Mechanical stress related to brain atrophy in Alzheimer’s disease

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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...
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 search 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...
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).

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

The reduction in brain volume (shrinkage or \( \Delta BV \)) 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 (\( \Delta BV/BV \)) 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.

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

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

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

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

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

### 2.3. Calculating mechanical stress (\( \sigma \)) 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 \( \Delta x \) 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 (\( \sigma \)) 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→NA) and young adults–AD (E_a→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.

\[ p + σ_c + σ_e = \text{constant} \]  
\[ p + (d \times c^2) + (E \times Δx/x) = \text{constant} \]  
\[ σ_e = E \times Δx/x \]  
\[ \text{Fig. 3. Proposed equilibrium relationship of three sources of pressure (σ) exerted permanently over an organ: external pressure (p), hemodynamic pressure (σ_c), and viscoelastic pressure (σ_e): } p + σ_c + σ_e = \text{constant.} \]

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), Lemaire 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.

\[ (ΔBV/BV)_a = 1 - [ (BV/ICV)_{AD}/(BV/ICV)_a ] \]  
\[ (ΔBV/BV)_a = 1 - (0.65/0.733) \]  
\[ (ΔBV/BV)_a = 0.26 \]  
\[ (ΔBV/BV)_NA = 1 - [ (BV/ICV)_{NA}/(BV/ICV)_a ] \]  
\[ (ΔBV/BV)_NA = 1 - (0.74/0.733) \]  
\[ (ΔBV/BV)_NA = 0.16 \]  

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 (Δx/x)_AD and NA (Δx/x)_NA conditions were estimated in 10% and 5.6%, respectively. As stated previously, (ΔBV/BV)_AD and (ΔBV/BV)_NA correspond to 0.26 (Equation 8) and 0.16 (Equation 9), respectively.

\[ (Δx/x)_A = 1 - [1 - (ΔBV/BV)_A]^{1/3} \]  
\[ (Δx/x)_A = 0.10 \]  
\[ (Δx/x)_B = 0.056 \]  
\[ (Δx/x)_B = 0.56 \]
Mechanical stress related to a deformation along an axis \( x \), relative changing in dimensions along an axis (or relative deformation); \( p \), external pressure; \( s \), relative changing in dimensions along an axis (or relative deformation); \( E \), elastic modulus or Young’s modulus of a material or tissue.

Relative brain deformation along an axis in AD and NA conditions

The Young’s modulus of the brain in AD \( (E_{AD} = 6.60 \text{ KPa}) \), NA \( (E_{NA} = 7.11 \text{ KPa}) \), 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 \( (E_a + E_{NA})/2 = 8.16 \text{ kPa} \) and \( (E_a + E_{AD})/2 = 7.90 \text{ KPa} \), respectively. The \( \Delta x/x \) of 0.10 in AD and 0.056 in NA were calculated using Equations 10 and 11, respectively.

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

\[
\sigma_{AD} = E_{a \rightarrow AD} \times (\Delta x/x)_{AD}
\]
\[\text{[Eq.13]}\]

\[
\sigma_{NA} = E_{a \rightarrow NA} \times (\Delta x/x)_{NA}
\]
\[\text{[Eq.14]}\]

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

Table 4 shows brain mechanical properties in normal adult, NA, and AD. The equivalent value of mechanical stress \( \sigma \) related to brain deformation in AD and NA \( (\sigma_{AD} \text{ and } \sigma_{NA}) \) 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 \( (E_{AD} = 6.60 \text{ KPa}) \), NA \( (E_{NA} = 7.11 \text{ KPa}) \), 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 \( (E_a + E_{NA})/2 = 8.16 \text{ kPa} \) and \( (E_a + E_{AD})/2 = 7.90 \text{ KPa} \), respectively. The \( \Delta x/x \) of 0.10 in AD and 0.056 in NA were calculated using Equations 10 and 11, respectively.

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

\[
\sigma_{AD} = E_{a \rightarrow AD} \times (\Delta x/x)_{AD}
\]
\[\text{[Eq.13]}\]

\[
\sigma_{NA} = E_{a \rightarrow NA} \times (\Delta x/x)_{NA}
\]
\[\text{[Eq.14]}\]

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
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 3
Volumetric MRI data provided by literature review

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>ICV (mL)</th>
<th>BV (mL)</th>
<th>BV/ICV (range)</th>
<th>Age (range)</th>
<th>MMSE</th>
<th>HBP (%)</th>
<th>Segmentation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed samples:</td>
<td>2081</td>
<td>1263 ± 106.8</td>
<td>(0.71–0.80)</td>
<td>60.6 ± 9.5</td>
<td>42.3</td>
<td>[17]</td>
<td>DeCarli et al. [18]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adult and aging</td>
<td>1300</td>
<td>1263 ± 106.8</td>
<td>(0.77–0.92)</td>
<td>60.6 ± 9.5</td>
<td>42.3</td>
<td>[17]</td>
<td>DeCarli et al. [18]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>subjects</td>
<td>465</td>
<td>1263 ± 106.8</td>
<td>(0.65–0.83)</td>
<td>29.5 (18–79)</td>
<td>0</td>
<td>SPM</td>
<td>Good et al. [20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 1288 ± 132</td>
<td>(0.78–0.93)</td>
<td>57 ± 20</td>
<td>0</td>
<td>Tina Bromiley et al. [19]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49 1384 ± 139</td>
<td>(0.85–0.93)</td>
<td>56 ± 16</td>
<td>0</td>
<td>[21] Matsuama et al. [22]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 1507 ± 111</td>
<td>1161 ± 93</td>
<td>53.9 ± 8.7</td>
<td>30–29</td>
<td>[23] Yasuda et al. [24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young adults</td>
<td>145F</td>
<td>1495 ± 96</td>
<td>1304 ± 88</td>
<td>0.873 ± 0.017</td>
<td>24.3 ± 2.9</td>
<td>BRIAN Kruggel [25]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>145M</td>
<td>1616 ± 91</td>
<td>1417 ± 86</td>
<td>0.877 ± 0.018</td>
<td>24.1 ± 2.6</td>
<td>BRIAN Kruggel [25]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly subjects</td>
<td>227</td>
<td>1055 ± 86</td>
<td>76.0 ± 4</td>
<td>29.1 ± 0.76</td>
<td>FreeSurfer ADNI¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>331F</td>
<td>1288 ± 100</td>
<td>960</td>
<td>0.747</td>
<td>69.5 ± 2.9</td>
<td>27.4 ± 2.0</td>
<td>37.4</td>
<td>SPM Lemaire et al. [26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>331M</td>
<td>1454 ± 107</td>
<td>1066</td>
<td>0.733</td>
<td>69.5 ± 3.1</td>
<td>27.7 ± 2.0</td>
<td>48</td>
<td>SPM Lemaire et al. [26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>122 1327</td>
<td>(0.61–0.76)</td>
<td>75.0 ± 7.6</td>
<td>29.2 ± 1.0</td>
<td>SPM Smith et al. [27]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>117 0.86 (0.79–0.92)</td>
<td>72.9 ± 6.7</td>
<td>29.1 ± 1.2</td>
<td>CLASP Simmons et al. [28]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD subjects*</td>
<td>188</td>
<td>1000 ± 88</td>
<td>75.3 ± 6.2</td>
<td>23.3 ± 1.75</td>
<td>FreeSurfer ADNI¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>178 1460 ± 126</td>
<td>983 ± 91</td>
<td>0.65</td>
<td>73.5 ± 6</td>
<td>18.8 ± 4.8</td>
<td>[23] Yasuda et al. [24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>969 ± 108</td>
<td>74.0 ± 8</td>
<td>17.1 ± 2.4</td>
<td>40</td>
<td>BSI Wilkinson et al. [29]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>0.82 (0.74–0.92)</td>
<td>75.9 ± 6.2</td>
<td>20.7 ± 4.8</td>
<td>CLASP Simmons et al. [28]</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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].

¹ADNI data visualized and analyzed on November 28, 2014.

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

<table>
<thead>
<tr>
<th>Physical properties</th>
<th>Unit</th>
<th>Young adults</th>
<th>Normal aging</th>
<th>AD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>kg/m³</td>
<td>1040</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiffness</td>
<td>kPa</td>
<td>3.5–3.8</td>
<td>2.5–2.7</td>
<td></td>
<td>Sack et al. [6]</td>
</tr>
<tr>
<td>Stiffness</td>
<td>kPa</td>
<td>3.07</td>
<td>2.37</td>
<td>2.2</td>
<td>Murphy et al. [7]</td>
</tr>
<tr>
<td>Stiffness (mice)*</td>
<td>kPa</td>
<td>25</td>
<td>19.3</td>
<td>19.3</td>
<td>Murphy et al. [31]</td>
</tr>
<tr>
<td>Young’s modulus¹</td>
<td>kPa</td>
<td>9.21</td>
<td>7.11</td>
<td>6.6</td>
<td>Murphy et al. [7]</td>
</tr>
<tr>
<td>Young’s modulus</td>
<td>kPa</td>
<td>9.21</td>
<td></td>
<td></td>
<td>Soza et al. [32]</td>
</tr>
<tr>
<td>Bulk modulus</td>
<td>kPa</td>
<td>2190</td>
<td></td>
<td></td>
<td>Omori et al. [33]</td>
</tr>
<tr>
<td>Poisson’s ratio</td>
<td></td>
<td>0.496</td>
<td></td>
<td></td>
<td>Soza et al. [32]</td>
</tr>
</tbody>
</table>

Abbreviation: AD, Alzheimer’s disease.

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

¹Conversion of stiffness (μ or effective shear modulus) to Young’s modulus (E) by a scaling factor E = 3 μ [16].

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

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 cranio-spinal 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 intra-neuronal 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

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Table 5
Physical characteristics of the intracranial fluids

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

*Physiologic measures.
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) e4 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 non-demented 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 presents 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


