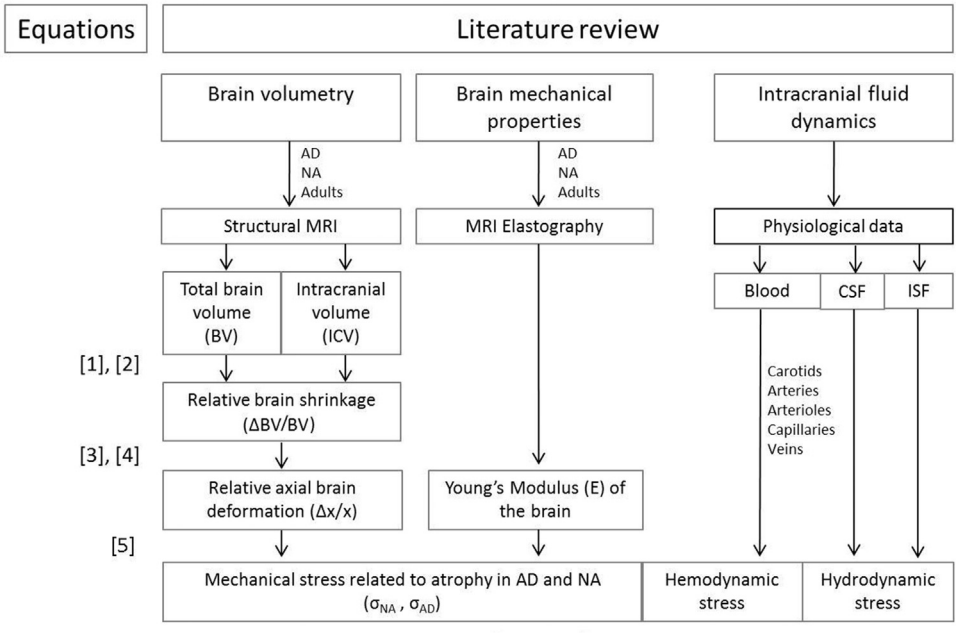

Fig. 1. Resume of the methods. Abbreviations: AD, Alzheimer's disease; NA, normal aging; MRI, magnetic resonance imaging; σ, mechanical stress; CSF, cerebrospinal fluid; ISF, brain interstitial fluid.

of pathophysiological modifications associated with AD in the ADNI population should be similarly represented in the selected sample studies.

Total BV provided from literature data retrieval was compared with the total ICV, the sum of the volumes of the whole brain, intracranial CSF, and blood (Fig. 2). The ICV was used as an adjustment factor considering its stability during almost the entire lifespan, after young adulthood, not being modified by the effect of brain atrophy [14]. The relative brain volume in AD, NA, and in normal young adulthood was expressed in terms of ratios $(BV/ICV)_{AD}$, $(BV/ICV)_{NA}$, and $(BV/ICV)_a$, respectively. Relative volumes were adopted instead of absolute volumes with the purpose of normalizing differences between individuals, genres, ages, and volumetric methods. Measures of relative brain volume not directly provided by selected studies were calculated by the division of the absolute measures (BV/ICV).

2.1.2. Brain mechanical properties

Brain mechanical properties in AD, normal adulthood, and aging situations were extracted from MEDLINE/PubMed databases using the following key words: "stiffness," "Young's modulus," "shear modulus," "Poisson's ratio," "elastography," "brain," and "Alzheimer." The objective of this research was to obtain, direct or indirectly, values of the Young's modulus (E) of the brain in AD and NA, required in Equation 7, to calculate mechanical stress related to brain shrinkage. Fig. 2 illustrates brain shrinkage and axial deformation in AD and NA with the related mechanical stress into each condition.

2.1.3. Intracranial fluid dynamics

Hemodynamic data and mechanical properties of intracranial fluids were attained using the following keywords: "dynamics," "model," "modelisation," "fluid," "pressure," "flow," "intracranial," and "brain." Furthermore, bibliography references from selected studies were used as research strategy. Scientific abstracts published in English and French languages were selected. Only data provided from human brain studies were collected. As we claimed that hemodynamic stress could have an impact and/or could drive brain atrophy in AD, we aimed to compare the results of mechanical stress related to brain shrinkage in AD and NA with the cerebrovascular hemodynamic stress data from literature.

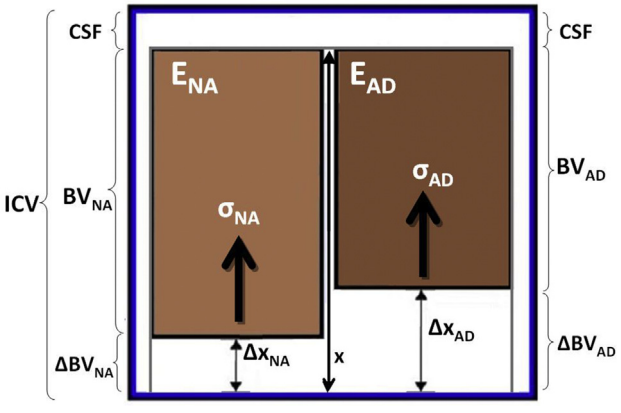

Fig. 2. Representation of the brain shrinkage and the axial deformation in Alzheimer's disease (AD) and in normal aging (NA) with the related mechanical stress (σ) in to each condition. Abbreviations: CSF, cerebrospinal fluid; BV, total brain volume; ΔBV, brain volume variation (or shrinkage); Δx, average changing in dimensions along an axis (or deformation); ICV, total intracranial volume; E, elastic modulus or Young's modulus of the brain.

2.2. Estimation of brain shrinkage and axial deformation in AD and NA

The reduction in brain volume (shrinkage or ΔBV) was calculated assuming the maximal volume (V) of the brain achieved across the entire lifespan. It corresponds to the total volume of the brain in the period of young adulthood (BV_a) [14]. Relative brain shrinkage (ΔBV/BV) due to AD pathology was calculated in Equation 1 using the ratio between the relative brain volume in AD $(BV/ICV)_{AD}$ and the relative brain volume in young adults $(BV/ICV)_a$. Brain shrinkage due to NA was obtained in Equation 2 using the ratio between the relative brain volume in NA $(BV/ICV)_{NA}$ and the relative brain volume in young adults $(BV/ICV)_a$. The age groups related to BV_{AD}, BV_{NA}, and BV_a were defined by the age of the participants in selected brain volumetric MRI studies. NA subjects refer to control groups described in these publications.

$$(\Delta BV/BV)_{AD} = 1 - \left[(BV/ICV)_{AD}/(BV/ICV)_a\right] \quad \text{[Eq.1]}$$

$$(\Delta BV/BV)_{NA} = 1 - \left[(BV/ICV)_{NA}/(BV/ICV)_a\right] \quad \text{[Eq.2]}$$

Finally, ΔBV/BV was converted to an average value of relative reduction in brain dimensions along an axis (brain axial deformation or Δx/x) for AD and NA conditions, as represented, respectively, by Equations 3 and 4.

$$(\Delta x/x)_{AD} = 1 - \left[1 - (\Delta BV/BV)_{AD}\right]^{1/3} \quad \text{[Eq.3]}$$

$$(\Delta x/x)_{NA} = 1 - \left[1 - (\Delta BV/BV)_{NA}\right]^{1/3} \quad \text{[Eq.4]}$$

2.3. Calculating mechanical stress (σ) related to brain atrophy

The mechanical stress related to brain atrophy in AD and NA was estimated using a physico-mathematical approach. Equation 6 describes the conservation law derived from fluid dynamics with mechanical constraints [15]. In biophysical terms, it relates the blood flow behavior within a tissue (C), the mass density of the blood (d), the Δx and the initial dimension of the tissue (x), the elastic modulus or Young's modulus (E) of the tissue, and an external pressure (p) applied over the tissue. In other words, Equation 6 symbolizes the equilibrium of three sources of pressure (σ) exerted permanently over an

organ: external pressure (p), hemodynamic pressure (σ_c), and viscoelastic pressure (σ_e), as shown in Equation 5. The proposed relationship is illustrated in Fig. 3.

The mechanical stress-related brain shrinkage due to AD and NA was calculated using the component "E × Δx/x" of Equation 6. This component is expressed in Equation 7 and denotes the viscoelastic stress (σ_e) related to the Δx of a material or tissue. The Young's modulus (E) of a material describes its resistance (or tendency) to deform in response to mechanical stress along an axis. The Young's modulus of the brain in AD and NA conditions was converted using measures of brain stiffness obtained from brain MRI elastography studies [7]. Stiffness (μ or effective shear modulus) differs from the Young's modulus (E) by a scaling factor E = 3 μ [16]. Intermediary values of brain viscoelasticity between young adults–NA ($E_{a\rightarrow NA}$) and young adults–AD ($E_{a\rightarrow AD}$) were used in the component "E × Δx/x" of Equation 6. They correspond to the mean values ($E_a + E_{AD}$)/2 and ($E_a + E_{NA}$)/2, respectively, considering changes of the Young's modulus of the brain from adulthood to NA and AD (Sack et al., 2011). Provided data of stress σ and elastic modulus E were stated in units of pressure (KPa or mm Hg) and the relative deformation (Δx/x) is dimensionless. All physico-mathematical variables and equations described in this section are summarized in Tables 1 and 2, respectively.

$$p+\sigma_c+\sigma_e=\text{constant} \quad \text{[Eq.5]}$$

$$p+\left(d\times C^2\right)+(E\times\Delta x/x)=\text{constant} \quad \text{[Eq.6]}$$

$$\sigma_e=E\times\Delta x/x \quad \text{[Eq.7]}$$

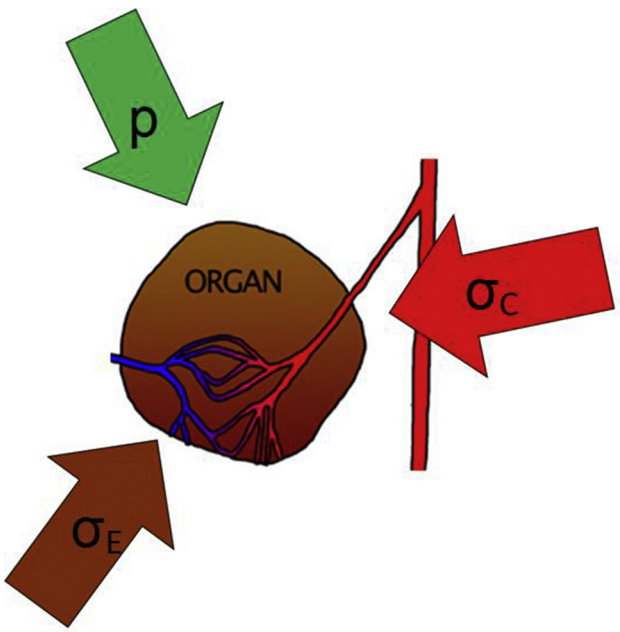

Fig. 3. Proposed equilibrium relationship of three sources of pressure (σ) exerted permanently over an organ: external pressure (p), hemodynamic pressure (σ_c), and viscoelastic pressure (σ_e): p + σ_c + σ_e = constant.

3. Results

3.1. Brain volumetry (literature review)

MRI brain volumetric studies reviewed from literature were categorized into four groups according to the age of the participants and the presence of AD: (1) mixed adulthood and NA, (2) young adulthood (3) NA and (4) AD. Publications were organized in Table 3 in descending order of number of participants (n) in each group.

3.2. Estimation of the ΔBV/BV in AD and NA

Volumetric MRI studies providing both absolute (BV and ICV) and relative (BV/ICV) measures of BV were selected from Table 3. Measures of $(BV/ICV)_a$, $(BV/ICV)_{NA}$, and $(BV/ICV)_{AD}$ retrieved in Kruggel [25] (0.875), Lemaître et al. [26] (0.747 + 0.733 = 1.48/2 = 0.74), and Yasuda et al. [24] (0.65), respectively, were extracted from Table 3 and used in the calculation of the ΔBV/BV. Volumetric studies with mixed normal adult and elderly subject populations were not selected. As a result, using Equations 1 and 2 exposed in methods, ΔBV/BV due to AD and NA were estimated at 26% and 16%, respectively. As signaled previously, $(BV/ICV)_a$ was taken into account as a reference of maximal brain volume during the entire lifespan.

$$\begin{aligned}(\Delta BV/BV)_{AD}&=1-\left[(BV/ICV)_{AD}/(BV/ICV)_a\right]\\(\Delta BV/BV)_{AD}&=1-(0.65/0.875)\\(\Delta BV/BV)_{AD}&=0.26 \text{ or } 26\%\end{aligned} \quad \text{[Eq.8]}$$

$$\begin{aligned}(\Delta BV/BV)_{NA}&=1-\left[(BV/ICV)_{NA}/(BV/ICV)_a\right]\\(\Delta BV/BV)_{NA}&=1-(0.74/0.875)\\(\Delta BV/BV)_{NA}&=0.16 \text{ or } 16\%\end{aligned} \quad \text{[Eq.9]}$$

3.3. Estimation of the Δx/x in AD and NA

The average axial deformation Δx of the brain related to NA and AD processes was defined by a mean reduction in brain dimensions in each one of these conditions, considering as a reference the dimensions of a normal adult brain. Using Equations 3 and 4 exposed in methods, the relative axial brain deformation due to AD $(\Delta x/x)_{AD}$ and NA $(\Delta x/x)_{NA}$ conditions were estimated in 10% and 5.6%, respectively. As stated previously, $(\Delta BV/BV)_{AD}$ and $(\Delta BV/BV)_{NA}$ correspond to 0.26 (Equation 8) and 0.16 (Equation 9), respectively.

$$\begin{aligned}(\Delta x/x)_{AD}&=1-\left[1-(\Delta BV/BV)_{AD}\right]^{1/3}\\(\Delta x/x)_{AD}&=1-[1-0.26]^{1/3}\\(\Delta x/x)_{AD}&=0.10 \text{ or } 10\%\end{aligned} \quad \text{[Eq.10]}$$

$$\begin{aligned}(\Delta x/x)_{NA}&=1-\left[1-(\Delta BV/BV)_{NA}\right]^{1/3}\\(\Delta x/x)_{NA}&=1-[1-0.16]^{1/3}\\(\Delta x/x)_{NA}&=0.056 \text{ or } 5.6\%\end{aligned} \quad \text{[Eq.11]}$$

Table 1
Physico-mathematical variables used in equations

Variable	Representation	Description
Volumes (V)	ΔBV, ΔBV/BV	Absolute and relative variation in total brain volume, respectively.
	BV_a, BV_{NA}, BV_{AD}	Total brain volume of a young adult, in normal aging (NA), and in AD subjects.
	ICV	Total intracranial volume.
	BV/ICV	Ratio of brain volume to intracranial volume.
Dimensions (x)	Δx, Δx/x	Average absolute and relative variations in dimensions along an axis, respectively (axial deformation).
Mechanical stress (σ)	p, σ_C, σ_E	Mechanical constraints (σ) exerted permanently over an organ: external pressure (p), hemodynamic stress (σ_C), and viscoelastic stress (σ_E) showed in Fig. 3 and Equation 5.
	σ_{AD}, σ_{NA}	Mechanical stress or equivalents of pressure related to brain shrinkage in AD and normal aging, respectively.
Mechanical properties	E	Young modulus or elastic modulus of a material or tissue.

NOTE. BV, total brain volume; ΔBV, brain volume variation (or shrinkage); ΔBV/BV, relative brain volume variation (or relative shrinkage); NA, normal aging; x: dimension along a axis; AD, Alzheimer's disease; ICV, total intracranial volume; Δx, changing in dimensions along an axis (or deformation); Δx/x, relative changing in dimensions along an axis (or relative deformation); p, external pressure; σ_C, hemodynamic stress induced by blood flow velocity; σ_E, viscoelastic stress related to the deformation along an axis; E, elastic modulus or Young's modulus of a material or tissue.

3.4. Estimation of the mechanical stress (σ) related to brain atrophy

Table 4 shows brain mechanical properties in normal adult, NA, and AD. The equivalent value of mechanical stress σ related to brain deformation in AD and NA (σ_{AD} and σ_{NA}) was estimated in 5.92 and 3.43 mm Hg, respectively, as shown in Equation 7 presented in methods. The Young's modulus of the brain in AD (E_{AD} = 6.60 KPa), NA (E_{NA} = 7.11 KPa), and normal adults (E_a = 9.21) was extracted from Table 4. Transitional values of brain viscoelasticity $E_{a\rightarrow NA}$ and $E_{a\rightarrow AD}$ were calculated by (E_a + E_{NA})/2 = 8.16 kPa and (E_a + E_{AD})/2 = 7.90 KPa, respectively. The Δx/x of 0.10 in AD and 0.056 in NA were calculated using Equations 10 and 11, respectively.

$$\sigma_e = E \times \Delta x/x \qquad \text{[Eq.12]}$$

$$\sigma_{AD} = E_{a\rightarrow AD} \times (\Delta x/x)_{AD}$$
$$\sigma_{AD} = 7.90 \text{ kPa} \times 0.10$$
$$\sigma_{AD} = 0.790 \text{ kPa} = 5.92 \text{ mm Hg} (1 \text{mm Hg} = 0.1332 \text{ kPa}) \qquad \text{[Eq.13]}$$

$$\sigma_{NA} = E_{a\rightarrow NA} \times (\Delta x/x)_{NA}$$
$$\sigma_{NA} = 8.16 \text{ kPa} \times 0.056$$
$$\sigma_{NA} = 0.457 \text{ kPa} = 3.43 \text{ mm Hg} (1 \text{ mm Hg} = 0.1332 \text{ kPa}) \qquad \text{[Eq.14]}$$

3.5. Intracranial fluids dynamics (literature research)

Table 5 summarizes data extracted from studies providing physical data of intracranial fluids (blood, CSF, and interstitial fluid), which contextualizes, in a physical point of view, the equivalents of pressures calculated previously. Fluid dynamic parameters of density, flow, pressure, and resistance were extracted from the selected publications.

4. Discussion

4.1. Implications of the results and possible interpretations

To the best of our knowledge, this is the first attempt to quantify the influence of mechanical interactions on brain atrophy in AD. To test the hypothesis, we used literature data

Table 2
Physico-mathematical formulas

Description	Equation	Text reference
Relative brain shrinkage in AD and NA conditions	$(\Delta BV/BV)_{AD} = 1 - [(BV/ICV)_{AD}/(BV/ICV)_a]$	[1]
	$(\Delta BV/BV)_{NA} = 1 - [(BV/ICV)_{NA}/(BV/ICV)_a]$	[2]
Relative brain deformation along an axis in AD and NA conditions	$(\Delta x/x)_{AD} = 1 - [1 - (\Delta BV/BV)_{AD}]^{1/3}$	[3]
	$(\Delta x/x)_{NA} = 1 - [1 - (\Delta BV/BV)_{NA}]^{1/3}$	[4]
Conservation law of solid and fluid mechanics	$p + \sigma_c + \sigma_e = \text{constant}$	[5]
	$p + (d \times C^2) + (E \times \Delta x/x) = \text{constant}$	[6]
Mechanical stress related to a deformation along an axis	$\sigma_e = E \times \Delta x/x$	[7]

NOTE. AD, Alzheimer's disease; NA, normal aging; BV, total brain volume; ΔBV, brain volume variation (or shrinkage); ΔBV/BV, relative brain volume variation (or relative shrinkage); ICV, total intracranial volume; x, dimension along a axis; Δx, changing in dimensions along an axis (or deformation); Δx/x, relative changing in dimensions along an axis (or relative deformation); p, external pressure; σ_C, hemodynamic stress induced by blood flow velocity; σ_E, viscoelastic stress related to the deformation along an axis; d, fluid mass density; C, fluid velocity; E, elastic modulus or Young's modulus of a material or tissue.

Table 3
Volumetric MRI data provided by literature review

Population	n	ICV (mL)	BV (mL)	BV/ICV (range)	Age (range)	MMSE	HBP (%)	Segmentation	Reference
Mixed samples:	2081	1263 ± 106.8		(0.71–0.80)	60.6 ± 9.5		42.3	[17]	DeCarli et al. [18]
adult and aging	1300			(0.77–0.92)	(20–90)			***	Bromiley et al. [19]
subjects	465			(0.65–0.83)	29.5 (18–79)		0	SPM	Good et al. [20]
	70	1288 ± 132		(0.78–0.93)	57 ± 20		0	Tina	Bromiley et al. [19]
	49	1384 ± 139	1227 ± 135	(0.85–0.93)	56 ± 16		0	[21]	Matsumae et al. [22]
	32	1507 ± 111	1161 ± 93	0.77	53.9 ± 8.7	30–29		[23]	Yasuda et al. [24]
Young adults	145F	1495 ± 96	1304 ± 88	0.873 ± 0.017	24.3 ± 2.9			BRIAN	Kruggel [25]
	145M	1616 ± 91	1417 ± 86	0.877 ± 0.018	24.1 ± 2.6			BRIAN	Kruggel [25]
Elderly subjects	227		1055 ± 86		76.0 ± 4	29.1 ± 0.76		FreeSurfer	ADNI†
	331F	1288 ± 100	960	0.747	69.5 ± 2.9	27.4 ± 2.0	37.4	SPM	Lemaître et al. [26]
	331M	1454 ± 107	1066	0.733	69.5 ± 3.1	27.7 ± 2.0	48	SPM	Lemaître et al. [26]
	122	1327		(0.61–0.76)	75.0 ± 7.6	29.2 ± 1.0		SPM	Smith et al. [27]
	117			0.86 (0.79–0.92)	72.9 ± 6.7	29.1 ± 1.2		CLASP	Simmons et al. [28]
AD subjects*	188		1000 ± 88		75.3 ± 6.2	23.3 ± 1.75		FreeSurfer	ADNI†
	178	1460 ± 126	983 ± 91	0.65	73.5 ± 6	18.8 ± 4.8		[23]	Yasuda et al. [24]
	144		969 ± 108		74.0 ± 8	17.1 ± 2.4	40	BSI	Wilkinson et al. [29]
	130			0.82 (0.74–0.92)	75.9 ± 6.2	20.7 ± 4.8		CLASP	Simmons et al. [28]

Abbreviations: ICV, total intracranial volume; BV, total brain volume; MMSE, mini-mental state examination; HBP, high blood pressure (percentage of hypertensive subjects when reported); F, female; M, male; ADNI, Alzheimer's Disease Neuroimaging Initiative; AD, Alzheimer's disease.

NOTE. ***Meta-study.

*AD cases defined by clinical NINCDS-ADRDA criteria [13].

†ADNI data visualized and analyzed on November 28, 2014.

and physico-mathematical formulas and estimated pressure equivalents of 5.92 mm Hg and 3.43 mm Hg related to the brain atrophy in AD and in NA, respectively. These results were calculated based on the average reduction in brain dimensions and the Young's modulus of the brain, which associates deformation and mechanical stress. Data provided from Equations 12–14 could imply that the brain undergoes 42% of additional pressure (1–3.43/5.92 = 0.42) in AD comparatively to NA. We hypothesized that the biological processes of neurodegeneration in AD, and consequently brain atrophy, could be co-driven by the cumulative impact of the pressure within brain tissues during the course of the lifespan.

Even though conclusive proof is still not available, but assuming that the equivalents of pressure related to brain atrophy could be exerted by the intracranial environment, we have compared the results with measures of physiological intracranial dynamics from the literature. According to the Monro-Kellie doctrine [38], the brain undergoes mechanical stress provided by hemodynamics and CSF dynamics. Fig. 4 illustrates the impact of different pressures exerted by intracranial fluids around brain tissues in physiological conditions and highlights the hemodynamic stress as principal contributor to the increment of pressure in intracranial environment.

Fig. 5 shows brain arterial blood flow curves in AD and NA populations, modified from El Sankari et al. [35] (data in Table 5). The mean arterial flow curve is plotted over time as a function of the models [Eq.15] and [Eq.16]. The curves represent the blood pulsatile cycle done with one fundamental sin [(2/75)πT], T in seconds, and its fourth harmonic multiplied by a small coefficient. The gray zone between red (NA) and blue (AD) curves may involve the phenomenon of "fatigue" a consequence of an increased amplitude of oscillations generated by brain arterial shock waves in AD [39]. In physics, "fatigue" refers to structural damage from repeated loading, with weakening of a biological or nonbiological

Table 4
Mechanical properties of the brain, including data from humans and animals

Physical properties	Unit	Young adults	Normal aging	AD	Reference
Density	kg/m^3	1040			Harper et al. [30]
Stiffness	kPa	3.5–3.8	2.5–2.7		Sack et al. [6]
Stiffness	kPa	3.07	2.37	2.2	Murphy et al. [7]
Stiffness (mice)*	kPa	25		19.3	Murphy et al. [31]
Young's modulus†	kPa	9.21	7.11	6.6	Murphy et al. [7]
Young's modulus	KPa	9.21			Soza et al. [32]
Bulk modulus	kPa	2190			Omori et al. [33]
Poisson's ratio		0.496			Soza et al. [32]

Abbreviation: AD, Alzheimer's disease.

*Brain stiffness evaluated by magnetic resonance elastography in AD APP-PS1 mice and normal controls.

†Conversion of stiffness (μ or effective shear modulus) to Young's modulus (E) by a scaling factor E = 3 μ [16].

Table 5
Physical characteristics of the intracranial fluids

Fluid	Condition	Physical parameter	Specifications	Value	Unit	Reference
Blood	Physiol*	Density		1.050	g/cm^3	Linninger et al. [2]
	Physiol	Flow (average)	Arterial	8.94	mL/s	Kim et al. [34]
	NA	Flow max		14.45	mL/s	El Sankari et al. [35]
	NA	Flow min		4.72	mL/s	El Sankari et al. [35]
	AD	Flow max		18.20	mL/s	El Sankari et al. [35]
	AD	Flow min		4.18	mL/s	El Sankari et al. [35]
	Physiol	Pressure	Carotids	100	mm Hg	Linninger et al. [2]
			Carotid segments	82	mm Hg	Linninger et al. [2]
			Arterioles	55	mm Hg	Linninger et al. [2]
			Capillaries	18	mm Hg	Linninger et al. [2]
			Veins	5	mm Hg	Linninger et al. [2]
CSF	Physiol	Density		1	g/cm3	Linninger et al. [2]
	Physiol	Pressure		9.1	mm Hg	Linninger et al. [2]
	NA			10.29	mm Hg	Silverberg et al. [36]
	AD			7.576	mm Hg	Silverberg et al. [36]
	Physiol	Pulsatile pressure	Ventricles	5	mm Hg	Linninger et al. [2]
			Subarachnoid space	3.5	mm Hg	Linninger et al. [2]
	Physiol	Flow (drainage)	Average	21	mL/s	Pollay 2010 [37]
			Max	60	mL/s	Pollay [37]
Interstitial	Physiol	Volume	% of brain volume	30	%	Linninger et al. [2]
	Physiol	Pressure		6	mm Hg	Linninger et al. [2]
	Physiol	Flow		7.2	mL/s	Linninger et al. [2]

*Physiologic measures.

material. We hypothesize that increased brain mechanical stress in AD is possibly a consequence of the incremental amplitudes (gray zone) of repetitive arterial pulsations, some 30 million/year [40], causing fatigue and fractures in neuronal microstructure [7,31,40–42]. This phenomenon of cumulative effect of pressure within brain tissues needs to be investigated as mechanobiological interactions [1] implicated to AD pathology that are currently not well understood.

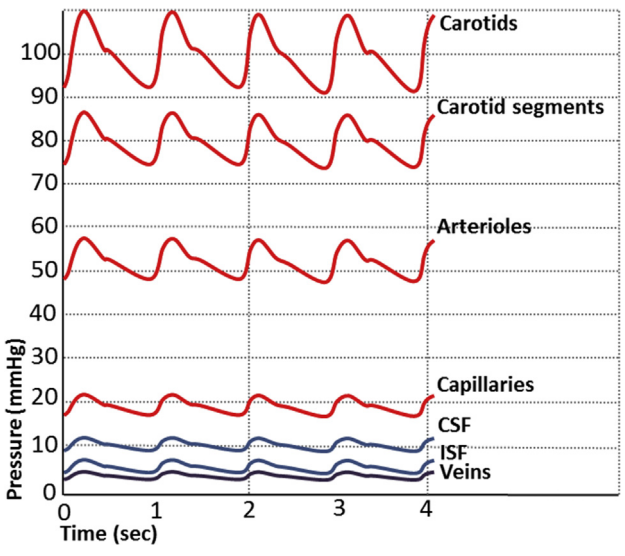

Fig. 4. MRI-based simulation of physiological measures (Table 5) of intracranial hemodynamic and hydrodynamic pressure waveforms, modified from Linninger et al. [2]. It illustrates different pressures exerted by intracranial fluids around brain tissues in physiological conditions, which suggests that arterial pulsatile pressure is the main contributing intracranial factor for brain mechanical fatigue during lifespan. Abbreviations: MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

The hypothesis of AD pathology being driven by mechanical forces has been previously suggested by numerous authors. Wostyn et al. and Silverberg et al. have initially evoked the causative link between intracranial pressure and AD [36,43–46]. Mechanical impedance, a measure of how much a structure resists motion when subjected to a given force, of the intracranial cavity and vessels has shown to take a role in the pathophysiology of AD [47]. The strength of the pulse waves induced by the vascular tree in the craniospinal cavity has been proposed to be the underlying vascular pathophysiology behind AD and other conditions such as vascular dementia and normal pressure hydrocephalus [39,48–50]. Barz et al. [51] propose a pressure wave theory to explain neurons degenerating similarly as vessels (atherosclerosis). According to these authors, it could be that intraneuronal neurofibrillary tangles and extracellular amyloid deposits evolve from extruded cyto-axoplasm after pressure-induced ruptures of neuronal processes.

Many studies in the field of mechanobiology have demonstrated that mechanical forces are sensed, transduced, and even generated in neurons. The influence of pressure in plasma membrane, ion channels, neurofilaments, microtubules, motor and adhesion proteins, and extracellular matrix have key roles in neuronal and glial function [1]. Mechanical forces also seem to influence protein aggregation, misfolding, and deposition in brain tissues. Computational simulations have shown that β-amyloid structure could be twisted, flexed, and bent by the imposition of shear forces [52]. Amyloid peptides, others then Aβ, have been described in conditions such as heart valves exposed to high shear

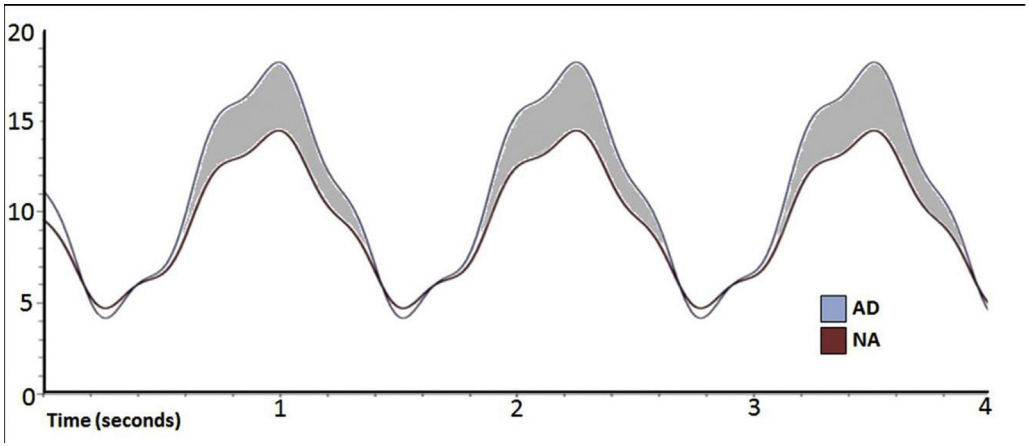

Fig. 5. Arterial blood flow curves in AD and NA populations, modified from El Sankari et al. [35] (unpublished data). The mean arterial flow (AF) curve is plotted over time as a function of models (equations) [Eq.15] and [Eq.16]. A and b are coefficients of the model and T corresponds to time in seconds. The gray zone between red (NA) and blue (AD) curves denotes the phenomenon of fatigue, as a consequence of an increased amplitude of oscillations generated by arterial shock waves in time. Abbreviations: AD, Alzheimer's disease; NS, normal aging.

$$AF_{NA} = a_{NA} + b_{NA}\{[\sin(2/75)\pi T] - 0.125\ \sin[(8/75)\pi T]\},\quad \text{where } a_{NA}: 9.585 \text{ and } b_{NA}: 4.547 \qquad \text{[Eq.15]}$$

$$AF_{AD} = a_{AD} + b_{AD}\{[\sin(2/75)\pi T] - 0.125\ \sin[(8/75)\pi T]\},\quad \text{where } a_{AD}:\ 11.19 \text{ and } b_{AD}:\ 6.55 \qquad \text{[Eq.16]}$$

stress [53] or in the joint cartilage [54]. Aβ deposits can be formed in conditions associated with brain mechanical load as after brain injury [55], in normal pressure hydrocephalus, or in glaucoma [44]. Hemodynamic stress is associated to β-amyloid deposition and cognitive decline in NA [56,57].

Abnormal accumulation of cytoskeletal proteins, including phospho-tau, has been observed after repetitive mild brain mechanical stress [58,59]. Cranial trauma [60], hypertension, atherosclerosis, and apolipoprotein E (*APOE*) ε4 status are risk factors for AD [61]. These conditions interact with intracranial mechanical constraints and so could be considered as "mechanical" risk factors [62]. Hypertension increases brain mechanical fatigue by arterial pulse wave stress [40]. Atherosclerosis can increase arterial stiffness inducing damage of environment tissue [63]. Deletion of the ApoE gene, in turn, is responsible for the development of atherosclerosis due to its interaction with the shear stress on vessel walls [64].

4.2. *Confounding factors and future focused studies*

Neuropathologic confirmations of AD and non-AD cases were not available in all studies selected from the literature (Table 3). In these studies, AD cases were defined by clinical NINCDS-ADRDA criteria [13], which implies that some cases in the demented group may not have, in reality, AD. Contrarily to recent AD cohorts, data for the tau-amyloid positron emission tomography (PET) burden were regrettably not available for these control groups. This is why we decided not to compare brain shrinkage directly between demented and nondemented groups but instead to calculate lifespan normal and pathologic shrinkage. Also, brain shrinkage is not specific of AD and has been found in NA and other neurodegenerative diseases [65].

Subjects with larger ICV may have more cognitive reserve against dementia. In other words, the differences between volume seen between AD and nondemented age-matched controls may be preordained if the controls "started out" with higher volumes in adulthood. To minimize this effect, shrinkage in AD and controls has been calculated using a common value of relative brain volume in adult life, which present low deviation from the mean (Table 3). Literature data were extracted from studies with different purposes, which implies wide data variability due to a diversity of MRI pulse sequences, definitions of the measurement space, and segmentation routines. Therefore, exact agreement between the various data should not be expected.

For future focused studies, it could be suggested to analyze few groups separately, to appreciate if the trends revealed in those results are similar to the aggregated group outcomes. Also, as the parameters chosen from the literature vary across studies, sensitivity analyses using a range of parameters from the literature could be carried out.

5. Conclusions

The purpose of this work was to estimate increments of mechanical stress the brain undergoes in neurodegenerative diseases. Selecting AD as a primary model of a nonlinear dynamic, chronically progressive degenerative disease, pressure equivalents were found to be 42% higher in AD brains (5.92 mm Hg) comparatively with NA brains

(3.43 mm Hg). The phenomenon of mechanical brain fatigue, or the increased amplitude of oscillations generated by arterial shock waves, was suggested to mainly contribute to the accumulation of cerebral viscoelastic pressure in AD.

Using mathematical tools, we have revisited an old hypothesis: the fact that mechanics play a key role in the pathogenesis of AD and dementia. Possibly, the results indicate that brain atrophy due to AD pathology may be impacted by cumulative hemodynamic stress during the lifespan. The fluid and solid mechanics equations presented in this study require validation before conclusions can be drawn. This is an alternative or complementary hypothesis article, not against other hypothesis, rather integrative and compatible with advances in the field of brain mechanobiology [1]. This hypothesis was supported by available data from the literature and mathematical arguments, offering a venue for future investigations in the physical mechanical processes underpinning the physiological and pathologic aging of the brain as well as their influence on neuronal and synaptic loss as well as on brain atrophy.

Acknowledgments

H.H. is supported by the AXA Research Fund, the Fondation Université Pierre et Marie Curie and the Fondation pour la Recherche sur Alzheimer, Paris, France. The research leading to these results has received funding from the program "Investissements d'avenir" ANR-10-IAIHU-06.

RESEARCH IN CONTEXT

1. Systematic review: The focus of our work concerns the role of mechanical forces on the pathophysiology of Alzheimer's disease (AD). Since the last 20 years, several hypotheses have described a link between AD and mechanical factors, such as intracranial pressure, intracranial impedance, cerebrospinal fluid dynamics, and cerebrovascular pulse waves.
2. Interpretation: Possibly, our results on increments of mechanical stress undergone by the brain in AD indicate that brain atrophy may be impacted by cumulative hemodynamic stress during lifespan. This is an alternative or complementary hypothesis, not against other hypothesis, rather integrative and compatible with recent advances in the field of brain mechanobiology.
3. Future directions: The presented work point clearly that there is a need for extending the focus of attention to the physical mechanical processes underpinning the physiological and pathologic aging of the brain as well as their influence on neuronal and synaptic loss as well as on brain atrophy.

References

[1] Tyler WJ. The mechanobiology of brain function. Nat Rev Neurosci 2012;13:867–78.
[2] Linninger AA, Xenos M, Sweetman B, Ponkshe S, Guo X, Penn R. A mathematical model of blood, cerebrospinal fluid and brain dynamics. J Math Biol 2009;59:729–59.
[3] Henneman WJP, Sluimer JD, Barnes J, van der Flier WM, Sluimer IC, Fox NC, et al. Hippocampal atrophy rates in Alzheimer disease. Neurology 2009;72:999–1007.
[4] Braak H, Braak E, Bohl J. Staging of Alzheimer-related cortical destruction. Eur Neurol 1993;33:403–8.
[5] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med;:a006189. 2011 Available from: http://perspectivesinmedicine.cshlp.org/content/1/1/a006189. Accessed March 4, 2015.
[6] Sack I, Streitberger K-J, Krefting D, Paul F, Braun J. The influence of physiological aging and atrophy on brain viscoelastic properties in humans. PLoS One 2011;6:e23451.
[7] Murphy MC, Huston J, Jack CR, Glaser KJ, Manduca A, Felmlee JP, et al. Decreased brain stiffness in Alzheimer's disease determined by magnetic resonance elastography. J Magn Reson Imaging 2011;34:494–8.
[8] Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci 1991;12:383–8.
[9] Hampel H, Lista S. Alzheimer disease: From inherited to sporadic AD-crossing the biomarker bridge. Nat Rev Neurol 2012;8:598–600.
[10] Hampel H, Wilcock G, Andrieu S, Aisen P, Blennow K, Broich K, et al. Biomarkers for Alzheimer's disease therapeutic trials. Prog Neurobiol 2011;95:579–93.
[11] Hampel H, Lista S, Khachaturian ZS. Development of biomarkers to chart all Alzheimer's disease stages: The royal road to cutting the therapeutic Gordian Knot. Alzheimers Dement 2012;8:312–36.
[12] Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W, et al. Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI). Alzheimers Dement J Alzheimers Assoc 2005;1:55–66.
[13] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.
[14] O'Brien LM, Ziegler DA, Deutsch CK, Kennedy DN, Goldstein JM, Seidman LJ, et al. Adjustment for whole brain and cranial size in volumetric brain studies: A review of common adjustment factors and statistical methods. Harv Rev Psychiatry 2006;14:141–51.
[15] Olbers D. Ocean Dynamics [Internet]. New York: Springer; 2010. Available from: https://login.libproxy.uregina.ca:8443/login?url=http://link.springer.com/openurl?genre=book&isbn=978-3-642-23449-1; 2010. Accessed September 11, 2013.
[16] Manduca A, Oliphant TE, Dresner MA, Mahowald JL, Kruse SA, Amromin E, et al. Magnetic resonance elastography: Non-invasive mapping of tissue elasticity. Med Image Anal 2001;5:237–54.
[17] DeCarli C, Maisog J, Murphy DG, Teichberg D, Rapoport SI, Horwitz B. Method for quantification of brain, ventricular, and subarachnoid CSF volumes from MR images. J Comput Assist Tomogr 1992;16:274–84.
[18] DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the Framingham heart study: Establishing what is normal. Neurobiol Aging 2005;26:491–510.
[19] Bromiley PA T N, Jackson A. Trends in brain volume change with normal ageing. Proc MIUA'05. 2005;247–250.
[20] Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14(1 Pt 1):21–36.
[21] Cline HE, Lorensen WE, Souza SP, Jolesz FA, Kikinis R, Gerig G, et al. 3D surface rendered MR images of the brain and its vasculature. J Comput Assist Tomogr 1991;15:344–51.

[22] Matsumae M, Kikinis R, Mórocz IA, Lorenzo AV, Sándor T, Albert MS, et al. Age-related changes in intracranial compartment volumes in normal adults assessed by magnetic resonance imaging. J Neurosurg 1996;84:982–91.
[23] Yamato K, Hata Y, Kamiura N, Kobashi S, Mori E. Automatic extraction of cerebral and intracranial regions from MRI images for functional cerebral diagnosis. Visual Computing 1995;6:96–7.
[24] Yasuda M, Mori E, Kitagaki H, Yamashita H, Hirono N, Shimada K, et al. Apolipoprotein E epsilon 4 allele and whole brain atrophy in late-onset Alzheimer's disease. Am J Psychiatry 1998; 155:779–84.
[25] Kruggel F. MRI-based volumetry of head compartments: Normative values of healthy adults. Neuroimage 2006;30:1–11.
[26] Lemaître H, Crivello F, Grassiot B, Alpérovitch A, Tzourio C, Mazoyer B. Age- and sex-related effects on the neuroanatomy of healthy elderly. Neuroimage 2005;26:900–11.
[27] Smith CD, Chebrolu H, Wekstein DR, Schmitt FA, Markesbery WR. Age and gender effects on human brain anatomy: A voxel-based morphometric study in healthy elderly. Neurobiol Aging 2007; 28:1075–87.
[28] Simmons A, Westman E, Muehlboeck S, Mecocci P, Vellas B, Tsolaki M, et al. The AddNeuroMed framework for multi-centre MRI assessment of Alzheimer's disease: Experience from the first 24 months. Int J Geriatr Psychiatry 2011;26:75–82.
[29] Wilkinson D, Fox NC, Barkhof F, Phul R, Lemming O, Scheltens P. Memantine and brain atrophy in Alzheimer's disease: A 1-year randomized controlled trial. J Alzheimers Dis 2012;29:459–69.
[30] Harper CG, Kril JJ, Daly JM. The specific gravity of the brains of alcoholic and control patients: A pathological study. Br J Addict 1987; 82:1349–54.
[31] Murphy MC, Curran GL, Glaser KJ, Rossman PJ, Huston J 3rd, Poduslo JF, et al. Magnetic resonance elastography of the brain in a mouse model of Alzheimer's disease: Initial results. Magn Reson Imaging 2012;30:535–9.
[32] Soza G, Grosso R, Nimsky C, Hastreiter P, Fahlbusch R, Greiner G. Determination of the elasticity parameters of brain tissue with combined simulation and registration. Int J Med Robot 2005;1:87–95.
[33] Omori K, Zhang L, Yang K, King A. Effect of cerebral vasculatures on the mechanical response of brain tissue: A preliminary study. Nihon Kikai Gakkai Tokai Shibu Chiku Koenkai Koen Ronbunshu 2001; 2001:148–50.
[34] Kim J, Thacker NA, Bromiley PA, Jackson A. Prediction of the jugular venous waveform using a model of CSF dynamics. AJNR Am J Neuroradiol 2007;28:983–9.
[35] El Sankari S, Gondry-Jouet C, Fichten A, Godefroy O, Serot JM, Deramond H, et al. Cerebrospinal fluid and blood flow in mild cognitive impairment and Alzheimer's disease: A differential diagnosis from idiopathic normal pressure hydrocephalus. Fluids Barriers CNS 2011;8:12.
[36] Silverberg G, Mayo M, Saul T, Fellmann J, McGuire D. Elevated cerebrospinal fluid pressure in patients with Alzheimer's disease. Cerebrospinal Fluid Res 2006;3:7.
[37] Pollay M. The function and structure of the cerebrospinal fluid outflow system. Cerebrospinal Fluid Res 2010;7:9.
[38] Mokri B. The Monro-Kellie hypothesis: Applications in CSF volume depletion. Neurology 2001;56:1746–8.
[39] Henry-Feugeas MC. Intracranial MR dynamics in clinically diagnosed Alzheimer's disease: The emerging concept of "pulse wave encephalopathy.". Curr Alzheimer Res 2009;6:488–502.
[40] O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: A clinical perspective. J Am Coll Cardiol 2007;50:1–13.
[41] O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: Cause and logic of therapy. Hypertension 2005;46:200–4.
[42] O'Rourke MF, Safar ME. Pulse wave encephalopathy. J Hypertens 2012;30:429.
[43] Wostyn P. Intracranial pressure and Alzheimer's disease: A hypothesis. Med Hypotheses 1994;43:219–22.
[44] Wostyn P. Can chronic increased intracranial pressure or exposure to repetitive intermittent intracranial pressure elevations raise your risk for Alzheimer's disease? Med Hypotheses 2004;62:925–30.
[45] Wostyn P, Audenaert K, De Deyn PP. Alzheimer's disease-related changes in diseases characterized by elevation of intracranial or intraocular pressure. Clin Neurol Neurosurg 2008;110:101–9.
[46] Wostyn P, Audenaert K, De Deyn PP. Alzheimer's disease: Cerebral glaucoma? Med Hypotheses 2010;74:973–7.
[47] Bateman GA. The role of altered impedance in the pathophysiology of normal pressure hydrocephalus, Alzheimer's disease and syringomyelia. Med Hypotheses 2004;63:980–5.
[48] Bateman GA. Pulse wave encephalopathy: A spectrum hypothesis incorporating Alzheimer's disease, vascular dementia and normal pressure hydrocephalus. Med Hypotheses 2004;62:182–7.
[49] Bateman GA, Levi CR, Schofield P, Wang Y, Lovett EC. The venous manifestations of pulse wave encephalopathy: windkessel dysfunction in normal aging and senile dementia. Neuroradiology 2008;50:491–7.
[50] Nagai K, Akishita M, Machida A, Sonohara K, Ohni M, Toba K. Correlation between pulse wave velocity and cognitive function in nonvascular dementia. J Am Geriatr Soc 2004;52:1037–8.
[51] Barz H, Schreiber A, Barz U. Impulses and pressure waves cause excitement and conduction in the nervous system. Med Hypotheses 2013;81:768–72.
[52] Xu Z, Paparcone R, Buehler MJ. Alzheimer's abeta(1-40) amyloid fibrils feature size-dependent mechanical properties. Biophys J 2010; 98:2053–62.
[53] Kristen AV, Schnabel PA, Winter B, Helmke BM, Longerich T, Hardt S, et al. High prevalence of amyloid in 150 surgically removed heart valves—a comparison of histological and clinical data reveals a correlation to atheroinflammatory conditions. Cardiovasc Pathol 2010; 19:228–35.
[54] Niggemeyer O, Steinhagen J, Fuerst M, Zustin J, Rüther W. Amyloid deposition in rheumatoid arthritis of the hip. Rheumatol Int 2012; 32:2645–51.
[55] Gatson JW, Warren V, Abdelfattah K, Wolf S, Hynan LS, Moore C, et al. Detection of β-amyloid oligomers as a predictor of neurological outcome after brain injury. J Neurosurg 2013;118:1336–42.
[56] Hughes TM, Kuller LH, Barinas-Mitchell EJM, Mackey RH, McDade EM, Klunk WE, et al. Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults. Neurology 2013;81:1711–8.
[57] Zhong W, Cruickshanks KJ, Schubert CR, Carlsson CM, Chappell RJ, Klein BEK, et al. Pulse wave velocity and cognitive function in older adults. Alzheimer Dis Assoc Disord 2014;28:44–9.
[58] Kanayama G, Takeda M, Niigawa H, Ikura Y, Tamii H, Taniguchi N, et al. The effects of repetitive mild brain injury on cytoskeletal protein and behavior. Methods Find Exp Clin Pharmacol 1996;18:105–15.
[59] Kane MJ, Angoa-Pérez M, Briggs DI, Viano DC, Kreipke CW, Kuhn DM. A mouse model of human repetitive mild traumatic brain injury. J Neurosci Methods 2012;203:41–9.
[60] Sivanandam TM, Thakur MK. Traumatic brain injury: a risk factor for Alzheimer's disease. Neurosci Biobehav Rev 2012;36:1376–81.
[61] Helzner EP, Luchsinger JA, Scarmeas N, Cosentino S, Brickman AM, Glymour MM, et al. Contribution of vascular risk factors to the progression in Alzheimer disease. Arch Neurol 2009;66:343–8.
[62] Lee SJ. A possible pathogenesis for Alzheimer's disease: Craniomaxillofacial dysfunction leading to localized cerebrospinal fluid stasis. Med Hypotheses 2009;72:199–210.
[63] Safar ME, Nilsson PM, Blacher J, Mimran A. Pulse pressure, arterial stiffness, and end-organ damage. Curr Hypertens Rep 2012;14:339–44.
[64] Ding SF, Ni M, Liu XL, Qi LH, Zhang M, Liu CX, et al. A causal relationship between shear stress and atherosclerotic lesions in apolipoprotein E knockout mice assessed by ultrasound biomicroscopy. Am J Physiol Heart Circ Physiol 2010;298:H2121–9.
[65] Bozzali M, Cercignani M, Caltagirone C. Brain volumetrics to investigate aging and the principal forms of degenerative cognitive decline: A brief review. Magn Reson Imaging 2008;26:1065–70.