BRAIN TISSUE VISCOLASTICITY & EEG OSCILLATIONS: TOWARDS NOVEL DRUGS FOR ALZHEIMER'S DISEASE

Arturo Tozzi
Center for Nonlinear Science, Department of Physics, University of North Texas, Denton, Texas, USA
1155 Union Circle, #311427 Denton, TX 76203-5017 USA
tozziarturo@libero.it
Arturo.Tozzi@unt.edu

Here we provide an effort to physically correlate two underrated features of Alzheimer's disease (AD), i.e., changes in brain tissue's viscoelasticity and increased power in the low-frequency EEG bands. Indeed, the brain displays less stiffness in AD than in normal individuals, making the brain of diseased subjects more "liquid". Because electric waves propagate more slowly in less solid mediums, we hypothesize that the EEG waves' reduction detected in AD could be correlated with the pathological viscoelastic alterations of the impaired brain tissues. We provide the mathematical apparatus to test our hypothesis, showing that the theoretically predicted electric oscillations' decrease in less viscoelastic mediums matches the reduced stiffness detected in real brain tissues from AD patients. We conclude with a testable hypothesis: the use of drugs able to modify and restore the proper brain viscoelastic features might provide a useful therapeutic tool able to quicken EEG electric waves' frequencies, thus contributing to improve AD symptoms.

KEYWORDS: viscoelasticity; dementia; electric oscillations; waves; drugs.

Electroencephalography (EEG) analyses, including both resting state and event-related stimulation protocols, are useful in early diagnosis and discrimination of different dementia subtypes, such as Alzheimer's (AD), Mild Cognitive Impairment (MCI), Vascular dementias and the Lewy Body Dementias (LBD) (Waninger et al., 2016). In particular, promising EEG biomarkers for detection of AD include: 1) excessive slowing in parietal and temporal regions; 2) increased power in the low frequency bands (i.e., theta, delta, slow alpha) with reductions in higher frequency ones (i.e., beta, gamma), particularly in the middle and superior temporal gyrus and fusiform gyrus; 3) significant decrease in parietal/temporal alpha and global sigma, beta; 4) significant increases in slow wave activity over the sensorimotor region (Waninger et al., 2016 and 2018). 5) changes in the amplitude and latency of evoked potentials for both cognitive and sensory stimuli. Studies on EEG (with Fast Fourier Transform, network- and connectivity measures) to discriminate between LBD and AD also emphasize the valuable role of EEG in discerning among dementing disorders (van der Zande et al., 2018). Kowalski et al. (2001) assessed EEG changes in ninety-five patients with AD, divided into three subgroups: mild, marked and severe dementia. The EEG findings were classified using an eight-degree scale according to the background activity, presence and amount of theta and delta waves, focal changes, lateralization of focal changes, synchronization, and presence of sharp and spike waves. A significant correlation between the degree of EEG abnormalities and cognitive impairment was detected (Kowalski et al., 2001).
Poil et al. (2013) combined information from multiple EEG biomarkers into a diagnostic classification index, to improve the accuracy of predicting conversion from MCI to AD. Following 86 patients initially diagnosed with MCI for 2 years, they showed that EEG biomarkers mainly related to activity in the beta-frequency range (13–30 Hz) predict conversion from MCI to AD (Poil et al., 2013). Kwak (2006) compared topographical spectral power and occipital peak frequency (OPF) among elderly controls, MCI subjects and patients with four stages of AD. In AD patients, except those with a Clinical Dementia Rating Scale (CDR) score of 0.5, OPF was lower than elderly controls. The left anterior alpha spectral power was reduced in CDR 0.5; both posterior theta spectral powers were increased and all alpha spectral powers were reduced in CDR 1; all alpha/beta spectral powers were reduced and theta spectral power was increased in CDR 2; all alpha/beta spectral powers were reduced and all delta/theta spectral powers were increased in CDR 3. Patients with MCI exhibited a reduction in both centrotemporal, posterior delta and left anterior, centrotemporal theta fields (Kwak 2006). This suggests that AD patients display quantifiable dynamic changes as the disease progresses.

Here we ask whether the above-mentioned EEG alterations in AD can be correlated with the well-documented pathological changes in viscoelastic properties and, consequently, with the occurrence of the typical symptoms. To test our hypothesis, we will describe the behavior of electric currents in mediums equipped with different viscoelastic properties and will show how the impaired stiffness detected in AD might be one of the causes of the increased power in the low frequency EEG bands. We will show that this suggested relationship might lead to a novel therapeutic approach to AD: the use of drugs that increase the viscoelasticity of the brain tissue, contributing to improve the impaired transmission of nervous electric waves.

MATERIALS AND METHODS

By using mathematical approaches to oscillation's behavior in mediums with different viscoelastic features, our aim is to achieve theoretical values and compare them with the experimental data detected in healthy and AD subjects.

Measuring viscoelastic properties of nervous tissues. The study of viscoelastic properties of biological tissues has been proven useful in the assessment of several human diseases. For example, the thromboelastographic technique allows qualitative interpretation of coagulation cascade in neurocritical care and trauma-associated coagulopathy (**Figure 1A**) (Kreitzer et al., 2015; Galvez and Cortes, 2012). Measurement of brain tissue's mechanical properties is challenging, due to its multifaceted nonlinear viscoelastic behavior and poroelastic deformation. Viscoelastic assessment of nervous tissues has been carried, both in animals and humans, through different techniques, such as, e.g., rheology, cavitation rheology and indentation stress relaxation (Bilston et al., 1997; Mijailovic 2016; Li et al., 2016). Bilston et al. (1997), examining disks of fresh bovine brain tissue with a shear rheometer, demonstrated that shear relaxation moduli display fluid-like behavior. Smith et al. (2007) used atomic force microscopy elasticity mapping to probe the biomechanics of the elusive dendritic spines in living neurons, which undergo rapid activity-dependent shape fluctuations. In cultures of neonatal rat hippocampal neurons, these spines display a wide range of rigidities correlated with morphological characteristics, axonal association and glutamatergic stimulation. It is noteworthy that dendritic spines exhibit a uniquely large viscosity (four to five times that of other cell types) consistent with a high density of solubilized proteins, so that their weak power-law rheology can be described in terms of soft-glassy models for cellular mechanics (Smith et al., 2007).
Lu et al. (2007) isolated individual neurons and glial cells from mammalian hippocampus and retina. Cellular viscoelastic features were assessed through scanning force microscopy, bulk rheology and optically induced deformation. They found that the elastic behavior dominates over the viscous one in all the examined cells. In distinct cell compartments, such as soma and cell processes, the mechanical properties differ, most likely because of the sparce local distribution of cell organelles. In comparison to other eukaryotic cells, both neurons and glial cells are soft ("rubber elastic"), glial cells being the softest (Lu et al., 2006). Magnetic resonance elastography (MRE) allows the non-invasive visualization of mechanical properties of brain tissue in humans (Green et al., 2008). The behavior of the viscoelastic liquid is correlated with G^{I} and G^{II}, where G^{I} stands for the elastic modulus and G^{II} for the viscous modulus. Green et al. (2008) extracted the complex shear modulus for in vivo brain tissue from healthy volunteers. The data for in vivo brain storage modulus (G') showed that grey matter is significantly stiffer than white matter (3.1 and 2.7 kPa, respectively) (Green et al., 2008). Budday et al. (2017) combined cyclic and relaxation testing under multiple loading conditions, shear, compression and tension, to quantify the rheology of human cortex, basal ganglia, corona radiata and corpus callosum. They concluded that a simple finite viscoelastic Ogden-type model, with just a single viscoelastic mode and a constant viscosity, is able to capture typical features of brain tissue, i.e., nonlinearity, pre-conditioning, hysteresis and tension-compression asymmetry. The gray matter cortex's stiffnesses and time constants are μ=0.7 kPa, μ1=2.0 kPa, and τ1=9.7 s, while the white matter corona radiata's values are μ=0.3 kPa, μ1=0.9 kPa and τ1=14.9 s (Budday et al., 2017).
In sum, studies are available in animals and humans that quantify the viscoelastic properties of the brain tissue and describe the differences in stiffness among dissimilar neural structures and areas.

Brain tissue's viscoelastic properties in Alzheimer's disease. It has been hypothesized that amyloid-β peptide (Aβ) deposition in AD might modify the membrane/cytoskeletal structure of neural cells and their mechanical responses/viscoelastic features (Gong et al., 2016). Using atomic force microrheology, Gong et al. (2016) assessed the viscoelastic properties of primary neurons undergoing different Aβ treatments. They found that both the storage (G′G′) and loss (G″G″) moduli of neural cells are rate-dependent, growing by orders of magnitude as the driving frequency ωω varies from 1 to 100 Hz. However, a much stronger frequency dependence was observed in the loss modulus G″G″ than in G′G′. Both cell moduli increase gradually within the first 6 h of Aβ treatment before steady-state values are reached, while a higher dosage of Aβ leads to larger changes in cell properties obeying a power law structural damping model (Gong et al., 2016). Therefore, a quantitative link can be established between Aβ accumulation and the physical viscoelastic features of neural cells. Using MRE brain exam with a soft vibration source, Murphy et al. (2011) demonstrated reduced brain tissue stiffness in seven patients with AD, compared with ten controls. The median stiffness of the 10 healthy subjects was 3.07 kPa, with a range of 0.40 kPa (median and maximum coefficients of variation: 1.71% and 3.07%), compared with 2.20 kPa (0.33 kPa range) within the AD group (Murphy et al., 2011).
Quantitative changes in brain structure show unique regional brain stiffness patterns between dementia subtypes. ElSheikh et al. (2017) investigated MRE findings in four dementia cohorts (8 patients with AD, 5 with LBD, 5 with frontotemporal dementia, and 20 with normal pressure hydrocephalus). Once shear waves of 60-Hz vibration frequency were transmitted into the skull, brain stiffness was quantified in different areas. Regional stiffness patterns unique to each dementing disorder were observed: in particular, patients with AD showed decreased cerebral stiffness with regional softening of the frontal, temporal, parietal lobes and sensorimotor region (ElSheikh et al., 2017). Gerischer et al. (2017) investigated whether multifrequency-MRE (MMRE) can detect differences in hippocampal stiffness between patients with clinical diagnosis of AD and healthy controls (HC). In 21 AD patients and 21 HC (median age 75 years),

hippocampal volume and mean diffusivity (MD) were calculated. Maps of the magnitude |G*| and phase angle φ of the complex shear modulus were reconstructed using multifrequency inversion. Hippocampal stiffness (|G*|) and viscosity (φ) were significantly reduced in the patient group (Gerischer et al., 2017).
In conclusion, decreased brain stiffness and viscosity are detected in patients with clinical diagnosis of AD, in particular in the hippocampal regions.

Oscillatory waves's behavior in different viscoelastic mediums. Here we examine the behavior of a wave (in our case, the EEG electric currents) traveling in mediums with different viscoelastic properties (in our case, the healthy and HA brain tissues). It has been demonstrated that, when approaching dynamic problems of elasticity theory, a damping of oscillations in viscoelastic mediums occurs (Lombardo 1988). As a general rule, Arun et al. (2009) established that the electric field-driven surface instability of viscoelastic films is subjected to two different regimes: a) viscoelastic films with liquid-like behavior (in our case, AD brain tissue) display long wavelengths, governed by applied voltage and surface tension, independent of its elastic storage and viscous loss moduli; b) films with solid-like behavior (in our case, healthy brain tissue) require a threshold voltage for the instability, whose wavelength always scales as ~4×film thickness, independent of its surface tension, applied voltage, loss and storage moduli; 3) wavelength in a narrow transition zone between these regimes depends on the storage modulus. These observations allow us to build fluids shear flow curves for EEG electric oscillations traveling in brain tissues with different viscoelastic behavior, i.e., the more "solid" normal brain and the more "liquid" AD brain. In order to shape our model, we need at first a suitable choice of brain tissue parameters for our viscoelastic tool, including a number of internal variables (each representing a specific damping mechanism), such as unipolar, bipolar, M-shaped and W-shaped waveforms, as well as their orientation, amplitudes and pulse durations (Gan et al., 2009). Other criteria, such as behavior of Newtonian and non-Newtonian fluids under different actuating waveforms, need to be imposed to select a spectrum function with the potential of describing a wide range of brain tissue's viscoelastic behaviors.
Which are the best suitable models? Some approaches are worth of mention. Joseph and Saut (1986) discussed concepts associated with viscosity, elasticity, hyperbolicity, and ill-posedness of Cauchy problems in the flow of viscoelastic fluids, framing their analysis in terms of vorticity, relations between change of type in steady flow and regularization of Hadamard instabilities by addition of Newtonian contributions to the constitutive equations. Magnetoelasticity assesses the interaction between externally applied magnetic fields (governed by the Maxwell equations for electromagnetic fields) and the elastic motion/deformation of a lattice (governed by stress-strain relations) (Datta, 1986). Ogilvie and Proctor (2003) demonstrated a correlation between viscoelastic mediums and electrically conducting fluids containing a magnetic field. These Authors compared the stability properties of differentially rotating viscoelastic flows, showing that an instability of the Oldroyd-B fluid occurs which, physically distinct from the inertial/elastic well-known instabilities, is equivalent to the magneto-rotational instability. This behavior is correlated with the kinetic energy of the shear flow, rather than depending on the streamlines' curvature (Ogilvie and Proctor, 2003). Further, fractional order models of polymers' viscoelasticity allow the assessment of time-domain responses as stress relaxation as well as frequency domain, in terms of Volterra integral equations of the second kind (Adolfsson et al., 2005; Harvill 2003). Sullivan (2006) introduced a novel spectrum-based model for the description of the materials' behavior, in which the time-dependent response of viscoelastic materials is not expressed through the use of series. He used the Laplace transform technique to achieve the required formulae for viscoelastic Lame' functions, relaxation and bulk moduli, creep bulk and shear compliance, as well as Poisson's ratio (Sullivan 2006).

Our operational approach. Taking into account the limitations and the concerns raised by the rheological models described in the above paragraph, we aim to build theoretical curves which correlate oscillation frequencies and viscoelastic behavior, using the following procedures. Del Giudice et al. (2017), explored, via seven rheological techniques, the viscoelastic properties of hydroxyethyl cellulose solutions dissolved in water, at different time and length scales. They found an excellent convergence between various rheological techniques over a broad range of frequencies and concentrations, allowing them to derive microstructural information from direct readings, rather than inferring them from fitting procedures of fluids shear flow curves. Martínez-Mardones et al. (2002) used the Deborah number, defined as the ratio between the relaxation time (i.e., the time it takes for a material to adjust to applied stresses or deformations), and the characteristic time scale of an experiment (or a computer simulation) probing the material's response. The Deborah number Γ can be written as follows:
$\Gamma = t_c / t_p$
Where t_c stands for the relaxation time and t_p for the "time of observation", i.e., the process' timescale. The Deborah number combines both the material's elasticity and viscosity: at lower Deborah numbers, the material behaves in a more fluid-like manner, with an associated Newtonian viscous flow. At higher Deborah numbers, the material enters the non-Newtonian regime, demonstrating solid-like behavior increasingly dominated by elasticity. Tomar et al. (2013), assessing the propagation of time harmonic waves in thermo-viscoelastic material with voids, detected four basic waves traveling with distinct speeds: three dilatational waves (coupled due to the presence of voids of the material), and a shear wave (uncoupled) which traveled independently.
Also, we require a mathematical model that describes the one-dimensional vibrations of a multi-layered composite lattice with periodic structure, in touch with Shamaev and Shumilova (2018). Indeed, we entail that the brain tissue consists of a large number of alternating layers of an isotropic elastic material and an isotropic non-aging viscoelastic

material with long-term memory, for which the regular part of the shear relaxation kernel is approximated by one exponential function. In addition, oscillations are assumed here to be perpendicular to the layers.
In sum, at first, we need to calculate through parametric simulations the approximate behavior of waves frequencies in mediums with different stiffness; then, to investigate the tangible counterparts in the real brain, both in healthy subjects and AD patients. In particular we, took into account the values of brain stiffness calculated by Murphy et al. (20111). For technical readers, the formula used for our simulations can be found in: Del Giudice et al. (2017), Martínez-Mardones et al. (2002), Gan et al. (2009), Tomar et al. (2013), Shamaev and Shumilova (2018).

RESULTS

Once numerical simulations were performed for specific models with various oscillations frequencies and medium viscoelasticity, some the achieved results were portrayed in the plots illustrated in **Figures 1B** and **1C**. Note that increases in viscoelasticity correspond, in our simulations, to increased amounts of high-frequency oscillations. In order to check whether the real oscillatory responses from experimental available neurodata match our simulations, the plots describing the material's properties were used to assess the behavior of EEG oscillations in different brain tissue's loading configurations. **Figure 1D** summarizes what happens in the brain of normal subjects and AD patients. Healthy subjects' brain tissues display higher values of viscoelastic indexes and encompassed higher EEG frequencies. In turn, AD's brain tissues display a more liquid behavior: this corresponds to lower EEG frequencies, as expected.
In sum, theoretical results from simulations agree well with the real measured data in both controls and AD patients.

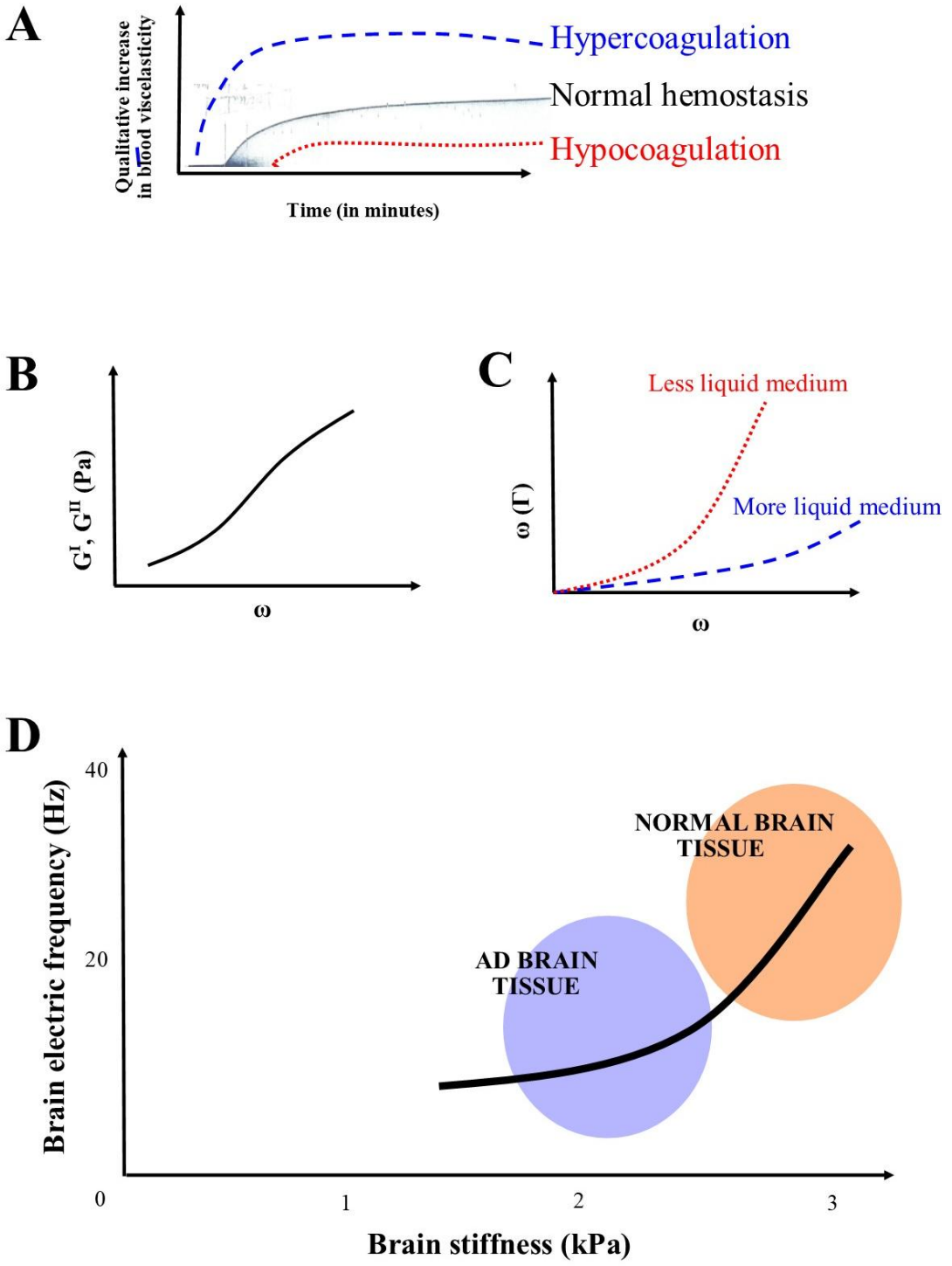

Figure 1A. A real thrombolastogram. The behavior of the blood from a control subject (black line) is compared with the blood features of patients with slowed hemostasis (thick red line) and thrombotic syndromes (blue dotted line). Modified from Vittorio Tozzi, Ospedale Cardarelli, personal communication.
Figure 1B. Linear viscoelastic moduli versus frequency for a wave with well-established initial conditions. The behavior of the viscoelastic liquid is correlated with G^{I} and G^{II}, where G^{I} stands for the elastic modulus and G^{II} for the viscous one. Modified from: Del Giudice et al. (2017). **Figure 1C**. Critical oscillation frequency ω (Γ) versus Deborah number Γ for viscoelastic mediums with different coefficients Λ, corresponding to tissues with higher (blue dotted line) or lower stiffness (thick red line). Modified from: Martínez-Mardones et al. (2002). **Figure 1D**.

Correlation between brain tissue's viscoelasticity and EEG frequencies (mean values). The plot highlights the occurrence of two different regimes: low EEG frequencies/low tissue viscoelasticity in AD patients; high EEG frequencies/high tissue viscoelasticity in healthy subjects.

DISCUSSION

The rheology of ultrasoft materials such as the human brain is highly sensitive to regional and temporal variations and to the type of loading (Budday et al., 2017). Here we showed that the decrease in brain stiffness occurring in AD can be correlated with the experimentally detected pathological EEG frequencies' slowing. Starting from the observation that electromagnetic waves display lower frequencies when traveling through a more liquid medium (compared with a more solid one), we were able to match theoretical simulations, based on well-established mathematical formulas from elasticity theory, with real data available from the current neuroscientific literature.

What is the rationale that permits us to throw a bridge between brain tissue's viscoelastic features and neural electric currents? In AD, brain degeneration starts from the medial temporal lobes (enthorinal/perirhinal cortex and hippocampus), inferolateral temporal cortex and Meynert's nucleus basalis, then spreads to lateral and medial temporal lobes and lateral frontal cortex. As AD progresses, posterior-predominant cortical atrophy becomes symptomatically apparent, along with the loss of memory due to the atrophy of the medial temporal structures. The impact of cell and tissue mechanics on brain homeostasis and neural degeneration is well-recognized. When mechanical force is translated into biochemical signals, it influences cell differentiation, survival, proliferation, migration and tissue behavior (Barnes et al., 2018). Some diseases develop when the normal viscoelastic tissue properties are lost, e.g., when aberrant increase of interstitial pressure/compression force, or abnormal stiffening of the extracellular matrix, occurs. Many pathological states are characterized by dramatic changes in cell/tissue mechanics, so that dysregulation of local forces may lead to activation of mechano-signaling which compromises biological integrity/function and promotes disease progression. (Barnes et al., 2018). The histopathological features of AD are characterized not just by neuritic plaques, but also by amyloid angiopathy and decrease in the cortical levels of several proteins and neurotransmitters. Simultaneous EEG–fMRI and simulations based on a biophysical model of the hemodynamic response to neuronal activity suggest that the blood oxygen level-dependent response becomes faster for rapidly varying stimuli (Lewis et al., 2018). Consequently, identifying vascular delays due to vessels damages in AD might be of increasing importance in the evaluation of higher-frequency electric activity.

Understanding the brain tissues' rheology and its correlation with EEG frequencies could allow us to more accurately model the behavior of the brain during neurological pathologies. EEG is a reliable tool in dementia research and diagnosis, contributing to the differential diagnosis and the prognosis of diseases progression (Tsolaki et al., 2014). The slowing of EEG waves in AD may lead to the clinical symptoms and signs, and this paves the way to novel feasible therapeutic approaches. Indeed, if a correlation does exist between the more "liquid" brain and the generalized decrease of EEG frequencies, it could be hypothesized that drugs able to increase the brain tissues' viscoelasticity might lead to an improvement of electric frequencies, and therefore to (at least) partial restoration of AD symptoms. This idea has been at least partially put forward by Munder et al. (2018), who investigated the potential therapeutic effects of physical, cognitive and social stimulation on brain viscoelasticity and histopathological characteristics. They used MRE in female APP23 mice (i.e., a transgenic mouse model of AD) at early stages of disease progression, detecting hippocampal alterations in viscoelasticity related to histopathological changes. In such a vein, the use of mannitol as a drug potentially able to increase brain viscoelasticity could be suggested. Interestingly, in a few pilot studies, mannitol has been already proposed for the treatment of brain diseases, although based on standpoints, frameworks and premises rather different from ours. Sil (2016) hypothesized that neurodegeneration in AD patients may be associated with changes of peripheral immune responses. Starting from the observation that peripheral immune responses can be altered due to neuroinflammation in colchicine induced AD (cAD) rats, the Author suggested that their leaky blood-brain barrier (BBB) may be involved in inducing peripheral inflammation. In sum, Sil (2016) states that the peripheral immune responses in cAD rats after 30 and 60min of mannitol (BBB opener) injection are related to the magnitude of BBB impairment. Gonzales-Portillo et al. (2014) point towards the mannitol as a drug with the potential to transiently disrupt the BBB and facilitate the entry of stem cells and neurotrophic factors, in order to restore the injured brain in adult stroke and neonatal cerebral palsy. In turn, Shaltiel-Karyo et al. (2013) were interested in the ability of mannitol to inhibit the formation of alpha synuclein aggregates (clumps of the protein associated with Parkinson's disease). They suggested that mannitol administration, due to its ability to inhibit the formation of alpha synuclein, could be a promising new approach for treating brain-related diseases such as AD. Indeed, when administered to a Parkinson Drosophila model, mannitol dramatically corrected behavioral defects and reduced the amount of α-synuclein aggregates in the brains of treated flies (Shaltiel-Karyo et al., 2013).

Apart from mannitol, other drugs (such as, e.g., hyaluronic acid) might help to increase the impaired brain tissues' viscoelasticity in AD patients. For example, trials with hyperosmolar drugs could be performed in murine models of AD. To provide another feasible candidate, osmolytes are small, naturally occurring compounds which protect intracellular macromolecules exposed to denaturing conditions and stabilize proteins, acting as chemical chaperones under changing environmental conditions/disease states (Rabbani and Choi, 2018). Osmolytes naturally accumulate at high concentrations in the intracellular environment when cells/tissues are exposed to stressful conditions: this is a noteworthy remark, because protein aggregation, misfolding and destabilization underlie the pathogenesis of several neurodegenerative disorders. The chaperone abilities of osmolytes, which could be able to increase brain stiffness, suggest that they might be used for the treatment of AD symptoms.

ACKNOWLEDGMENTS:

The Author would like to thank Vittorio Tozzi, M.D., Ospedale Cardarelli (Naples, Italy) who provided the thrombolastographic plot depicted in Figure 1A.

REFERENCES

1) Adolfsson K, Enelund M, Olsson P. 2005. On the Fractional Order Model of Viscoelasticity. Mechanics of Time-Dependent Materials, January 2005, Volume 9(1): 15–34.
2) Arun N, Sharma A, Pattader PSG, Banerjee I, Dixit HM, Narayan KS. 2009. Electric-Field-Induced Patterns in Soft Viscoelastic Films: From Long Waves of Viscous Liquids to Short Waves of Elastic Solids. Phys. Rev. Lett., 102, 254502.
3) Barnes JM, Przybyla L, Weaver VM. 2017. Tissue mechanics regulate brain development, homeostasis and disease.J Cell Sci. 2017 Jan 1;130(1):71-82. doi: 10.1242/jcs.191742.
4) Bilston E, Liu Z, Phan-Thien N. 1997. Linear viscoelastic properties of bovine brain tissue in shear. Biorheology, Volume 34, Issue 6, November–December 1997, Pages 377-385. https://doi.org/10.1016/S0006-355X(98)00022-5.
5) Budday S, Sommer G, .Haybaeck J, Steinmann P, Holzapfel GA, Kuhl E. 2017. Rheological characterization of human brain tissue. Acta Biomaterialia, Volume 60, 15 September 2017, Pages 315-329. https://doi.org/10.1016/j.actbio.2017.06.024.
6) Datta BK. 1986. Magneto-viscoelastic interaction on one-dimensional wave propagation. Current Science,Vol. 55, No. 1 (January 5, 1986), pp. 19-21. https://www.jstor.org/stable/24088688.
7) Del Giudice, F., Tassieri, M. , Oelschlaeger, C. and Shen, A. Q. 2017. When microrheology, bulk rheology, and microfluidics meet: broadband rheology of hydroxyethyl cellulose water solutions. Macromolecules, 50(7), pp. 2951-2963. doi:10.1021/acs.macromol.6b02727.
8) ElSheikh M, Arani A, Perry A, Boeve BF, Meyer FB, et al. 2017. MR Elastography Demonstrates Unique Regional Brain Stiffness Patterns in Dementias. AJR Am J Roentgenol. 2017 Aug;209(2):403-408. doi: 10.2214/AJR.16.17455.
9) Galvez KC, Cortes CL. 2012. Thromboelastography: New concepts in haemostasis physiology and correlation with trauma associated coagulopathy. Volume 40, Issue 3, August–October 2012, Pages 224-230. Colombian Journal of Anesthesiology. https://doi.org/10.1016/j.rcae.2012.05.002.
10) Gan HY, Shan X, Eriksson T, Lok BK, Lam YC. 2009. Reduction of droplet volume by controlling actuating waveforms in inkjet printing for micro-pattern formation. Journal of Micromechanics and Microengineering, 19 (5).
11) Gerischer LM, Fehlner A, Köbe T, Prehn K, Antonenko D, et al. 2017. Combining viscoelasticity, diffusivity and volume of the hippocampus for the diagnosis of Alzheimer's disease based on magnetic resonance imaging. Neuroimage Clin. 2017 Dec 20;18:485-493. doi: 10.1016/j.nicl.2017.12.023.
12) Gong Z, You R, Chang R C-C Lin Y. 2016. Viscoelastic response of neural cells governed by the deposition of amyloid-β peptides (Aβ). Journal of Applied Physics 119, 214701; https://doi.org/10.1063/1.4952704.
13) Gonzales-Portillo GS, Sanberg PR, Franzblau M, Gonzales-Portillo C, Diamandis T, et al. 2014. Mannitol-Enhanced Delivery of Stem Cells and Their Growth Factors Across the Blood–Brain Barrier. Cell Transplant. 2014; 23(0): 531–539. doi: 10.3727/096368914X678337.
14) Green MA, Bilston LE, Sinkus R. 2008. In vivo brain viscoelastic properties measured by magnetic resonance elastography. NMR in Biomedicine 21(7):755-64. DOI: 10.1002/nbm.1254
15) Harvill LR. 2003. Vito Volterra and viscoelasticity. Journal of the Franklin Institute, Volume 282, Issue 2, August 1966, Pages 85-91, https://doi.org/10.1016/0016-0032(66)90354-1.

16) Joseph DD, Saut JC. 1986. Change of type and loss of evolution in the flow of viscoelastic fluids. Journal of Non-Newtonian Fluid Mechanics, Volume 20, 1986, Pages 117-141. https://doi.org/10.1016/0377-0257(86)80018-0.
17) Kowalski JW, Gawel M, Pfeffer A, Barcikowska M. 2001. The diagnostic value of EEG in Alzheimer disease: correlation with the severity of mental impairment. J Clin Neurophysiol. 2001 Nov;18(6):570-5.
18) Kwak YT. 2006. Quantitative EEG findings in different stages of Alzheimer's disease. J Clin Neurophysiol. 2006 Oct;23(5):456-61.
19) Kreitzer NP, Bonomo J, Kanter D, Zammit C. 2015. Review of Thromboelastography in Neurocritical Care. Neurocrit Care. 2015 Dec;23(3):427-33. doi: 10.1007/s12028-015-0187-9.
20) Lewis LD, Setsompop K, Rosen BR, Polimeni JR. 2016. Fast fMRI can detect oscillatory neural activity in humans. Proc Natl Acad Sci U S A. 2016 Oct 25; 113(43): E6679–E6685. doi: 10.1073/pnas.1608117113.
21) Li Y, Deng J, Zhou J, Li X. 2016. Elastic and viscoelastic mechanical properties of brain tissues on the implanting trajectory of sub-thalamic nucleus stimulation. J Mater Sci Mater Med. 2016 Nov;27(11):163. doi: 10.1007/s10856-016-5775-5.
22) Lombardo VN. 1988. Consideration of damping of oscillations in a viscoelastic medium in numerical methods of solving dynamic problems of elasticity theory. Hydrotechnical Construction, 22 (6): 334–338.
23) Lu YB, Franze K, Seifert G, Steinhäuser C, Kirchhoff F, et al. 2006. Viscoelastic properties of individual glial cells and neurons in the CNS. Proc Natl Acad Sci U S A. 2006 Nov 21;103(47):17759-64.
24) Martínez-Mardones J, Tiemann RO, Walgraef D. 2002. Convection in binary viscoelastic fluid. Revista Mexicana de Fisica 48, Suplemento 3, 103-105.
25) Mijailovic MS. 2016. Methods to measure and relate the viscoelastic properties of brain tissue. Thesis: S.M., Massachusetts Institute of Technology, Department of Mechanical Engineering URI: http://hdl.handle.net/1721.1/106778.
26) Munder T, Pfeffer A, Schreyer S, Guo J, Braun J, et al. 2018. MR elastography detection of early viscoelastic response of the murine hippocampus to amyloid β accumulation and neuronal cell loss due to Alzheimer's disease. J MagnReson Imaging. 2018 Jan;47(1):105-114. doi: 10.1002/jmri.25741.
27) Murphy MC, Huston J IIIrd, Jack CR Jr, Glaser KJ, Manduca A, et al. 2011. Decreased brain stiffness in Alzheimer's disease determined by magnetic resonance elastography. J MagnReson Imaging. 2011 Sep;34(3):494-8. doi: 10.1002/jmri.22707.
28) Ogilvie GI, Proctor MRE. 2003. On the relation between viscoelastic and magnetohydrodynamic flows and their instabilities. Journal of Fluid Mechanics, Volume 476 10 February 2003 , pp. 389-409. https://doi.org/10.1017/S0022112002003051.
29) Poil SS, de Haan W, van der Flier WM, Mansvelder HD, Scheltens P, Linkenkaer-Hansen K. 2013. Integrative EEG biomarkers predict progression to Alzheimer's disease at the MCI stage. Front Aging Neurosci. 2013 Oct 3;5:58. doi: 10.3389/fnagi.2013.00058.
30) Rabbani G, Choi I. 2018. Roles of osmolytes in protein folding and aggregation in cells and their biotechnological applications. International Journal of Biological Macromolecules, Volume 109, 1 April 2018, Pages 483-491. . https://doi.org/10.1016/j.ijbiomac.2017.12.100.
31) Shaltiel-Karyo R, Frenkel-Pinter M, Rockenstein E, Patrick C, Levy-Sakin M, et al. 2013. A blood-brain barrier (BBB) disrupter is also a potent α-synuclein (α-syn) aggregation inhibitor: a novel dual mechanism of mannitol for the treatment of Parkinson disease (PD). J Biol Chem. 2013 Jun 14;288(24):17579-88. doi: 10.1074/jbc.M112.434787.
32) Shamaev AS, Shumilova VV. 2018. Calculation of natural frequencies and damping coefficients of a multi-layered composite using homogenization theory. IFAC-PapersOnLine, Volume 51, Issue 2, 2018, Pages 126-131. https://doi.org/10.1016/j.ifacol.2018.03.022.
33) Sil S, Ghosh A, Ghosh T. 2016 Impairment of blood brain barrier is related with the neuroinflammation induced peripheral immune status in intracerebroventricular colchicine injected rats: An experimental study with mannitol. Brain Res. 2016 Sep 1;1646:278-286. doi: 10.1016/j.brainres.2016.05.052.
34) Smith BA, Roy H, De Koninck P, Grütter P, De Koninck Y. 2007. Dendritic Spine Viscoelasticity and Soft-Glassy Nature: Balancing Dynamic Remodeling with Structural Stability. Biophysical Journal, Volume 92, Issue 4, 15 February 2007, Pages 1419-1430. https://doi.org/10.1529/biophysj.106.092361.
35) Sullivan RW. 2006. On the use of a spectrum-based model for linear viscoelastic materials. Mechanics of Time-Dependent Materials, September 2006, Volume 10, Issue 3, pp 215–228.
36) Tomar SK, Bhagwan J, Steeb H. 2013. Time harmonic waves in a thermo-viscoelastic material with voids. Journal of Vibration and Control. https://doi.org/10.1177/1077546312470479.
37) Tsolaki A, Kazis D, Kompatsiaris J, Kosmidou V, Tsolaki M. 2014. Electroencephalogram and Alzheimer's Disease: Clinical and Research Approaches. International Journal of Alzheimer's Disease, Volume 2014, Article ID 349249, 10 pages. http://dx.doi.org/10.1155/2014/349249.
38) van der Zande JJ, Gouw AA, van Steenoven I, Scheltens P, Stam CJ, Lemstra AW. 2018. EEG Characteristics of Dementia With Lewy Bodies, Alzheimer's Disease and Mixed Pathology. Front Aging Neurosci. 2018 Jul 3;10:190. doi: 10.3389/fnagi.2018.00190.

39) Waninger S Ahlfors S, Stikic M, Korszen S, Berka C, et al. 2016. Identification of neurophysiological biomarkers of mci using resting state EEG. Alzheimer & Dementia. Volume 12, Issue 7, Supplement, Page P882. DOI: https://doi.org/10.1016/j.jalz.2016.06.1823.
40) Waninger S, Berka C, Meghdadi A, Karic MS, Stevens K, et al. 2018. Event-related potentials during sustained attention and memory tasks: Utility as biomarkers for mild cognitive impairment. Alzheimers Dement (Amst). 2018; 10: 452–460. Published online 2018 Jul 2. doi: 10.1016/j.dadm.2018.05.007.