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Research Article

The Multisystemic Origins of Alzheimer's Disease

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ABSTRACT

The author discusses the fundamental relationship which exists between sense perception, brain function, and changes of molecular biology and uses Grakov's mathematical model of the relationship between sense perception, brain function, the autonomic nervous system and physiological systems, and cellular and molecular biology to explain this complex relationship in the Alzheimer patient.

This paper illustrates that changes of molecular biology (the a-Beta amyloid protein and fibrils) are the consequence of the failure of the brain to optimise the function of the physiological systems, in particular sleep, posture, intercellular pH and blood glucose.

It is shown that Alzheimer's Disease is a polygenomic, multisystemic and multi-pathological indication, with cognitive and neurological origins, and that knowledge of this mechanism has the potential to screen and treat the autonomic dysfunction which characterizes Alzheimer's Disease and all common pathologies.

Case studies of how the technology can be used to screen the Alzheimer patient, and to treat a wide range of cognitive and/or pathological indications, are used to support the presented arguments.

Keywords: Autonomic nervous system; Physiological systems; Cellular biology; Molecular biology; Strannik

ABBREVIATIONS:

AD: Alzheimer's Disease; SVS: Strannik Virtual Scanning; SLT: Strannik Neuromodulation therapy; SCI: Spinal Cord Injury

INTRODUCTION

What we have come to know as Alzheimer's Disease (AD) has perplexed the greatest minds of our time. To illustrate the point, the EC's Human Brain Project was conceived in order to evaluate how the brain functions and determine what it does, create a cognitive diagnostic test which would determine the pathological correlates of complex conditions such as AD, and understand and adapt with therapeutic effect the multi-level nature of brain function.

The common origin and/or causes of cognitive impairment in the elderly can be categorised as those which cause changes to brain function, the autonomic nervous system, and associated metabolic imbalances. Medications, metabolic imbalance(s), hormonal imbalances, vitamin and mineral deficiencies, damage to brain neurons, and substance abuse are all considered to be responsible for cognitive decline. It illustrates that the conventional drug-based approach, based upon the effect of a single pharmacological entity to block or ameliorate a pathological sequence, has significant limitations. An immense amount of resources has been devoted to the development of drugs which ameliorate the effects of AD however all, almost without exception, have failed [1]. This paper considers why this should be so. It looks at the issues from a neurological and systemic perspective i.e. how cognitive input influences brain function, the autonomic nervous system and the coherent function of the organ networks which we recognise as 'physiological systems', and results in changes to cellular and molecular biology. It considers the hypothesis that AD is the consequence of the failure of the brain to regulate the autonomic nervous system and physiological systems when challenged by specific lifestyle-related factors, in particular excess weight, lack of exercise, age [2], stress, brain injury, etc.

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MATERIALS AND METHODS

Background

60-80% of Alzheimer patients have diabetes [3] i.e. 20-40% of Alzheimer patients do not have diabetes therefore AD can have genetic and non-genetic origins which are independent of blood glucose metabolism i.e. there is more than one mechanism.

Many articles have been written which attest to the relationship between blood glucose and what we know as AD [4] - sometimes called type 3 diabetes [5] - although there is not yet a clear understanding of why this should be so. The presence of amyloid plaques and tau tangles is not necessarily a requirement for AD [6]. Patients with clinical indications of AD can have the plaques and tau tangles which are associated with AD but they function normally without any of the apparent signs of the condition i.e. they are cognitively normal when they were expected to be experiencing cognitive decline.

Eminent Alzheimer researchers have recognised the need to consider a systems biology approach [7] and neuromodulation technologies based upon various levels of understanding of this phenomena are now available in the market and showing signs of being able to effect some improvements in the health of Alzheimer patients [8]. So what are these systems and why are they significant? Knowledge of the physiological systems forms the rudimentary basis of the doctor's medical examination however the inability to define these systems in any detail led to the onset of histopathology testing in efforts to determine the molecular and/or pathological correlates of medical conditions. The initial definition of physiological systems referred to a cardiovascular system and immune 'system'. Skin was also considered to be a system.

Grakov's revised methodology considers there to be 13 physiological systems – most being defined by the subscript 'hyper' or 'hypo' e.g. hyperthermia and hypothermia, hypertension and hypotension, hyperglycaemia and hypoglycaemia. Accordingly it appears reasonable to conclude that the existence of these systems is accepted in practice but, strangely, not in theory!

The physiological systems regulate and/or optimise the following parameters: blood glucose, blood pressure, blood volume, blood cell content, breathing, intercellular pH, body temperature, sleep, posture, digestion, urination, osmotic pressure and sexual function. Each of these systems comprises a network of organs. This poses significant questions for the biomedical community. If these physiological systems exist, and it is clearly evident that they do, what are the mechanism(s) by which they function?

The author has illustrated, in an extensive bibliography, the relationships between sense perception, brain function, the autonomic nervous system and/or physiological systems, and cellular and molecular biology i.e. what the brain does and how it does it – it functions as a neuromodulator which regulates the stable and coherent function of the physiological systems [9]; how this can be used as the basis of a cognitive diagnostic technique which can screen the health of the patient – using cognitive data as the basis of a screening modality; and how such knowledge can be used to comprehend the multilevel nature of brain function - and adapt such knowledge with therapeutic effect as a neuromodulation technique.

Consider for a moment.....

i) If we are stressed; perhaps as the result of a bereavement, divorce or work-stress; this leads to pathological onset of varying levels e.g. influencing digestive function, giving back-ache, headaches, migraines, etc. The fundamental cause is the psychological event – the bereavement, divorce or work-stress – and the emergent pathologies are the consequence of this process.

ii) If we eat and drink too much of the wrong things, and/or if we exercise too little, we will ultimately become diabetic and/or obese. The fundamental cause is that we eat and drink too much of the wrong things. The diabetes and/or obesity is the symptomatic consequences. So why do we behave in such a dysregulated manner?

iii) If we get a viral infection this alters our genetic profile, perhaps on a short-term or long-term basis, and leads to a range of symptoms. In this case the viral infection is the cause whilst the symptoms are the consequences. The symptoms of viral infection could vary widely e.g. the coughs and sneezes of the common cold, fever, vomiting, diarrhoea, inflammation, etc. A herpes simplex outbreak is often seen as the characteristic skin blotches or blisters which occur when the patient is stressed.

iv) If we use antibiotics or antivirals to treat an infection we are treating the fundamental cause of the condition and killing or suppressing the invading organism however with most lifestyle-related indications the drugs are treating the symptomatic expression of the condition i.e. the consequences, not the fundamental neurological origins and/or cause.

v) We adapt such knowledge to provide protection against viral infections by exposing the patient to viral antigens which prevent infection.

The significance of the genetic profile remains unclear, because AD is often associated with being physically inactive and how this influences metabolism of insulin in the brain. Genes and genetic alleles have not yet been linked to AD to any significant extent [10-12] although they have been associated with a range of gene-related parameters e.g. lipid metabolism, inflammatory response, and endocytosis.

The 'theoretical fog' lifts if we consider that body is a sophisticated and precisely regulated entity in which blood glucose, blood pressure, body temperature, and all other body systems are regulated between upper (hyper-) and lower (hypo-) limits i.e. a range of parameters within which the body functions at an optimal level. Pathological onset influences the brain's ability to maintain systemic stability within these limits.

Changes of molecular biology due to pathological onset influences cellular biology; changes of cell biology influences organ function; changes of organ function influence the coherent function of the organ networks (physiological systems); however biology alone cannot explain the regulated function of the physiological systems. We experience stress through the

senses and the brain; we feed food and medication through the visceral organs which ultimately influences brain function; and we experience genetic changes through exposure to gene-altering moieties. There is a relationship between sense perception, brain structure and function [13], the autonomic nervous system and/or physiological systems, and cellular and molecular biology i.e. the brain is continuously regulating, in a best-fit manner, the body's function (Figure 1).

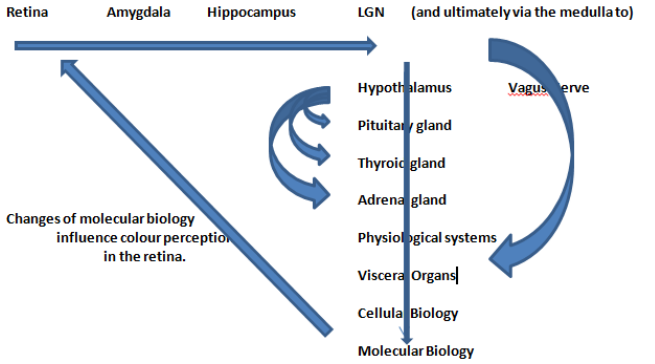


Figure 1: Schematic of Data Flow through the Brain and the Autonomic Nervous System.

In earlier papers the author described how the Strannik Virtual Scanning (SVS) technology is able to precisely screen patients who had a range of cognitive/cancer-related issues [14] and cognitive/Alzheimer-related issues [15]. SVS is a neurosimulation and/or predictive technique which is based upon the light absorbing and emitting properties of proteins which influences visual perception. The results are related to protein expression (genotype), protein reactivity (phenotype), cell morphology, organ and system function. Each SVS 'cognitive' test reports the genotype and phenotype for each of the 15 pathologies which are reported in each of the 30+ main organs e.g. as type 1 and type 2 diabetes (Table 1).

Table 1: List of Cardiac Pathologies and Indications which can be determined by SVS.

List of Cardiac Pathologies		
Ischaemic Heart Disease	Angina Pectoris	Myocardial Infarction
Cardio Sclerosis	Myocardial Dystrophy	Myocarditis
Cardiac Insufficiency	Cardiac Myopathy	Cardiac Arrhythmia
Degenerative process	Allergic process	Age Related Changes
Post-Stress effects	Abnormalities of development	Growth of New Cells

It is also able to define subsequent cellular pathologies such as increased or decreased flow of arterial or venal blood, increased or decreased cell function, and growth or death of cells. Such a technique, developed by Grakov IG between 1981-1997/2006 [16], meets in its entirety the stated aims and objectives of the Human Brain Project [17]: (i) to understand what the brain does and how it does it; (ii) develop a new generation of diagnostic modality based upon cognitive input; and (iii) identify the pathological correlates of complex conditions such as dementia and AD.

The technique is based upon the observation of bioluminescence, in particular that changes of colour perception in the retina (which responds to 10^2 to 10^9 biophotons per second) accompany the emission of biophotons from each pathological reaction and hence can be used as the basis of a technique which can diagnose pathological onset earlier and better than any other diagnostic test or scientific principle [18]. It is a direct measure of protein expression and reactivity. This compares with the normal biomarker-type techniques which are often fraught with inherent limitations [19]. Moreover it enables us to recognise that disorders which are considered by convention to have cognitive origins instead have pathological origins i.e. that it is the pathological origins of the condition which influence cognition.

There are two prevalent theories for AD however neither theory explains the mechanisms responsible for the manifestation of AD (involving amyloid and tau proteins). The amyloid hypothesis is based upon A-beta plaques in brain tissue, or of formation of neurofibrillary tangles (fibrils) containing aluminium [20] and tau protein i.e. that there is an imbalance between A-beta production and its clearance. [21] There are genes and genetic alleles which are to some extent associated with the condition however none can, as yet, be identified as a causal factor for AD [6]. If so, what is the origin and significance of these genetic mutations? The presence of aluminium, and its significance, is now largely ignored although its level and reactivity is associated with the prevailing level of intercellular pH [22,23] i.e. only at neutral pH is aluminium relatively inert and unreactive.

Dendritic spines are neuronal protrusions which contain neurotransmitter receptors and signaling systems. They contribute to synapse function and plasticity. A-beta fibrils are formed by phosphorylation of tau proteins. They alter the function and structure of the dendritic spines which leads to neuronal death and changes of synapse function. Moreover dendritic spine dysfunction [24] can be caused by a large number of mechanisms [25,26] which ultimately contribute to neurodegenerative and cognitive disorders prior to neuronal depletion and death.

The A-beta amyloid plaques/fibrils adopt different conformational states for reasons [27] which have yet to be defined although differential conformational states could reasonably be expected to be associated with reactivity and/or energetics which would be associated with for example lower levels of intercellular pH (and elevated intercellular acidity).

In the spine, the incidence of AD in patients with spinal cord injury (SCI) is greater than in patients who have not suffered such injuries. This indicates that SCI patients have increased risk of developing AD [28,29]. In addition, patients with

impaired gait as a result of spinal cord deviations appear also to be predisposed to the onset of AD [30]. Such observations implicate the spinal cord in the etiology of dementative pathologies.

This is significant because the regulation and optimisation of sleep, in which the spinal cord is an organ, is a physiological system which performs the essential function of clearing the brain of the accumulation of metabolic by-products [9,10,31-34], but it does so much more. Abnormal changes to the function of the physiological systems involving the spinal cord i.e. in particular posture and sleep, influence the ability to clear the brain of neurotoxins [32,34].

Organs in the Sleep and Posture systems

That sustains optimal position of body in the environment (posture).

Organs: Brain, Spinal Cord, Peripheral Nervous System, Pituitary Gland, Thyroid Gland, Adrenal Glands, Blood and Peripheral Blood Vessels, Skeletal and Muscular System

That sustains optimal sleeping pattern.

Organs: Brain, Pituitary Gland, Spinal Cord, Peripheral Nervous System, Ear and Nose

Sleep has been associated with the formation of dendritic spines (small protrusions from a neuron's dendrite which receives input from an axon at the synapse. The dendritic spines support synapses and the transmission of electrical signals to the neuron) which are considered to be associated with the physical correlate of a memory i.e. lack of sleep influences the formation of dendritic spines and the fixation of memories [35]. If so, we would expect to see, in an AD patient, problems with sleep, memory and/or with dysfunction in the organs which are components in the organ network/ physiological system which regulates sleep [10] i.e. brain [36,37], spinal cord [38,39], nose [40], ears [41], HPA and/or pituitary gland [42,43], and peripheral nervous system [44].

Excess weight influences the regulation of physiological parameters including sleep [45] and posture [46,47]. Moreover, the issue is often resolved when the patient loses weight [48-50]. This leads to consideration of 'cause' and/or 'effect' i.e. does AD cause sleep problems and ultimately problems with the listed organs or, vice versa [19], does problems with the listed organs influence sleep and ultimately our predisposition to neurological and/or dementative conditions such as AD? Perhaps both can be valid explanations. Damage to the spinal cord would influence the ability to sleep and hence the ability to clear out the accumulation of neurotoxins which accumulate throughout the 24 hour cycle [33] yet it is recognised that damage to the spinal cord has a neurological component [51] which influences immune function [52].

In addition, could a treatment for AD - based upon a precise level of understanding of the function of the autonomic nervous system - be possible? Environmental or lifestyle causes (phenotype) are linked with the onset and progression of AD i.e. lack of exercise [53], being overweight [54,55], lack of exposure to natural sunlight [56] throughout the year (which adversely influences endocrine function), poor diet [57], exposure to stress [58], consumption of alcohol [59,60], smoking cigarettes [61], etc.

Exercise maintains metabolic rate, the elimination of excess intercellular acidity (the expulsion of CO2 and absorption of O_2), metabolises blood glucose, maintains blood pressure, conditions smooth muscle throughout the body, optimises immune function, etc. It is essential for the body's regulated multi-systemic function. Moreover, as outlined earlier, many with AD also have Diabetes [62-64] which is often the consequence of lack of exercise i.e. the onset of type 2 diabetes in particular appears to indicate future predisposition to AD however [65] AD has particular features which overlap with both type 1 and type 2 diabetes e.g. increased intercellular acidity, lower levels of essential minerals [66,67], elevated levels of transition metals which catalyse free radical reactions [68], and leads to the protein uncoiling [69] which is a common feature of diabetes and diabetic comorbidities including AD. Accordingly the causal factors for Alzheimer's disease are likely to include low or unstable levels of insulin and/or unreactivity of insulin (insulin resistance), being physically inactive and/or overweight i.e. the inability to pump blood, and hence oxygen, to the brain and hence of hypoxia/oxygen-deprived brain cells.

Elevated levels of intercellular acidity create the essential conditions for the onset of oxidative stress arising from the presence of Reactive Oxygen Species [70] which reacts with our DNA, subsequently influences the immune response [71-74], and leads to immune deficiencies and/or disorders.

Elevated levels of Reactive Oxygen Species impair normal metabolic processes including the oxidation of DNA, lipids, glycation and other related reactions involving sugars, and protein metabolism. This is significant because AD has been shown to be associated with a range of pathological processes including the accumulation of A-Beta-amyloid. Moreover, treatment with anti-oxidants/free radical scavengers e.g. vitamin C, melatonin (which is produced during sleep by the pineal gland); may provide protection against oxidative stress and A β toxicity [75,76].

AD is therefore, for the reasons outlined above, a polygenic, multi-systemic and multi-pathological disorder.

The primary function of the brain is to regulate and/or maintain at all times the normal level and function of brain chemistries. There is clearly a dynamic relationship between the function of the brain and its capacity to influence the regulated function of the autonomic nervous system and physiological systems. There are no precedents whereby the brain or the body (and its component parts: nerves, physiological systems, organs, and cellular and molecular biology) could work without being connected together. They are mutually dependent parts of the whole body system [77].

This conceivably highlights areas of inconsistency and/or limitations of medical research:

i) In most cases it takes many genes to express a particular protein. There are few, if any, cases whereby a single gene

expresses a single protein. Accordingly it is the rate of genetic expression which is significant;

ii) The process of protein expression by the genes is a chemical reaction therefore the laws of chemistry must apply to such processes;

iii) The expressed protein circulates in the blood in which the intercellular pH influences the degree of coiling or uncoiling of the expressed protein and which influence protein reactivity;

iv) Proteins react with their reactive substrates but there is not yet any technique which directly measures the rate at which each protein reacts with its substrate, the factors which influence rate of reaction;

v) Cell morphology is influenced by protein conformation which influences intercellular communication within each organ;

vi) There is not a precise level of understanding of the mechanisms which regulate the body's function i.e. the stable and coherent function of the physiological systems;

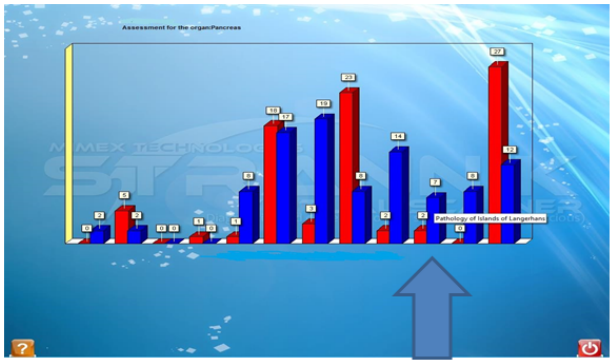
vii) In AD research: the need to consider that AD does not have simple pathological origins and hence that treatments must be developed which slow and/or reduce the onset of particular aspects of the condition e.g. through an understanding of how the brain regulates physiological stability and hence of the significance and/or effect of exercise, nutritional programmes, medication (e.g. insulin), etc; and/or which can reduce the damaging effects of AD by medication.

viii) The lack of understanding of the precise significance and function of the EEG frequencies.

Such issues have largely been addressed by the Strannik technology and, in particular, by the Strannik Neuromodulation Therapy (SLT) which is based upon a precise understanding of the mechanism by which the brain regulates the autonomic nervous system and coherent function of the physiological systems. This technique has been available in various manifestations since before 1997 although it was in 1997 that the completed version of the technology was first placed in the market. It has been validated through ca 15-20 clinical studies [78-80] which have been carried out since then. At peak over 550 medical doctors were using the technique. Over 1M patients have been tested and/or treated using Strannik. Over 80 peer-reviewed medical papers have been published reporting case studies and clinical studies including how the technology has been used to screen and/or treat diabetes and diabetic comorbidities [81-88] including cardiac pathologies [89], cancer [90], Alzheimer's Disease [8] and mental health and depression [91]; migraine [92,93]; dyslexia [94]; dysarthria [95]; Raynaud's phenomenon [96]; sleep disorders [97]; etc.

Strannik

If the doctor or patient does not have a complete understanding of the patient's health the selection of the treatment may be imprecise e.g. the wrong drug may be prescribed. In the case of the SVS (Figure 2) test the patient's health report determines which particular medical indications should be treated, which drugs may be appropriate treatment, and/or the precise parameters for their SLT treatment. If the wrong treatment parameters are selected it is conceivable that the patient's health could worsen, side-effects could occur, etc.



Report: this particular patient has reduced expression of insulin (7 units(blue)) and low phenotype (2units(red)) which are at presymptomatic level (below 10 units) for both type 1 and type 2 diabetes i.e. the patient has pre-diabetes.

Note: This particular example is of the pancreas. The SVS test determines determine ca 15 pathological indications in each of the 30 main organs.

Figure 2: Strannik Virtual Scanning Test Report.

SVS RESULTS

In an earlier report [8] the author reported how the Strannik Virtual Scanning (SVS) test could be used to screen for the onset of pathologies which were associated with the onset or progression of AD and that initial studies have illustrated that SVS is 2-23% more accurate than the entire range of biomarker-type diagnostic and scanning tests against which it was compared.

Each pathology is described by two parameters. The first is the phenotype. The number is a mathematical expression or correlate of the number of pathological reactions which occur per unit of time. The second is the genotype. The greater the number, the greater is the pathological indication. In general, numbers below 10 units are pre-symptomatic whilst the numbers above 10 units are at the symptomatic level e.g. pathology of the islets of Langerhans is the diabetic indication. A patient with a 14/4 result would be a type 2 diabetic (at the symptomatic level) but would also be experiencing reduced levels of insulin expression although at a minor presymptomatic level. A patient with a 3/21 result would be a type 1 diabetic whilst a patient with a 15/20 result would have both type 1 and type 2 diabetes. Diabetic indications would likely be accompanied by cardiovascular indications, perhaps cardiosclerosis, and/or cardiac insufficiency, and a range of pathological indications in other physiological systems e.g. blood pressure; and related organs e.g. kidneys, liver, peripheral blood vessels, etc.

Each report also provides a numerical indication of the most destabilized physiological system and organs.

Patient 1:

The following patient 53yrs, 105kgs, male was suffering from cognitive and/or concentration problems. His health was badly

affected by a fall onto rocks on a beach which damaged his upper spine, neck and lower cranial region. The injuries sustained required significant surgical intervention and remedial treatments.

SVS detected a range of conditions including: The Most Destabilised Physiological System was the System that sustains optimal sexual function. The most destabilised organs were blood & peripheral blood vessels 94 units and prostate gland 92 units.

Significant pathologies detected in this patient included (but were not limited to):

Encephalopathy 15/4, Spinal Arachnoiditis 15/5, Impaired spinal circulation 0/2 (n.b. previous operation on spine), Diabetes 14/4 (predominantly type 2), Cardiac insufficiency 25/0, Calculosing Prostatitis 24/7, Sclerosing Prostatitis 15/0, Haemorrhagic Diathesis 36/13, Idiopathic Hypotension 21/7, Hypertonia 49/13, Dyskinesia/Duodenum 46/0, Ulcerative Disease/Stomach 36/0, Hepatocirrhosis 10/5, Neurosis of Oesophagus 13/5.

Conclusion: The results were consistent with the patient's known health. The patient was suffering from cognitive problems which were increasingly influencing his ability to function. As a result he no longer felt competent to drive his car. The test results indicated an inflammatory problem of unknown origin which was manifest primarily as a range of disorders including Arachnoiditis (a pain disorder caused by the inflammation of the arachnoid, one of the membranes that surrounds and protects the nerves of the spinal cord), the presence of myelitis and radiculitis i.e. inflammation of nerve roots which was directly or indirectly influencing the function of his brain which was diagnosed as 'encephalopathy', etc. The patient's results indicate a general disposition to cognitive decline and, perhaps, the onset of a neurological condition such as AD. The results are consistent with the pathological correlates of AD, in particular of diabetes and encephalopathy. A lack of physical exercise is contributing to increased weight, the onset of diabetes, cardiac insufficiency and can be expected to result in the emergence of other comorbidities which would influence the supply of oxygen and nutrients to the brain. Moreover, the inability to provide an adequate income for his family resulted in the onset of various stress-related conditions e.g. neuroses of the oesophagus, gastric ulcer.

Patient 2

The following patient 50 yrs, 64kgs, male was suffering from cognitive and/or concentration problems.

SVS detected a range of conditions including: (i) The Most Destabilised Physiological System: System that sustains optimal position in the environment (posture). (ii) The most destabilised organ: Spinal Cord 102 units (iii) The most significant pathologies detected in this patient included (but were not limited to): Encephalopathy 9/4, Spinal Arachnoiditis 56/31, Impaired Spinal Circulation 24/14 (n.b. previous operation on his spine), Myelitis 56/33, Radiculitis 25/34, Diabetes 14/7 (predominantly type 2), Cardiac insufficiency 17/9, Bronchial asthma 23/13, Pyelonephritis 30/17.

Conclusion: The results were consistent with the patient's known health. The patient was suffering from cognitive problems which were increasingly influencing his ability to function. The test results indicated an inflammatory problem of unknown origin which was manifest primarily as a range of disorders including Arachnoiditis, myelitis and radiculitis i.e. inflammation of nerve roots which was directly or indirectly influencing the function of his brain as 'encephalopathy' and was conceivably the cause his progressive inability to carry out his duties. The patient's results indicate a general disposition to cognitive decline and, perhaps, the onset of a neurological condition such as AD. The results are consistent with the pathological correlates of AD, in particular of diabetes and encephalopathy. Finally, and unsurprisingly, a lack of physical exercise is contributing to the onset of diabetes, cardiac insufficiency and can be expected to result in the emergence of other comorbidities which would influence the supply of oxygen and nutrients to the brain.

Patient 3

The following patient 35yrs, 83kgs, male was suffering from cognitive and/or concentration problems. The most destabilised Physiological System was that which sustains optimal sexual function.

The major pathologies identified by the SVS test included: Encephalopathy 4/12, Impaired spinal circulation 10/3 (n.b. previous operation on spine), Cardiac insufficiency 12/5, Calculous prostatitis 24/17, Sclerosing prostatitis 19/7, Diabetes 2/7 (prediabetes), ganglioradiculitis.

Conclusion: The results were consistent with the patient's known health. The patient, a medical doctor, was suffering from cognitive problems which were increasingly influencing his ability to function, in particular to concentrate. The test results indicated a problem of spinal circulation which was associated with an earlier back injury and resultant surgical procedure. This was accompanied by the presence of a range of disorders including ganglioradiculitis i.e. inflammation of spinal ganglia and nerve roots, which was directly or indirectly influencing the function of his brain as 'encephalopathy' and was conceivably influencing his increasing inability to function. The patient's results indicate a general disposition to cognitive decline and, perhaps, the onset of a neurological condition such as AD. The results are consistent with the pathological correlates of AD, in particular of diabetes and encephalopathy. Finally, a lack of physical exercise contributes to the onset of diabetes, cardiac insufficiency and can be expected to result in the emergence of other comorbidities which would influence the supply of oxygen and nutrients to the brain.

STRANNIK NEUROMODULATION THERAPY - OUTCOMES

The Strannik Neuromodulation therapy (SLT) has been used to treat a wide range of patients with an extraordinary diversity of medical condition however it has not been used to treat patients with the cognitive decline which is characteristic of AD. Initial clinical studies have illustrated that SLT is 75-96% effective, in ca 30 common categories of medical condition, depending upon the degree of onset of the condition(s) being treated.

Nevertheless it has been used to treat patients with a wide range of medical and/or cognitive indications which could reasonably be considered to be the pathological precursors of dementative indications including Alzheimer's disease.

We include the following example case studies of patients in Russia, US, and the UK who have been tested and treated using SLT.

Patient: H.A; Sex: female; Age: 43 y.o.

Diagnosis: Spinal disc herniation L-3, L-4; hernia of thoracic spine (6,7,9), sense shock and paralysis of the left upper and left lower extremities; sense shock and excentric pain in the sciatic nerve area with the left lower extremity malfunction. During the SLT course of treatment back pain went away, the return of sensation of the patient's left side of the thoracic cage was observed, lameness and excentric pain in the sciatic nerve area went away.

Patient: T.B; Sex: male; Age: 54 y.o.

Diagnosis: Multiple sclerosis, disability, Group 1. The patient complained of general weakness, dizziness, irritability, sleep disorder, lack of appetite, lack of weight, depression. He was not able to walk without assistance. During the first quarter of the SLT course of treatment the patient began to walk without help, gained 2 kgs in a month, appetite was restored, and the sleep disorder went away. Later the patient began to do simple domestic chores.

Patient: S.O; Sex: male; Age: 44 y.o.

Diagnosis: The patient had been disabled for 3 years, spinal disc herniation L-3, L-4, spondylosis, constant pain in the area of loin, sense of shock, lameness, erectile dysfunction. The patient could walk with the help of a cane and could not sit for long.

He was prescribed « Spinal cord» and « Peripheral Nervous System » additional courses SLT treatment. This resulted in the complete return of sensation. The pain in the area of loin went away. After the first treatment course the patient could walk without a cane. There was also return of erectile function and successful sexual activity after the second treatment course. The patient began driving a car. The disability status was canceled after a medical re-examination. Within a year after undergoing a course of Strannik treatment, the patient had good state of health.

Patient S.I; Sex: male; Age: 65 y.o.

Diagnosis: The patient was diagnosed with bronchial asthma, paranasal sinuses pathology, intoxication, full allergic reaction. X-ray examination confirmed left sided purulent maxillary sinusitis and large intestine pathology. The patient was prescribed suppurative focus debridement and colon cleansing.

After 40 sessions of the SLT course treatment bronchial asthma attacks had stopped, blood pressure had stabilized, sleep efficiency was restored; general health condition improved.

Patient: G.A; Sex: male; Age: 48 y.o.

Diagnosis: The patient complained of insomnia which was a result of psychological stress. Over the past year, the patient sometimes was taking hypnotic drugs. Using the service, the patient has stopped taking hypnotic drugs.

Upon commencing a course of SLT his general health condition improved, working efficiency had recovered. Insomnia went away; the patient fell asleep easily; sleep became calm and deep.

Patient: B.J; Sex: female; Age: 65 y.o.

Diagnosis: The weight was 93 kg (205 pounds). The patient was diagnosed with dyscirculatory encephalopathy, hearing loss, chronic sinusitis, calcium deficiency, chronic hepatitis A, chronic cholecystitis, chronic pancreatitis, cardiomyopathy, heart arrhythmia, iron deficiency, chronic gastroduodenitis, irritable bowel syndrome, osteochondrosis with neurological symptoms. The patient had the risk of cholelithiasis, diabetes, allergic bronchitis and allergic dermatitis. The organism was unable to maintain normal blood sugar level, normal circulating blood volume and normal blood pressure. Peripheral vessels, pancreas and large intestine were under pressure. Nine organs had organically changed.

The client was prescribed the SLT (including the Overweight Protection treatment) courses. Now the patient's condition was much improved. Any organic changes of the organs were absent; remission of chronic diseases and weight loss were fixed. The patient's weight was 84 kg (185 pounds).

Patient: F.L; Sex: female; Age: 68 y.o.

Diagnosis: The patient complained of lack of appetite (she had not eaten for three weeks), apathy, depression, sweatiness, high temperature, severe tremor, dizziness, slow speech, flaccid movements, an abdominal cavity is tense, the patient suffered pain during palpation. For 1.5 years, the patient was under stress, since her husband, a brother and a sister had died. She did not seek medical help. Previously, the patient had been tested with the help of the Strannik program and was prescribed treatment, but didn't complete the recommended course.

During the first months of the SLT treatment course, her sleep disorder went away, body temperature decreased, tremor and sweatiness went away. The patient cheered up and wanted to live a full life again. She also had resolved an important problem: broke up with a friend. The patient had a diary of life improvements. She could easily drink tea and juice, eat cookies and broth. She was prescribed light protein diet. The patient was satisfied with the results.

Patient: P.A; Sex: female; Age: 38 y.o.

Diagnosis: Neurosis. The patient was repeatedly treated in neurological department; the effect of the treatment was short-range.

By the end of the first month of using SLT the health condition had improved. Sleep was stabilized; headache, anxious feeling

and sweatiness had gone away; working efficiency had been restored, and psychoemotional state had improved.

Patient: D.C; Sex: male; Age: 59 y.o.

Diagnosis: Patient with sleep apnoea was suffering from uncontrollable sleep episodes which were affecting his ability to drive and also the quality of his private life. Oxygen therapy was able to reduce the severity of the symptoms. He was offered surgery to improve his breathing which was hoped would mitigate the condition.

He refused the surgery and undertook several months of SLT therapy. After c6 months his consultant advised that he was no longer suffering from sleep apnoea.

Patient: A.C; Sex: male; Age: ca 65 y.o.;internationally respected doctor of medicine

Diagnosis: The SVS test identified to the patient's satisfaction his known medical condition including diabetes and a range of diabetic and other comorbidities. The patient was suffering from type 1 diabetes and a diabetic leg ulcer which, over many months, had refused to heal (after many courses of antibiotics) and affected his gait. At the time of the test he was in poor health.

He undertook a course of SLT which reduced his insulin requirement by 20-25%. The leg ulcer started to heal, the associated muscle pain and weakness declined, and his gait improved. His health improved very significantly. Testimonial available upon request.

DISCUSSION

The common causes of cognitive impairment in elderly adults, which preceeds and/or accompanies the development and/or progression of AD, can be categorised as those which cause changes to brain function, the autonomic nervous system, and changes of cellular and molecular biology i.e. associated metabolic imbalances which are due to the effect of Medications: Benzodiazepines and Non-benzodiazepine prescription sedatives e.g. zolpidem, zaleplon, eszopiclone; Anticholinergics e.g. donepezil; Antipsychotics and mood-stabilizers e.g. risperidone, quetiapine, olanzapine, aripiprazole; Opiate pain medications e.g. hydrocodone, oxycodone, morphine, codeine, methadone, hydromorphone, fentanyl; Metabolic imbalances e.g. abnormal levels of blood sodium, calcium, or glucose; Kidney or liver dysfunction; Hormonal Imbalances e.g. imbalances in estrogen and other sex hormones; Vitamin and Mineral Deficiencies e.g. low levels of vitamin B vitamins, folic acid; Substance abuse e.g. alcohol, illegal drugs; Damage to the brain due to an injury which influences the function of blood vessels or to a neurodegenerative condition e.g. the presence of neurotoxins, Lewy-Body disease, Alzheimer's disease, Parkinsonism, frontotemporal degeneration, etc.

Drugs are, with few exceptions, artificial substances of non-human origins. They are designed to interfere with pathological processes which occur as a result of autonomic dysfunction. If they are given in too low a dose they are ineffective whereas if the dose is too high it can have toxic implications. Moreover they depend, for their effect, upon the autonomic nervous system. Often the long-term effect of the drug can be debilitating e.g. of chemobrain following chemotherapy [98]. Following a surgical intervention the patient is left to recover i.e. for the patient's autonomic nervous system to revert to its normal regulated function. It surely makes more sense to consider a better understanding of the natural mechanisms by which the autonomic nervous system functions and is regulated! Such observations fits into Grakov's mathematical model of the relationship between sense perception, brain function, the autonomic nervous system and physiological systems, and cellular and molecular biology.

The rationale for Grakov's Strannik technology is based upon the recognition that cognitive changes are indicative of the fundamental causal mechanism whereas the pathological and symptomatic manifestations are the consequences of this process. Such rationale is supported by Noble's work [77] in which he discusses the relationship between molecular biology, cell biology, organ function, body systems and/or 'the organism'.

The SVS test results were consistent with the patient's known medical condition. The SLT case studies illustrate how such a treatment could influence the health of patients who have conditions which could be reasonably expected in time, if their conditions did not change, to result in dementative-type indications. Moreover it leads us to consider the systemic nature of the body's function and how the dysfunction of specific physiological systems – in particular (but not limited to) the optimisation of posture, sleep, blood glucose and intercellular pH - play a significant role in the etiology of dementative-type indications such as AD.

Problems with sleep, perhaps arising from stress or from postural problems and/or from pathological onset in any of the organs within each physiological system (the network of organs which have a functional role e.g. to regulate or optimise blood glucose, body temperature, etc) influences the removal of neurotoxins from the brain and steadily influences the brain's ability to regulate the coherent and stable function of the physiological systems. The altered inter-cellular and extra-cellular conditions in the brain influence dendritic spine formation [99] and neural connectivity which influences short-term memory [100]. The lack of sleep adversely influences stress and appetite.

For those that, for various reasons, are not able to exercise and maintain their weight at normal levels this leads to diabetes and obesity (Note 1), influences their posture and influences their ability to sleep. Such a Catch-22 situation can only be broken by recognising that the brain functions as a neuromodulator [10] which has the potential to reset dysfunctional sleep patterns and re-establish the body's normal regulated function.

Note 1: This would equally well apply to underweight people

Current market developments remain experiential i.e. without a clear understanding of the nature of the phenomena. The various mechanisms which seek to manipulate brain function include using electrical impulses in Deep Brain Stimulation, magnetic fields in Transcranial Magnetic Stimulation, using sensory feedback to influence the autonomic nervous system

(heart rate, blood flow, blood pressure, etc) in Biofeedback, influencing nerve activity by electrical stimulation or using drugs in Neuromodulation, etc. Each of these approaches influences brain function and structure [101] and acts upon the mechanism by which the autonomic nervous system functions.

Progress is being made in understanding the role of the prefrontal cortex [102] and in the treatment of a range of medical indications including multiple sclerosis [103,104], Parkinsonism [105,106], Alzheimer's Disease [107-108], migraine [109], etc. See Note 2.

Note 2: If the condition has solely genetic origins it is unlikely or less likely that any form of therapy including drugs or neuromodulation will reverse the condition and/or have long-term effect i.e. the effectiveness of such therapies will decline over a period of time. Nevertheless it presents a mechanism which can be used to reduce the effect of stress, prevent, inhibit and/or slow the onset of such conditions by acting on the autonomic dysfunction which is a part of the pathological process.

During sleep physiological changes occur which influence, mainly, the sympathetic response e.g. heart rate, blood pressure, blood flow, metabolic function and/or rate, respiration, reduction in the oxygen content or increase in the carbon dioxide content of blood, increased cerebral blood flow, decreased excretion of essential minerals sodium, potassium, chloride, and calcium and hence of more concentrated and reduced urine flow, endocrine functions e.g. production of human growth hormone, thyroid hormone, melatonin secretion, etc.

The human brain comprises four primary ranges of EEG frequency [110]. During sleep only the delta and theta frequencies are significantly active whereas during the period of awakenedness all ranges of brain waves (EEG) are active. This emphasises the significance of the delta and theta frequencies i.e. they are essential for life. There are no precedents which illustrate that human life can be sustained without the brain or its delta and theta brainwave (EEG) activity i.e. during non-rapid eye movement (NREM) sleep which accounts for up typically 80% of sleep in most humans.

The cerebral cortex generates slow waves which have the purpose of stimulating neural formations and/or networks which modulate the coherent function of the physiological systems [111]. The EEG waves are generated by neurons in the cortex which fire in a coherent manner. Lack of neuro-cortical synchrony impairs signalling through neural networks and leads to systemic which influences the function of the organs, the cells within the various organs, and the molecular processes within the cells i.e. pathological onset. Moreover such changes of molecular biology circulate through the blood and blood vessels to, and throughout, the brain and thereby influence the rate of neuro-cortical firing.

Accordingly, lack of sleep leads to the reverse phenomena - poorer memory [112] and/or retention of memories [100], particularly so in the elderly. Sleep is essential for the growth and consolidation of long-term memories in the prefrontal cortex thereby illustrating the link between the frontal cortex, which stores long-term memories; and the hippocampus, which stores short-term memories [100]; and the nature and extent of long-term memories which influence autonomic stability [113,114].

CONCLUSION

The hypothesis outlined in this paper provides a coherent explanation for the onset and progression of the cognitive dysfunction, and associated symptoms and observations, which characterises dementative conditions such as Alzheimer's Disease. It explains the relationship between cognitive dysfunction/changes of sense perception and pathological onset and/or progression; and how and why neuromodulation techniques can be used to treat patients with cognitive dysfunction and/or decline e.g. as in the Alzheimer patient. It follows the recent publication of a paper entitled 'the autonomic hypothesis' which illustrates how the body is regulated, and why it ultimately degenerates and expires.

CONFLICT OF INTEREST

The author is Chief Executive of Mimex Montague Healthcare – a company devoted to the commercialisation of the Strannik technology which is outlined in this paper. The author confirms that this paper is privately funded without any financial support.

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