Why brain functions may deteriorate with aging: a thermodynamic evaluation

Cennet Yildiz and Mustafa Özilgen*

Department of Food Engineering,
Yeditepe University,
34755 Atasehir, Istanbul, Turkey
Email: yildizcennet@outlook.com
Email: mozilgen@yeditepe.edu.tr
*Corresponding author

Abstract: Oxidative Gibbs free energy utilisation capacity and the entropy generation rate of the brain decreases with ageing. At the present level of our knowledge, we may say that the ageing damage to the brain functions may be caused by the decreasing brain work performance ability due to deterioration of the energy generation capacity of the mitochondria and the decreasing work performance ability of the warned-out ion pumps. Thermodynamic assessment points to the muscle work performance ability as the place to look at. Nature has equipped the muscle cells with healing capability, in terms of fixing the damage to the mitochondria or multiplying their numbers. If the same natural healing technologies may be implemented to the brain cells, ageing damage to the brain cells may be at least partly recovered.

Keywords: ageing in the brain; mitochondrial energy; entropy generation; Gibbs free energy utilisation; ion pumps; work performance efficiency.

Reference to this paper should be made as follows: Yildiz, C. and Özilgen, M. (2022) 'Why brain functions may deteriorate with aging: a thermodynamic evaluation', *Int. J. Exergy*, Vol. 37, No. 1, pp.87–101.

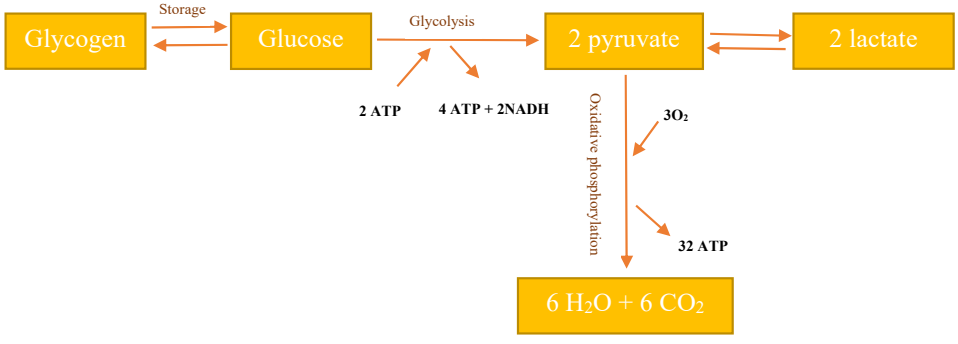
Biographical notes: Cennet Yildiz is a Food Engineer and a PhD candidate in the Biotechnology Program at Yeditepe University at Istanbul, Turkey. She holds a BS degree in Food Engineering from Cumhuriyet University in Sivas, Turkey and an MS degree in Chemical Engineering from Yeditepe University, in Istanbul, Turkey. Her current research interests focus on thermodynamic aspects of the biological processes.

Mustafa Özilgen is a Chemical Engineer and a Professor at Yeditepe University in Turkey. He has BS and MS degrees from the Middle East Technical University (Turkey) and PhD from University of California at Davis (USA). He taught classes at the Middle East Technical University, Massey University (New Zealand) and University of California at Davis (USA) and worked as a consultant at Marmara Research Center (Turkey). He is an author of five books and more than 120 refereed articles. His current research focuses on biothermodynamics, bioenergetics, kinetic aspects of cellular systems and environmentally friendly food and bioprocessing.

1 Introduction

Human brain is a highly sophisticated organ, consisting of approximately 1,011 neurons and glial cells, and 1,015 connections. Homeostatic mechanisms, emotions, feelings and mental activity and behaviours are controlled by the brain (Steiner, 2019). Brain achieves its evolution, and maintenance of these functions by expending energy (Kuzawa et al., 2014; Shokri-Kojori et al., 2019) and generating entropy (Seely et al., 2014). Although it constitutes only 2% of the body weight, energy expenditure of an adult brain equals to 20% of the energy expenditure of the whole-body at the resting state. Brain of a child may expend 60%–70% of the energy of the body in the resting state and 43% of the energy of the entire body during the daily activities (Kuzuwa et al., 2014; Steiner, 2019). In the brain, neurons consume 70%–80% of the total energy and the residual portion is expended by the glial cells (Camandola and Mattson, 2017). Regulation of the metabolite supply is crucial for the central nervous system to maintain its functions. Energy consumption by the brain increases in parallel with the neural activity; which in turn results in increased consumption of the metabolites (Watts et al., 2018). In the biological systems, unlike with the non-biological systems, a major fraction of the available energy is used for internal work performance, including the transmission of the information among different parts of the body (Semerciöz et al, 2020). In the neuronal system and the cortex, ion pumps, which transmit the information utilise most of the energy (Yalcinkaya et al, 2018). Brain cells deliver work output in the form of action potential while transmitting the information. Energy employed in this process is so large that ATP produced by the neuronal cells do not suffice to supply it, so the glial cells contribute to provide additional energy to perform the work (Genç et al, 2011, 2013a, 2013b).

Figure 1 The schematic summary of the brain metabolism from glycolysis to oxidative phosphorylation (see online version for colours)



Glucose is the primary energy source for the brain, it is converted into CO_2 and H_2O via aerobic metabolic activity. When glucose is not available in adequate amounts to provide the needed energy, lactate and ketones are used to supply the remaining portion. Brain uses fatty acids and amino acids as the minor energy supplements (Dienel, 2019). Glycolysis and oxidative phosphorylation meet energy requirements for the neural activities in the brain by producing adenosine triphosphate, ATP (Figure 1). Small

amounts of excessive glucose may be stored as glycogen in the astrocytes and converted into glucose and then used in metabolism when needed. When oxygen consumption mismatches glucose utilisation, after glycolysis, pyruvate is converted to lactate (Raichle and Mintun, 2006).

Maintenance of the ionic gradients over the plasma membrane is essential for excitability, and requires the highest energy among all of the energy utilising processes carried out in the brain. Ionic gradients are sustained by the activity of Na +, K +–ATPase (adenyl pyrophosphatase) pumps located in the neuron and the glial cells. These pumps utilise nearly 50% of the ATP produced via basal glucose oxidation (Squire, 2008): 20% of which is utilised for the reversal of the Na + entry upon completion of the action potential; 22% of it is utilised to support Na + entry to the sodium pumps at the resting potentials, 4% is utilised for presynaptic Ca+ and the remaining 4% is utilised for glutamate recycling (Vergara et al., 2019). Energy required by these ion pumps is supplied mostly by glycolysis, since ATP production is much faster in glycolysis than that of oxidative phosphorylation (Vaishnavi et al., 2010). Energy requirement differs in every brain region depending on the glia to neuron ratio, active metabolic pathways, neurotransmitter distributions, regional morphometries and axonal and dendritic densities.

After the age of 40, volume and/or weight of the brain may decrease 5% per decade, ventricular system may get larger, morphological changes may increase the risk of stroke, dementia and lesions, and the changes in the levels of neurotransmitters and hormones may increase the risk of disorders (Fjell and Walhovd, 2010). Variation in the brain metabolism shows that aging occurs in the brain in stages (Goyal et al., 2019). Impairment of the brain energy metabolism might result in glial cell inflammation, stem cell exhaustion, abnormal neural network activity, dysregulation of the Ca+2 homeostasis, oxidative destruction, mitochondrial dysfunction and failure of the DNA repairing process (Mattson and Arumugam, 2018). Ageing damages to the electron-transport chain increases production of the reactive oxygen species which cause dysregulation of the energy metabolism in the neurons leading to excitotoxicity and simulation of apoptosis (Palomar-Bonet et al., 2020). Glucose utilisation levels in the brain are crucial for sustaining learning and memory especially in aged people, and any decrease in the circulating levels of glucose in the brain weakens the cognitive functions (Gold, 1995).

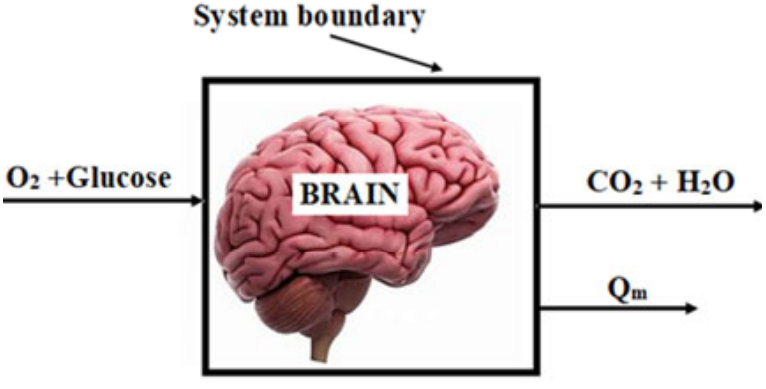
Thermodynamically, brain is an open and far-from-equilibrium system with its environment; energy, entropy and information flows through its boundaries. Its activities and cognitive functions are interrelated with internal and external thermodynamic variables such as energy, temperature and pressure (Collell and Fauquet, 2015; Yildiz et al., 2020). Brain is considered as an isothermal and isobaric system and the related thermodynamic calculations are based on its chemical nourishment through the blood vessels (Kirkaldy, 1965; Haynie, 2008). In the living systems, exergy dissipation caused by work performance via interaction with the environment, such as respiratory work, is among the entropy generating processes (Lucia and Grisolia, 2017). Energy utilisation and entropy generation in the brain increases at awareness and thinking states (Carhart-Harris et al.,2014; Plikynas et al., 2019). Entropy generation is higher at the high metabolic activity regions of the brain in a healthy person (Yildiz et al., 2020). This study

aims at evaluating the age-dependency of the aerobic (AG) and the cerebral metabolic (CMRGlc) Gibbs free energy utilisation rates and the related entropy generation rates in the whole brain and in its regions with the expectation of finding thermodynamic clues about the damage caused to the brain while aging.

2 Materials and methods

Goyal et al. (2017) presented the PET (positron emission tomography) - based measurements of brain glucose uptake, oxygen utilisation, and blood flow in 20 to 82 years old cognitively normal adults. Their data is employed in the present study. Brain is described in Figure 2 as a thermodynamic system, with its inputs and outputs. Influx of the blood into the brain of a healthy dynamic person equals its outflow (Voss and Schiff, 2014).

Figure 2 Graphical representation of the brain as a thermodynamic system, with its boundary, inputs and outputs (see online version for colours)



Glucose is converted into pyruvate with glycolysis, in the lack of sufficient oxygen pyruvate may be converted into lactic acid, in the availability of sufficient oxygen, pyruvate may be converted into CO2 and H2O. Detailed kinetic and thermodynamic aspects of this process was discussed by Genç et al (2011, 2013a, 2013b). The rates of glucose and O_2 consumption, and production of CO_2 and H_2O in metabolism may be related by using equation (1).

$$C_6H_{12}O_{6(s)} + 6O_{2(g)} + 6H_2O_{(g)} \tag{1}$$

While using equation 1, it was assumed that glucose and O_2 are taken into the body at 25°C, and then CO_2 and H_2O are exhaled out at 37°C. The weight of the brain was assumed to be 1,400 g for a 70 kg man (Squire et al., 2008). With the availability of sufficient amounts of oxygen AG is calculated from equation (2):

$$\Delta G_{system} = \Delta H_{system} - T\Delta S_{system} \tag{2}$$

Equation (2) was employed by Sorgüven and Özilgen (2015) to determine the limits of heat generation and work performance by an ideal muscle. When the muscle cell does not generate any heat, the term $T\Delta S_{system} = 0$, then the maximum work performance rate

equals $W_{max} = \Delta G_{system} = \Delta H_{system}$. When the muscle does not perform any work, $W_{max} = \Delta Gs_{system} = 0$ and $Q_{muscle} = T\Delta S_{system}$. Heat generation rate in metabolism Q_m may be calculated with equation (3):

$$Q_m = \sum n_p \left(h_f^- + h^- - h^-\right)_p - \sum n_f \left(h_f^- + h^- - h^-\right)_r \tag{3}$$

where n_p and nr indicate the mole number of products and reactants, h_f^-, h^- and h^- are the formation enthalpies at the standard conditions, respectively. Thermodynamic properties of the chemicals are given in Table 1.

Table 1 Thermodynamic properties of the chemicals (data adapted from Kuddusi, 2015)

Chemical	h_f^- *(kJ/kmol)*	h_{298k}^- *(kJ/kmol)*	h_{310k}^- *(kJ/kmol)*	s_i^- *(kJ/kmol K)*
Glucose $C_6H_{12}O_6$	–1,260×103	–	–	212 (at 298 K)
O2	0	8,682	9,030	218.02 (at 298 K) 219.68 (at 310 K)
H2O	–241,820	9,904	10,302	218.9 (at 310 K)
CO2,	–393,520	9,364	9,807	243.64 (at 310 K)
N_2	0	8,669	9,014	193.66 (at 310 K)

Metabolic work performance efficiency of the brain is described in equation (4):

$$\eta_{ATP} = \frac{W_{ATP}}{Q} = \frac{Total\ work\ obtained\ \ from\ ATP\ molecules}{Total\ heart\ \ production} \tag{4}$$

where, W_{ATP} = Gibbs free energy change calculated based on the CMRGlc, and Qm is the total metabolic heat generation calculated from equation (3). Work performance efficiency η_{ATP} was calculated for glucose metabolisms in the whole body as 34.6% (Silva and Annamalai, 2008). At the first glance, equation (4) looks similar to the work performance efficiency of the Carnot cycle, but it refers to a totally different phenomenon at the theoretical level: In the Carnot cycle Q describes the energy supplied to a steam engine by combusting the coal, in the brain this is analogous to the energy provided by glucose. Equation (4) describes the partitioning of the energy supplied by glucose into energy allocated for work performance, W_{ATP}, and the waste heat, Q. Equation 4 was rearranged as:

$$T_b S_{gen} = Q = (1-\eta) Q_{2l} \tag{5}$$

Equation 5 defines the entropy with 'waste heat generated with the brain as a result of metabolic activity, divided by the brain temperature (310 K). The cerebral metabolic Gibbs free energy utilisation in the whole brain and its regions is calculated by using equation (3) and equation (5). In this study, age dependence of AG and CMRGlc and the entropy generation rates in the brain metabolism are determined with the data adapted from Goya et al (2017) for the whole brain and its regions praecuneus, precentral, hippocampus, cerebellum, corpus callosum to understand their variation with ageing.

3 Results and discussion

Variation of the Gibbs free energy and entropy generation rates, when calculated based on AG and CMRGlc in the whole brain and its regions as a function of the age of a person is presented in Table 2. Gibbs free energy and entropy generation rates, when calculated based on the cerebral blood flow metabolic rates turned out to be a larger number than when it is calculated depending on AG. Their ratios were defined as the use efficiency in the brain and its regions:

$$\mu = \frac{\dot{\Delta}G \text{ based on } A\dot{G}}{\dot{\Delta}G \text{ based on celebral blood flow}} \tag{6}$$

$$\mu = \frac{\dot{\Delta}G \text{ based on } A\dot{G}}{\dot{\Delta}G \text{ based on celebral blood flow}} \tag{7}$$

It was argued by Değerli and Özilgen (2018) that the energy or exergy uptake capacity of a microbial system depend on their composition. A similar behaviour is observed here, energy uptake capacity of a biological system changes as its structure changes with ageing. In Table 2, in the whole brain or in its regions, work performance rate by the brain was calculated as:

$$\dot{W}_{Brain} = \eta_{ATP}\dot{\Delta}G_{AG} \tag{8}$$

where, η_{ATP} = 0.346 as suggested by (Silva and Annamalai, 2008). Based on the observations of Sherwood (2019) and Guyton and Hall (2016) η_{ATP} may also be assumed as 0.333, Silva and Annamalai's estimation was preferred in this study, after considering the thermodynamic nature of their study.

The Gibbs free energy change in the brain must be smaller than zero, since it has spontaneous activity. Brain always tries to minimise this free energy change as much as possible and this event in the brain is reflected as behavioural responses (Collell and Fauquet, 2015). Therefore, the cells regulate their consumption of the resources to maintain sustainability of their functions. This may be an explicit result of the cellular activities that have high energy demands, such as synaptic activity in the neurons. Regulations for the minimisation of the utilisation of the energy sources cause the alterations in the synaptic plasticity (Vergara et al., 2019).

If the oxidative phosphorylation and AG are compared in terms of Gibbs free energy, it is observed that oxidative phosphorylation produces much more free energy. Since production of ATP is higher in the process of oxidation of glucose. Regional Gibbs free energy dependent on oxidative phosphorylation is higher in praecuneus with relating to metabolic activity and lower in corpus callosum. CMRGlc is the total metabolic rate of glucose use in the brain, AG represents the fraction that is not metabolised by oxidative phosphorylation. The normal aging human brain undergoes characteristic metabolic changes, largely driven by changes in AG, which accounts for much of the aging-related changes in the brain metabolism (Goyal et al., 2017). The same researchers also hypothesised that the degree of aging-related change in a particular region would be

related to its AG in young adulthood. It had also been demonstrated by Goyal et al (2014) that the regions with high AG during young adulthood correlate with the relative persistence of gene expression that is characteristic of childhood development. Gibbs free energy utilisation rate of the whole brain depend on the oxidative glucose (AG) use and $\Delta G^{\cdot}_{AG}$ does not change with ageing and remains constant at around -5.5×10^5 kJ/ kg glucose per year (Table 2), in a similar manner, work performance rate of the whole brain, $\dot{W}_{Brain}$ does not change much, and remains constant around -5.5×10^5 kJ/ kg glucose per year. However, in corpus callosum, $\dot{W}_{Brain}$ decreases by 58%, implying that this region of the brain is affected by the ageing related changes, at a higher rate than the rest of the brain. The corpus callosum, is a wide, thick flat bundle of commissural fibres, beneath the cerebral cortex in the brain, it connects the left and right cerebral hemispheres and enables them to communicate. It is the largest white matter structure in the human brain. It has about ten centimetres of length and consist of 200–300 million axonal projections. Table 2 shows that $\dot{W}_{Brain}$ increases in most parts of the brain from age 60 to 80. We already know that after the age of 40, volume and/or weight of the brain may decrease 5% per decade, ventricular system may get larger and some morphological changes occur in the brain (Fjell and Walhovd, 2010). But we do not know what happens to the disappearing mass. The muscle system is known to decrease upon aging, and the proteins may be used in metabolism. A well-balanced diet is recommended to prevent the loss of the muscle proteins (Öngel et al, 2020). It is also known that, some diseases make body use its healthy tissues to manufacture the diseased tissue, or use the healthy tissue to fuel the energy metabolism (Öngel et al, 2021). Similar metabolic processes are possible occurring in the brain between the ages between 60 and 80, but we do not know the details yet.

Table 3 shows that entropy generation by the whole brain with oxidative (AG) glucose use decreases slightly with ageing. However, this decrease would be higher, if CMRGlc were used in only oxidative glucose metabolism. This difference is related to glucose metabolism because CMRGlc decreases with ageing although the amount of oxidative glucose does not change on a small scale. Table 3 shows that while AG decreases with aging the associated entropy generation rate is increasing (Table 3). After the age of 60, CMRGlc is completely oxidised with oxygen. If CMRGlc were used in aerobic glycolysis instead of oxidative phosphorylation, entropy generation rate of the whole brain would be lower. Several studies associate Alzheimer's disease with a decrease in AG (Vlassenko and Raichle, 2015; Vlassenko et al., 2018). According to An et al. (2018), the critical levels of glucose use because of diminished glycolysis at vulnerable regions of the brain cause appearing of the symptoms of the Alzheimer's disease. Thermodynamically, this relationship can be explained with that the amount of oxidative glucose use is higher for energy requirements and with ageing, the amount of glucose used in aerobic glycolysis decreases and therefore, entropy generation rate decreases. An increase in the entropy causes Alzheimer's disease by leading the impairments in cognitive functions (Boccardi et al., 2017).

Table 2 Variation of the Gibbs free energy utilisation, AG and CMRGlc, and brain work performance, $\dot{W}_{Brain}$,, rates with age in the whole brain and in its regions based on AG and CMRGlc

$\Delta \dot{G}_{AG}$ *and (kJ/ kg glucose per year) based on AG*												
Age	*Whole brain*		*Praecuneus*		*Precentral*		*Hippocampus*		*Cerebellum*		*Corpus*	
	$\Delta \dot{G}_{AG}$	$\dot{W}_{Brain}$	$\Delta \dot{G}_{AG}$	$\dot{W}_{Brain}$	$\Delta \dot{G}_{AG}$	$\dot{W}_{Brain}$	$\Delta \dot{G}_{AG}$	$\dot{W}_{Brain}$	$\Delta \dot{G}_{AG}$	$\dot{W}_{Brain}$	$\Delta \dot{G}_{AG}$	
20	-1.6×10^{6}	-5.5×10^{5}	–2.0×106	-6.9×10^{5}	-1.8×10^{6}	-6.2×10^{5}	-1.2×10^{6}	-4.2×10^{5}	-7.5×10^{5}	-2.6×10^{5}	-3.6×10^{5}	
40	-1.6×10^{6}	-5.5×10^{5}	–1.9×106	-6.6×10^{5}	-1.7×10^{6}	-5.8×10^{5}	-1.2×10^{6}	-4.2×10^{5}	-7.1×10^{5}	-2.5×10^{5}	-2.8×10^{5}	
60	-1.5×10^{6}	-5.2×10^{5}	–1.9×106	-6.6×10^{5}	-1.7×10^{6}	-5.8×10^{5}	-1.4×10^{6}	-4.8×10^{5}	-6.7×10^{5}	-2.3×10^{5}	-2.5×10^{5}	
80	-1.6×10^{6}	-5.5×10^{5}	–1.9×106	-6.6×10^{5}	-1.6×10^{6}	-5.5×10^{5}	-1.4×10^{6}	-4.8×10^{5}	-6.6×10^{5}	-2.3×10^{5}	-2.2×10^{5}	
$\Delta \dot{G}_{CMR}$ *(kJ/ kg glucose per year) based on CMRGlc*												
20	-2.0×10^{6}		-3.7×10^{6}		-3.3×10^{6}		-1.6×10^{6}		-1.4×10^{6}		–6.6	
	μ = 0.80		μ = 0.54		μ = 0.54		μ = 0.75		μ = 0.53		μ =	
40	-1.7×10^{6}		-3.1×10^{6}		-2.8×10^{6}		-1.4×10^{6}		-1.1×10^{6}		–3.5	
	μ = 0.94		μ = 0.61		μ = 0.60		μ = 0.86		μ = 0.68		μ =	
60	-1.6×10^{6}		-2.8×10^{6}		-2.5×10^{6}		-1.3×10^{6}		-9.6×10^{5}		–2.8	
	μ = 0.93		μ = 0.67		μ = 0.68		μ = 1.08		μ = 0.70		μ =	
80	-1.5×10^{6}		-2.6×10^{6}		-2.3×10^{6}		-1.3×10^{6}		-9.5×10^{5}		–3.2	
	μ = 1.06		μ = 0.73		μ = 0.70		μ = 1.08		μ = 0.70		μ =	

Table 3 Variation of the entropy generations rates with age in the whole brain and in its regions based on AG and CMRGc

$\dot{S}_{gen,\,AG}$ *(kJ/K kg glucose per year) based on AG*						
Age	*Whole brain*	*Praecuneus*	*Precentral*	*Hippocampus*	*Cerebellum*	*Corpus callosum*
20	9.8×10^6	1.4×10^7	1.2×10^7	8.0×10^6	5.1×10^6	2.5×10^6
40	9.5×10^6	1.3×10^7	1.2×10^7	7.9×10^6	4.8×10^6	1.9×16^6
60	9.2×10^6	1.3×10^7	1.1×10^7	7.7×10^6	4.5×10^6	1.7×10^6
80	9.1×10^6	1.3×10^7	1.1×10^7	7.7×10^6	4.5×10^6	1.5×10^6
$\dot{S}_{gen,\,CMR}$ *(kJ/K kg glucose per year) based on CMRGlc*						
20	1.2×10^7 $\gamma = 0.82$	2.1×10^7 $\gamma = 0.67$	2.0×10^7 $\gamma = 0.60$	9.4×10^6 $\gamma = 0.85$	8.3×10^6 $\gamma = 0.61$	3.9×10^6 $\gamma = 0.64$
40	1.0×10^7 $\gamma = 0.95$	1.8×10^7 $\gamma = 0.77$	1.7×10^7 $\gamma = 0.70$	8.0×10^6 $\gamma = 0.99$	6.7×10^6 $\gamma = 0.72$	2.1×16^6 $\gamma = 0.90$
60	9.3×10^6 $\gamma = 0.99$	1.6×10^7 $\gamma = 0.81$	1.5×10^7 $\gamma = 0.73$	7.5×10^6 $\gamma = 1.03$	5.7×10^6 $\gamma = 0.79$	1.7×10^6 $\gamma = 1.00$
80	8.9×10^6 $\gamma = 1.02$	1.6×10^7 $\gamma = 0.81$	1.3×10^7 $\gamma = 0.85$	7.6×10^6 $\gamma = 1.01$	5.6×10^6 $\gamma = 0.80$	1.9×10^6 $\gamma = 0.79$

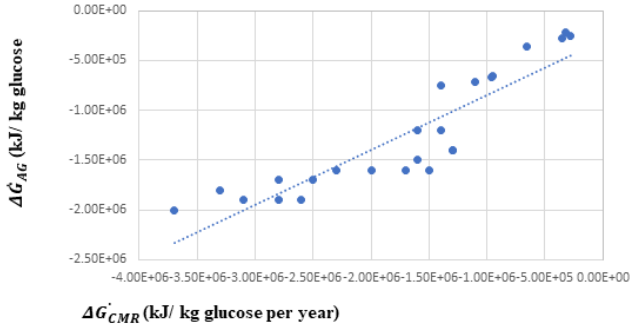
Entropy generation rates based on both AG and CMRGlc were decreasing with age in the whole brain and its regions (Table 3). Entropy generation rates in praecuneus and precentral regions were higher than those of the other regions (Table 3). It is shown that praecuneus has high metabolic activity at the resting state of the brain and therefore it is considered that it takes a task in the interwoven network of the neural correlates of self-consciousness, engaged in self-related mental representations during rest (Cavanna and Trimble, 2006). However, lower entropy generation has been accounted in the corpus callosum, which is the main white matter fibre bundle that enables the interaction of the cortexes of the two cerebral hemispheres of the brain (Table 3). It transfers visual information to both hemispheres (Mooshagian, 2008). For a given age, the relations between $\Delta\dot{G}_{AG}$ and $\Delta\dot{G}_{CMR}$, and $\dot{S}_{genAG}$ and $\dot{S}_{genCMR}$ may be described as

$$\mu = \frac{\Delta\dot{G}_{AG}}{\Delta\dot{G}_{CMR}} \tag{9}$$

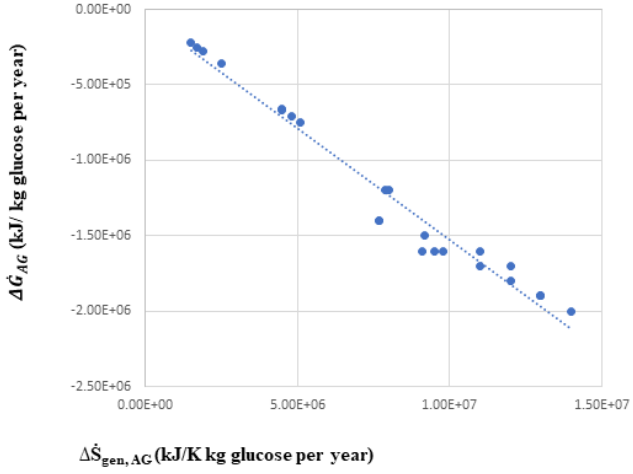
$$\gamma = \frac{\dot{S}_{genAG}}{\dot{S}_{genCMR}} \tag{10}$$

where, μ and γ may be regarded as proportionality coefficients, these factors were attempted to be plotted versus the time, similar, but not unified behaviour observed, therefore not presented here. Experimental data, pertinent to equation (8) is plotted in Figure 3(a). Experimental data, describing equation (2) are plotted in Figures 3(b) and Figure 3(c), with the data of $\Delta\dot{G}_{AG}$ and $\Delta\dot{G}_{CMR}$, respectively. Interrelation of the efficiency factors γ and μ is described in Figure 4.

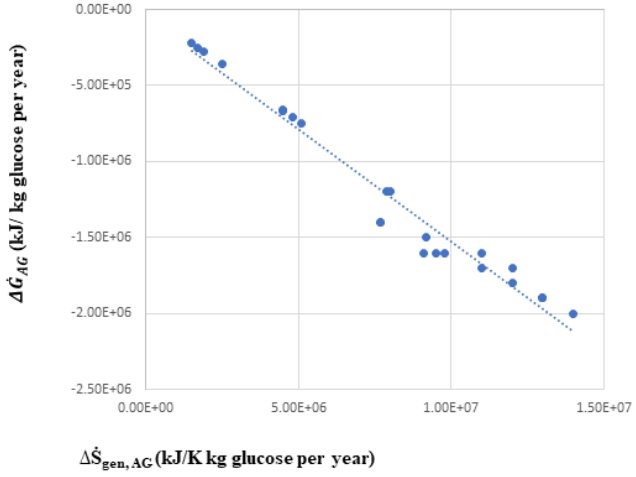
Figure 3 (a) Experimental data, pertinent to equation 8, and equation 2 as plotted with the data of (b) $\Delta \dot{G}_{AG}$ and (c) $\Delta \dot{G}_{CMR}$, respectively (see online version for colours)



(a)



(b)

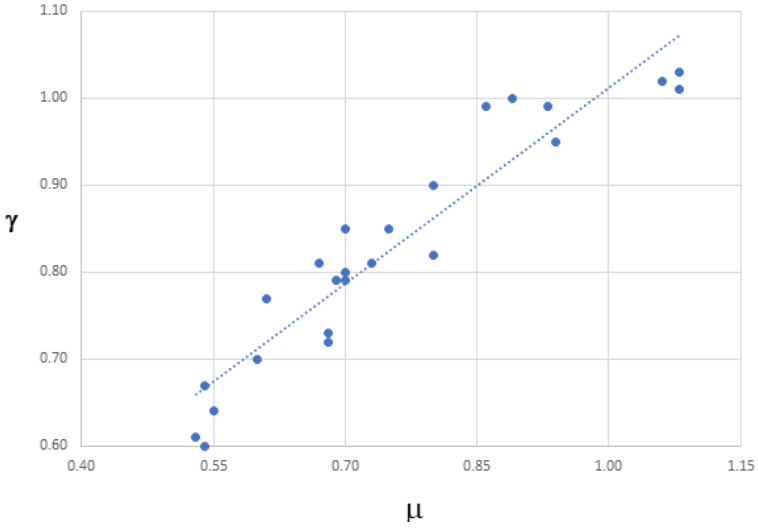


(c)

In Figures 3(b) and 3(c), it is clearly visible that, entropy generation rate increases with the rate of Gibbs free energy generation (negative number, since this is a spontaneous number). In its simplest context, entropy generation may be regarded like paying taxes: the higher is the work performance, the higher will be the unavoidable entropy generation (Yildiz et al., 2020).

Jeffery and Rovelli (2020) in agreement with contractual law (Bejan and Lorente, 2011), suggested that evolution of the brain is an entropy-enhancing process, leading organism to generate new regions of space of states, which in turn allow access through channels to additional new spaces, and thus entropy to continue growing and evolve. However, continued evolution of biological complexity is not assured, because some newly accessible regions of the state space may be small and may not exist in such a case extinction is not avoidable; at the level of an individual, the word 'extinction' may be synonymous with 'death'.

Figure 4 Interrelation of the proportionality factors μ and γ (see online version for colours)



What causes the difference between $\Delta G^{\cdot}_{AG}$ and $\Delta G^{\cdot}_{CMR}$ needs to be understood in order to understand aging related phenomena better, and thermodynamic assessment appears to be the best option at the moment for this, when combined with reliable data. Ion pumps are the essential components of both muscle and brain physiology. Since in the brain, the largest fraction of the energy is allocated to the ion pumps, it may be useful to refer to the discussion regarding the deterioration of the ion pumps in the muscles. The other important point to be referred is the deterioration of the work performance efficiency of the mitochondria (Çatak et al, 2018). Which may be caused by deterioration of the mitochondrial membrane by reactive oxidative species over time. In the muscle systems, with the decline in mitochondrial activity, the rate of the ATP generation slows down (Stucki, 1980; Cairns et al., 1998), the lower rate of ATP generation causes fatigability (Santanasto et al., 2015). Improper work of the aged warned old ion pumps may not work efficiently and cause accumulation of the pools of chemicals around them, causing inefficient performance (Sorgüven and Özilgen, 2015). Increased energy need for pumping ion in active transportation may also cause a decrease in the muscle efficiency

(Shigenaga et al., 1994). As a result, the muscle cells of the aged people become different than those of the young people (Toussaint et al., 1995). In the muscle cells, number of the mitochondria increases as the cells need for more energy, there are also repair mechanism available for the damaged mitochondria (Yalçınkaya et al., 2018). It is also known that, in the muscle systems, there are more mitochondria available in the oxygen accessible regions (Yalçinkaya et al., 2016). Even under normal functioning periods, neuronal cells require so much ATP that there are glial cells around them to provide the energy for their work performance (Genç et al., 2011; 2013a, 2013b); therefore, any ATP insufficiency should be expected to affect their work performance at a much higher extent than that of the muscle cells. Most of the deterioration or remediation mechanisms of the ion pumps of the muscle cells are not confirmed to exist in the neuronal cells yet; however, deterioration of the mitochondrial membrane with oxidation and deterioration warn out of the ion pumps with aging may be strongly valid options for the deterioration of the neuronal work performance in the brain.

4 Conclusions

Gibbs free energy utilisation rate of the whole brain depend on the oxidative glucose (AG) use and $\Delta G^{\cdot}_{AG}$ does not change with ageing and remains constant at around -5.5×10^5 kJ/ kg glucose per year. In a similar manner, work performance rate of the whole brain,

$\dot{W}_{Brain}$ does not change much, and remains constant around –5.5×10^5 kJ/ kg glucose per year. However, in corpus callosum, which is the main white matter fibre bundle that enables interaction of the cortexes of the two cerebral hemispheres, $\dot{W}_{Brain}$ decreases by 58%, implying that this region of the brain is affected by the ageing related changes, at a higher rate than the rest of the brain.

Aging in the brain is characterised with decrease of the oxygen utilisation ability of the whole brain and its regions; which may be caused mainly by deterioration of the ion pumps and mitochondria. It is highly possible that in corpus callosum, mitochondrial ATP generation efficiency, η_{ATP}, and the ion pumps may be deteriorating much faster than the other parts of the brain. Aging of the brain may be compared with aging of the muscles since both of them share common features. At the moment we have more information regarding the aging of the muscles, than that of the brain. Although nature has equipped the muscles with remedies to slow down aging, we do not know at the moment, if similar remedies are available to slow down aging of the neuronal cells. Jackson and Robinson (2018) provided a highly comprehensive review of glial dynamics, but no information available there about the aging effects on the energy supply by these cells. Our knowledge regarding the aging of the muscle cells, may be employed while studying the aging of the brain. If medical practitioners can implement the aging-slowing down mechanisms of the muscle cells to the neurons, we may be successful in our fight against ageing.

References

An, Y., Varma, V.R., Varma, S. et al. (2018) 'Evidence for brain glucose dysregulation in Alzheimer's disease', *Alzheimers Dement*., Vol. 14, No. 3, pp.318–329.

Bejan, A. and Lorente S. (2011) 'The constructal law and the evolution of design in nature', *Phys Life Rev*, Vol. 8, No. 3, pp.209–240, DOI: org/10.1016/j.plrev.2011.05.010.

Boccardi, V., Comanducci, C., Baroni, M. and Mecocci, P. (2017) 'Of energy and entropy: the ineluctable impact of aging in old age dementia', *Int. J. Mol. Sci*., Vol. 18, No 12, p.2672.

Cairns, C.B., Walther, J., Harken, A.H. and Banerjee, A. (1998) 'Mitochondrial oxidative phosphorylation thermodynamic efficiencies reflect physiological organ roles', *Am. J. Physiol.-Reg. I*., Vol. 274, No. 5, pp.R1376–R1383.

Camandola, S. and Mattson, M. (2017) 'Brain metabolism in health, aging, and neurodegeneration', *EMBO J*., Vol. 36, No. 11, pp 1474–1492.

Carhat-Harris, R.L., Leech, R., Hellyer, P.J. et al. (2014) 'The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs', *Front. Hum. Neurosci*., Vol. 8, No. 20, p.22.

Çatak, J., Özilgen, M., Olcay, A.B. and Yilmaz, B. (2018) 'Assessment of the work efficiency with exergy method in aging muscles and healthy and enlarged hearts', *Int. J. Exergy*, Vol. 25, No. 1, pp.1–33.

Cavanna, E. and Trimble, M.R. (2006) ', The precuneus: a review of its functional anatomy and behavioural correlates', *Brain*, Vol. 129, No. 3, pp.564–583.

Collell, G. and Fauquet, J. (2015) 'Brain activity and cognition: a connection from thermodynamics and information theory', *Front. Psychol*., Vol. 6, p.818.

Değerli, B. and Özilgen, M. (2018) 'The mode of interaction of the constituents of a microbial system determines the attainable exergy utilization', *Int. J. Exergy*, Vol. 25, No 2, pp.132–149.

Dienel, G.A. (2019) 'Brain glucose metabolism: integration of energetics with function', *Physiol. Rev*., Vol. 99, No. 1, pp.949–1045.

Fjell, A.M. and Walhovd, K.B. (2010) 'Structural brain changes in aging: courses, causes and cognitive consequences', *Rev. Neurosc*., Vol. 21, No. 3, pp.187–221.

Genç, S., Aksan Kurnaz, I. and Özilgen M. (2011) 'Astrocyte-neuron lactate shuttle may boost ATP supply to the neurons under hypoxic conditions - an in-silico study', *BMC Syst. Biol*., Vol. 5, No. p.162, DOI:10.1186/1752-0509-5-162.

Genç S, Sorguven E, Özilgen M, Aksan Kurnaz I. (2013a) 'Unsteady exergy destruction of the neuron under dynamic stress conditions', *Energy*, Vol. 59, pp.422–431.

Genç S, Sorguven E, Aksan Kurnaz I, Özilgen M. (2013b) 'Exergetic efficiency of ATP production in neuronal glucose metabolism. *Int. J. Exergy* Vol. 13, No. 1, pp.60–84.

Gold, P.E. (1995) 'Role of glucose in regulating the brain and cognition', *Am J Clin Nutr*, Vol. Vol. 61, No. 4, pp.987S–95S.

Goyal, M.S, Blazeya, T.M., Sua, Y. et al. (2019) 'Persistent metabolic youth in the aging female brain', *Proc. Natl. Acad. Sci. U.S.A*., Vol. 116, No. 8, pp.3251–3255.

Goyal, M.S, Hawrylycz, M., Miller, J.A., Snyder, A.Z. and Raichle, M.E. (2014) 'Aerobic glycolysis in the human brain is associated with development and neotenous gene expression', *Cell Metab*., Vol. 19, No. 1, pp.49–57.

Goyal, M.S., Vlassenko, A.G., Blazey, T.M. et al. (2017) 'Loss of brain aerobic glycolysis in normal human aging', *Cell Metab*., Vol. 26, No. 2, pp.353–360.

Guyton, A.C. and Hall, J.E. (2016) '*Guyton and Hall Textbook of Medical Physiology*, 13th ed., Elsevier, USA.

Haynie, D. (2008) '*Biological Thermodynamics*, Cambridge University Press, New York.

Jackson, J.G and Robinson, M.B. (2018) 'Regulation of mitochondrial dynamics in astrocytes: mechanisms, consequences, and unknowns', *Glia*, Vol. 66, No. 6, pp.1213–1234.

Jeffery, K.J. and Carlo Rovelli, C. (2020) 'Transitions in Brain Evolution: Space, Time and Entropy. '*Trends Neurosci*. Vol. 3, No. 7, pp.467–474.

Kirkaldy, J.S. (1965) 'Thermodynamics of the human brain', *Biophys*. J., Vol. 6, No. 5, pp.981–986.

Kuddusi, L (2015) 'Thermodynamics and life span estimation', *Energy*, Vol. 80, pp 227–238.

Kuzawa, C.W., Chugani, H.T., Grossman, L.I. et al. (2014) 'Metabolic costs and evolutionary implications of human brain development', *Proc. Natl. Acad. Sci. U.S.A*., Vol. 11, No. 36, pp.13010–13015.

Lucia, U. and Grisolia, G. (2017) 'Second law efficiency for living cells', *Front. Biosci. Scholar*, Vol. 9, No. 2, pp.270–275.

Mattson, M.P. and Arumugam, T.V. (2018) 'Hallmarks of brain aging: adaptive and pathological modification by metabolic states', *Cell Metab*., Vol. 27, No. 6, pp.1176–1199.

Mooshagian, E. (2008) 'Anatomy of the corpus callosum reveals its function', *J. Neurosci*., Vol. 28, No. 7, pp.1535–1536.

Öngel ME, Yıldız C, Akpınaroğlu C, Yılmaz B, Özilgen, M. (2020) 'Why women live longer than men do? A telomere-length regulated and diet - based entropic assessment', *Clin Nutr*., Vols. S0261–5614, No. 20, pp.30392–30395, DOI: 10.1016/j.clnu.2020.07.030.

Öngel ME, Yildiz C, Özilgen M, Yilmaz B. (2021) 'Nutrition and disease-related entropy generation in cancer', *International Journal of Exergy*, Vol. 34, No. 4, pp.411–423.

Palomar-Bonet, M., Atienza, M. and Cantero, J.L. (2020) 'Blood total antioxidant status is associated with cortical glucose uptake and factors related to accelerated aging', *Brain Struct. Funct*., Vol. 225, No. 2, pp.841–851.

Plikynas, D., Sakalauskas, L. and Raudys, A. (2019) 'Conceptual modelling of brain state dynamics as free energy and entropy-based processes', *Informatica*, Vol. 30, No. 4, pp.749–780.

Raichle, M.F. and Mintun, M.A. (2006) 'Brain work and brain imaging', *Annu. Rev. Neurosci*., Vol. 29, pp.449–76.

Santanasto, A.J., Glynn, N. W., Jubrias, S.A., Conley, K.E., Boudreau, R.M., Amati, F., Mackey, D.C., Simonsick, E.M., Strotmeyer, E.S. and Coen, P.M. (2015) 'Skeletal muscle mitochondrial function and fatigability in older adults', *J. Gerontol. A Biol. Sci. Med. Sci*., Vol. 70 No. 11, pp.1379–1385.

Seely, A.J.E., Newman, K.D. and Herry, C.L. (2014) 'Fractal structure and entropy production within the central nervous system', *Entropy*, Vol. 16, No. 8, pp.4497–4520.

Semerciöz, A.S., Yilmaz, B. and Özilgen, M. (2020) 'Thermodynamic assessment of the allocation of the energy and exergy of the nutrients for the life processes during pregnancy', *Brit. J. Nutr*. Vol 124, No. 7, pp.742–753.

Sherwood, L. (2019) *Human Physiology: From Cells to Systems*, 9th ed., Cengage Learning, Canada.

Shigenaga, M.K., Hagen, T.M. and Ames, B.N. (1994) 'Oxidative damage and mitochondrial decay in aging', *Proc. Natl. Acad. Sci. U.S.A*., Vol. 91 No. 23, pp.10771-10778.

Shokri-Kojori, E, Tomasi D, Alipahani B et al. (2019) 'Correspondence between cerebral glucose metabolism and BOLD reveals relative power and cost in human brain', *Nat. Commun*., Vol. 690, No. 1, pp.10.

Silva, C.A. and Annamalai, K. (2008) 'Entropy generation and human aging: Lifespan entropy and effect of physical activity level', *Entropy*, Vol. 10, No. 2, pp.100–123.

Sorgüven, E. and Özilgen, M. (2015) 'First and second law work production efficiency of a muscle cell', *Int. J. Exergy*, Vol. 18, No. 2, pp.142–156.

Squire, L.R., Bloom, F.E., Spitzer, N.C. et al. (2008) '*Fundamental of Neuroscience*,' 3rd ed., Academic Press, London.

Stenier, P. (2019) 'Brain fuel utilization in the developing brain', *Ann. Nutr. Metab*., Vol. 75, No. 1, pp.8–18.

Stucki, J. W. (1980) 'The optimal efficiency and the economic degrees of coupling of oxidative phosphorylation', *European Journal of Biochemistry*, Vol. 109, No. 1, pp.269–283.

Toussaint, O., Michiels, C., Raes, M. and Remacle, J. (1995) 'Cellular aging and the importance of energetic factors', *Exp. Gerontol*., Vol. 30, No. 1, pp.1–22.

Vaishnavi, S.N., Vlassenko, A.G., Rundle, M.M. et al. (2010) 'Regional aerobic glycolysis in the human brain', *Proc. Natl., Acad., Sci. USA*, Vol. 107, No. 41, pp.17757–17762.

Vergara, R.C., Jaramillo-Riveri, S, Luarte, A. et al. (2019) 'The energy homeostasis principle: Neuronal energy regulation drives local network dynamics generating behavior', *Front. Comput. Neurosci*., Vol. 13, No. 49, pp.18.

Vlassenko, A.G. and Raichle, M.E. (2015) 'Brain aerobic glycolysis functions and Alzheimer's disease', *Clin. Transl. Imaging*., Vol. 3, No. 1, pp.27–37.

Vlassenko, A.G., Gordon, B.A., Goyal MS et al. (2018) 'Aerobic glycolysis and tau deposition in preclinical Alzheimer disease', *Neurobiol. Aging*., Vol. 67, pp.95–98.

Voss, H.U. and Schiff, N.D. (2014) 'Searching for conversation laws in brain dynamics- BOLD flux and source imaging', *Entropy*, Vol. 16, No. 7, pp.3689–3709.

Watts, M.E., Pocock, R. and Claudianos, C. (2018) 'Brain energy and oxygen metabolism: Emerging role in normal function and disease', *Front. Mol. Neurosci*., Vol. 11, No. 216, p.13.

Yalcinkaya, B.H. Genç, S. Özilgen M. and Yilmaz, B. (2018b) 'Neuronal energy production', in Dincer, I. (Ed.): *Comprehensive Energy Systems*, Elsevier, Holland.

Yalçınkaya, B.H., Erikli, Ş., Özilgen, B.A., Olcay, A.B., Sorgüven, E. and Özilgen, M. (2016) 'Thermodynamic analysis of the squid mantle muscles and giant axon during slow swimming and jet escape propulsion', *Energy*, Vol. 102, pp.537–549.

Yalçınkaya, B.H., Genç, S., Çatak, J., Özilgen, M. and Yilmaz B. (2018) 'Mitochondrial energy production' in Dincer, I. (Ed.): *Comprehensive Energy Systems*, Elsevier, Amsterdam.

Yildiz, C., Semerciöz, A.S., Yalcinkaya, B.H, Ipek, T.D., Öztürk-Özışık, E. and Özilgen, M. (2020) 'Entropy generation and accumulation in biological systems', *Int. J. Exergy*, Vol. 33, No. 4, pp.444–467.