IJMPR 2020, 4(3), 186-201

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

BOOSTING THE BRAIN'S INTRINSIC NEUROPROTECTIVE ACTIVITY IN TREATMENT OF DEMENTIA

Gargi Velhal, Kedar S. Prabhavalkar* and Lokeshkumar Bhatt

Department of Pharmacology, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle (W), Mumbai, India.

Received on: 25/05/2020
Revised on: 16/06/2020
Accepted on: 06//07/2020

***Corresponding Author**
Kedar S. Prabhavalkar
Department of Pharmacology, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle (W), Mumbai, India.

ABSTRACT

Dementia is considered as a progressive disease, which is accompanied with irretrievable memory impairment, loss of cognitive abilities and reduction in the capacity for independent living. Population aging has a noteworthy impact on the occurrence of the dementia rampant. Individuals with dementia are known to suffer from problems affecting them throughout their life. Therefore, treating dementia in the initial stages has proved to be the current focus of the worldwide research work. By reviewing the current understanding of the pharmacological and non-pharmacological approaches, this review intends to deliver new perceptions in treating dementia at the early stages by targeting the brain's intrinsic neuroprotective activity resulting in an increased resistance of the cells, increased cognitive function, and improved process of memory formation and lifestyle of an individual.

KEYWORDS: Dementia; Brain plasticity; Cognitive Impairment; Memory Impairment; Brain repair; Neuroprotection.

1. INTRODUCTION

The term dementia is originated from *demens*, a Latin word, which refers to be, as out of one's mind (Lewis & Spillane, 2019). Dementia is considered as a progressive disease which is accompanied with an irretrievable memory impairment, loss of cognitive abilities and reduction in the capacity for independent living (Prince et al., 2013). It can also be stated as a medical disorder as a result of neurodegeneration (vascular dementia, Alzheimer's disease, frontotemporal dementia and Lewy body) (Prince et al., 2013). It can be best understood as a syndrome instead of as any one individual's particular disease. It is mostly seen that, multiple diseases play a role in contributing to any one person's dementia ailment (Barba et al., 2012).

Dementia suffering patients often show neurological and behavioural changes which can be understood by their slowed thinking, forgetfulness, depression, anxiety, disorientation, and loss of executive functions (problem solving, working memory, thinking, reasoning, judgment, planning and execution of tasks), with deteriorating performance and increasing task complexity (Venkat et al., 2015). Even though onset of dementia in young cases are now widely recognized, dementia is said to be a condition which affects the geriatric people at a higher rate. The geriatric people are viewed to be an important contributor of disability in terms of memory, cognition and difficulties in their daily activities. (Barba et al., 2012; Miss et al., 2009). Major risk factors for the advancement of dementia are progressing age, genetic profile, and systemic vascular disease. (Baumgart et al., 2015).

A standard method to theorize dementia is to take into consideration that this disease has two major types: few which are "neurodegenerative" (commonly referred to as "irreversible") and some that are non-neurodegenerative (also referred to as "reversible"). For instance, patients suffering from dementia may suffer from neurodegeneration due to multiple diseases (example, Lewy body dementia) and non-neurodegenerative (example, cerebrovascular disease), who together account for the damage (Schneider et al., 2007). Some diseases can sometimes cause cognitive impairment without causing a decline in the person's daily activities. Such a state is termed as Mild neurocognitive disorder and Mild Cognitive Impairment (MCI) (American Psychiatric Association, 5th edition, 2013).

On estimation, in the year 2015, the prevalence of people worldwide living with dementia was found to be 46.8 million and it is believed that this number is close to 50 million people in 2017. This number is estimated to double every 20 years, reaching 75 million in 2030 and 131.5 million in 2050. India, China, and their western Pacific and south Asian neighbours show the fastest growth in the elderly population who develop dementia.(*Dementia statistics | Alzheimer's Disease International*, n.d.). Another type of dementia which is the vascular dementia (VD) is also known to affect the cognitive abilities, accounting for 17–20% of all cases of dementia. After Alzheimer's disease (AD), vascular dementia is considered to be the second cause of

dementia (Venkat et al., 2015). As the populace ages, the number of people suffering from dementia will also increase (Prince et al., 2013).

1.1 Types of Dementia

Dementia is a condition where there is cognitive impairment, therefore impacting on the learning, language, memory, and various other roles of the brain. Alzheimer's disease is the well-known type of dementia which can be well-defined by its gradual decline in cognitive abilities and precise neurological variations in the brain-particularly the neuronal damage and the protein aggregates accumulation. Considering Alzheimer's disease as the principal and gradually increasing cause of dementia, it is therefore seen as an increasing problem on the health-care organizations around the world and has therefore been the focus of enormous research endeavour's in the course of the most recent 50 years. There are, however, many other causes of dementia, which helps to understand the molecular biology of Alzheimer's disease as well as the neurodegeneration (figure 1).

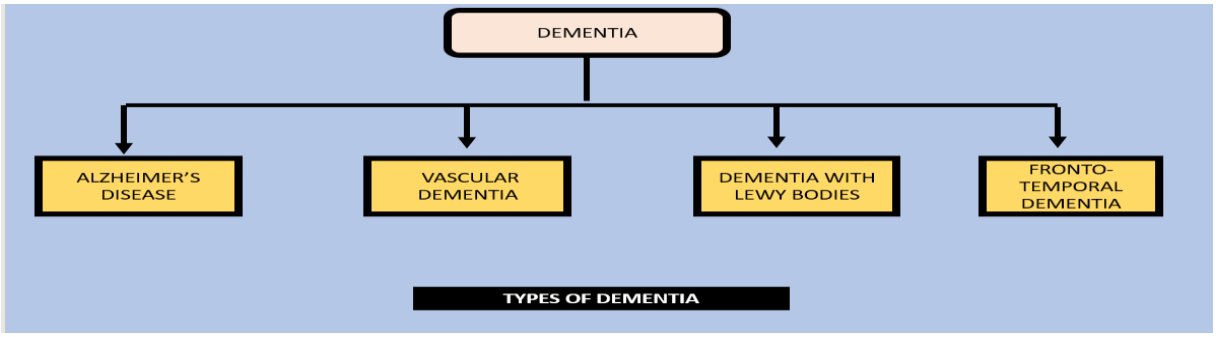

Figure 1: Types of dementia.

2. How truly the shaping of memory takes place?

The memory is a cognitive process in the brain that helps to encode, store, and reminds a person of the received information (Manuscript, 2014). The memory is a dynamic procedure and plays an important role in learning and communicating with the surrounding environment. In circumstantial conditions, it is imperative to settle on quick exact decisions considering the evolving circumstances. This requires neuronal systems to precisely anticipate results dependent on the earlier information (Palacios-Filardo & Mellor, 2019).

We experience an occasion, some aspects of this occasion are encoded, this encoding initiates a progression of procedures, typically categorized as "consolidation", which requires time, resulting in a permanent memory trace. Memory consolidation plays an important role in this sequence, as it regulates both, what will be preserved after initial encoding, and the time required for this process. Once consolidation has taken place, by definition, the permanent memory trace that results, cannot be disrupted in the normal course of events (Ber et al., 2006). There are three major stages, which is required to process information in the brain. The first main stage in information processing is encoding, where the surrounding data is detected and encoded in the form of physical and chemical stimuli. This is followed by the next phase, where the data generated from these stimuli is stored and preserved as well as sustained over a specific period. Lastly, in the third stage, the stored data is recovered as an outcome to a signal (Takeda, 2018). The process is mentioned in figure 2

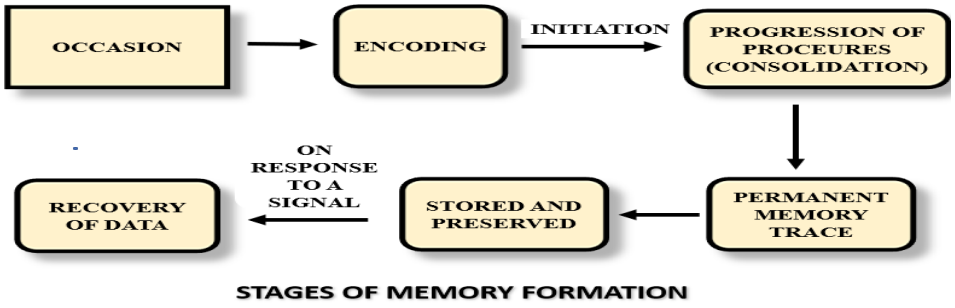

Figure 2: Stages of memory Formation.

Short-term, sensory, and long-term memory are the types of memory based on its time span. Sensory memory is an automated process which stores the information for not more than one second (Sperling, 1963). Retrieval of information without rehearsal in matter of few seconds is done by short-term memory (Cowan, 2001). In comparison to the short-term memory, where the capacity is limited, long-term memory on the other hand can maintain and store vast amount of information for a longer period. Memory can also be classified into

declarative and non-declarative memory (Eichenbaum, 2004; L. R. Squire & Zola, 1996; Larry R. Squire, 1992). Declarative memory can also be termed as explicit memory, is considered a conscious process. It can be further classified into semantic and episodic memories. In which, the semantic memory refers to encoding of the abstract knowledge such as items and facts (Jones & Roseman, 2013; Larry R. Squire, 1992), while the episodic memory refers to specific details of an event, where an individual can recollect information of his/her life events. In comparison to declarative memory, non-declarative memory does not require conscious retrieval and therefore is also called implicit memory. The basic types of human memory are classified in Figure 3.

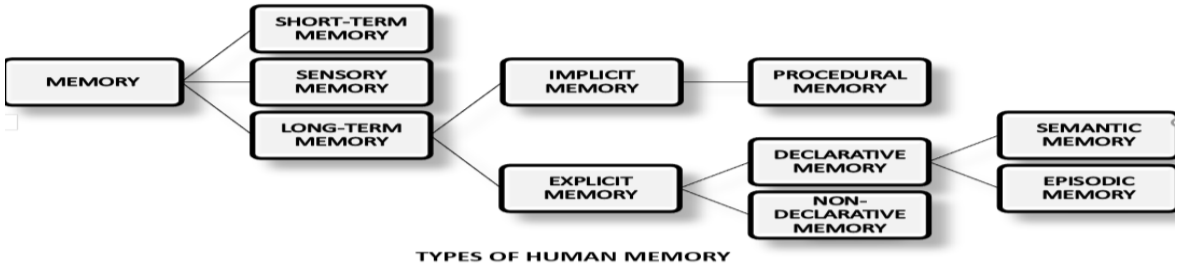

Figure 3: Types of Human Memory.

In the mammalian brain, hippocampus assumes a pivotal role in the arrangement, refreshing and recovery of recollections which shape the premise of result expectation (Palacios-Filardo & Mellor, 2019) as well as in the regulation of memory and learning. The development and the merging of memory depends on the inbuilt ability of the hippocampus to unite the new stimulus through the structural reorganization of the neurons and its plasticity (Bailey & Kandel, 1993; Bartsch & Wulff, 2015; Bishop et al., 2010; Leuner & Gould, 2010). The dentate gyrus present in the hippocampus is an area, which receives various sensory stimuli from the entorhinal cortex and includes a variety of cognitive processes; particularly memory based spatial setting and acquainted memory.

One of the most noteworthy highlights of the brain is its capacity to store a huge amount of information. Lifelong sustaining plasticity of chemical synaptic transmission is the main mechanism for storage of information in the brain. Specific synapse-dependent changes involved in the transmission from a wide range of inputs is important for sustaining brain capacity. Intrinsic plasticity in the form of activity-dependent is mainly done by the voltage-gated channels found to be located at the input or the output side of the neurons. In the hippocampus, the long-term plasticity is mainly observed in the CA1 area interneurons.

3. Brain's intrinsic protective mechanism after neurodegeneration

Blood brain barrier (BBB) as well as endogenous microglia and macrophages play an important role in the human brain as it selectively allows the passage of individual small lipid soluble molecules and pathogens to pass through the capillary endothelial membrane. To aid in the normal cerebral functions, brain requires glucose and oxygen for a large amount of energy supply. Under normal conditions in the brain, neuroinflammation is known to promote neuroprotection by repairing damaged brain tissue. A key event during several neurological diseases is the impairment of the blood brain barrier's (BBB) neuroprotective properties. This leads to its contribution in the neurodegeneration and neuroinflammation. Chronic condition like the neurodegenerative diseases are mainly characterized by a gradual accumulation of misfolded proteins, which contributes to further slow damage to the brain tissue. As the neurodegeneration progresses after its onset, it can also cause immune response alterations leading to infiltration of leucocytes and lymphocytes from the peripheral circulation to the brain, thereby activating the resident inflammatory cells, thereby affecting the individual's daily activity. This leads to loss of memory.

Oxidative stress is also seen to contribute to the neuroinflammation. It activates several neuroinflammatory parameters including the activation of astrocytes and microglia. They secrete the inflammatory chemokines and cytokines contributing to neuroinflammation and activate a highly atypical inflammatory response. This is the activation of the resident immune cells (Butnaru & Chapman, 2019). Reactive oxidative species contribute to DNA damage in the brain by endogenous metabolic activity leading to cellular dysfunction. After an insult to the brain, it is necessary to restore and maintain the ion gradient by the signalling processes involving neurotransmitter and action potential turnover (Alle et al., 2009; Attwell & Laughlin, 2001). This maintains a high basal metabolic rate, thus increasing the production of ROS. Scavenging molecules such as glutathione peroxidase, glutathione, peroxyredoxins and superoxide dismutase as well as enzymes involved with base excision repair (BER) have been evolved as an antioxidant defence system, to protect against the body's own destructive by-products (Dizdaroglu, 2005; Wilson & Bohr, 2007). Although these cells are competent enough to defend against elevated oxidative stress, it is known that the oxidative DNA damage accumulates as the age progresses. In order to recover from this injury, robust DNA repair system, are required by the neurons to preserve normal

brain function, avoid cell death, and repair the oxidative damage. The four major pathways for repairing damage to bases are nucleotide excision repair (NER), double-strand break repair (DSBR), mismatch repair (MMR) and base excision repair (BER). NER excises bulky helix-distorting DNA lesions, MMR is responsible for the correction of mismatched normal base pairs and BER is responsible for the repair of damage to the single nucleotide base. These are responsible for repairing the damages at a cellular cell (Kjølhede et al., 2011).

The innate as well as the adaptive immune system contribute to the inflammatory as well as the immune response after neuronal damage. In conditions like the chronic inflammation, there is damage of neurons as well as the activation of glial cells, which express chemotaxic molecules. These send the signal to the peripheral immune system regarding the injury in the brain. There is induction of chemokines and cytokines leading to upregulation of the vascular adhesion molecules on the immune cells as well as in the endothelial cells. Dementia leads to disruption of the BBB, thereby allowing the entry of peripheral immune cells into the brain (Farooqui, 2019a). This therefore helps in modulating the immune system. Thus allowing autoimmunity to respond to self-antigens in the brain. The CNS innate immune cell, microglia helps in the maintenance of a healthy environment for brain cells to survive by eliciting diverse action for the homeostasis and development of the brain (Aldana, 2019). When there is an injury, these immune cells immediately undergo functional and morphological changes and rapidly start responding to repair the brain insults. This process is termed as microglial activation and the steps involved in this process is the migration to the site of injury and releasing immune response molecules such as the reactive oxygen species (ROS), cytokines and proteases. It is the first- line innate response. Microglia also phagocytize the cells as well as the cell debris and participate in the remodelling of the extracellular matrix.

Targeting the brain's intrinsic neuroprotective activities to repair itself from the dementia induced changes

Regardless of the damage to the brain tissue, spontaneous recovery occurs days, weeks, and months after onset of dementia. As the time progresses, the intensity of the neurodegeneration also increases. Therefore, it is necessary to treat the onset of dementia at the initial stage. Mentioned ahead are some of the endogenous parameters which can be influenced to repair the damages caused in the brain (Massenzio et al., 2018).

Treatment of dementia requires complete understanding of the molecular mechanisms and processes that contribute to a neurodegenerative disease. Therefore, dementia treatment can be divided into two approaches:- pharmacological and non-pharmacological. The former includes treating dementia by treatment of symptoms rather than treating the underlying mechanism that triggers the dementia syndromes. Medications like anti-depressants, neuroleptics, hypnotics/sedatives are usually prescribed but they are accompanied with unwanted side-effects and issues with tolerability. These medications sometimes even contribute to decline in cognitive function, mortality, or may lead to progression of another disease. The latter approach is comparatively better tolerated and may help in preventing dementia. Therefore, it is necessary to boost and target the endogenous neuroprotective cells, which help to counter the mechanisms leading to neurodegenerative disorders.

4. Pharmacological Approaches

4.1 Brain plasticity

Vertebrate and the invertebrate animals show the presence of the most vital feature of the nervous systems which is its plasticity, therefore deviations in the activity or the connectivity of several circuits found to be inside the nervous system enables it as an important parameter for learning, to encode memory, and to drive the behaviour(Li et al., 2019)

Brain plasticity is a term, which refers to a brain's inherent capacity to reorganize its function and its structure as an outcome to any stimulus or injury from the internal as well as the external sources. Plasticity of the brain is mainly focused on its neuronal plasticity, which apparently is combined with the changes of different types of brain cells such as blood vascular cells, microglia and astrocytes. Brain plasticity enables the central nervous system to persistently adjust to the variations in the atmosphere (Zilles, 1992).

It can be understood at various stages, starting from cellular, systemic, and molecular to behavioural characteristics, also including fluctuations in neuroanatomy, neurochemistry, and neurogenesis. These changes are enough to affect the learning and memory of the individual (Yao et al., 2018). Substantial evidences show that the brain plasticity is seen to exist throughout a person's lifespan. The brain is always said to be developing which means that it can be constantly modified by learning and experiencing new things, starting from the development of an individual to the person's young adult period to its adulthood, which continues till the time the person is aging in both healthy and diseased conditions. (Article, 2011).

Due to the synaptic activity, there are two major mechanisms, which is known to drive the synaptic connectivity changes. These are the non-Hebbian and the Hebbian types of synaptic plasticity. Hebbian plasticity, is referred as a specific-input synaptic modification in the arrangements of long-term depression (LTD) and long-term potentiation (LTP). It is believed to be the underlying mechanism of the associative learning, through bidirectional modification of the synaptic strength. Hebbian plasticity on the other hand if left unchecked is believed to be self-reinforcing with a probability to run away (e.g. LTP will lead to synaptic

strengthening and therefore more correlated post-synaptic and pre-synaptic activity, which enables added LTP). The non-Hebbian plasticity is therefore considered important as its main mechanism is to prevent runaway Hebbian plasticity (Mcleod & Salinas, n.d.).

It is currently hypothesized that, in the aged hippocampus if the energy dynamics is sustained, it can help in boosting the memory storage by sustaining long term potentiation (LTP) as well as the synaptic functioning. Therefore, the pharmacological approaches that can help in sustaining the long-term potentiation in different structures of the brain, mainly the hippocampus, can help in reducing the loss of memory and contribute in the memory formation (Lisman et al., 2018). Hence, the LTP improving compounds can prove as an effective therapeutic intervention to treat cognitive deterioration.

4.2 Myelination

The normal functioning of the nervous system of the vertebrates requires rapid nerve impulse conduction. It has been achieved by the development of myelin-forming glial cells. Myelin can be described as a multilamellar plasma membrane found in the central nervous system (CNS) and Schwann cells (SCs) which are made by the oligodendrocytes (OLGs) situated in the peripheral nervous system (PNS) (Palacios-Filardo & Mellor, 2019). Its chief function is to act as a protective and insulating cover for the axons present in the sensory system. Myelin is primarily composed of proteins and lipids, which wrap around the axon and is also the organizational foundation known to permit quick conduction and integration of information in the brain (Hartline & Colman, 2007b), propagating the action potentials concentrated at regular, discontinuous sites along the axon. The most important role of myelin is to shield the inter-nodal regions which helps in decreasing the membrane capacitance and in increasing the membrane resistance, therefore enabling fast saltatory propagation of action potentials (Hartline & Colman, 2007a).

Normal emotional, behavioural and cognitive function requires a rapid information transfer. This is achieved by myelination. Protection of the axon, its insulation and the acceleration of the nerve impulses saltatory conduction are the main role of myelin. It also plays a part in the prevention of leakage of ions, thereby maintaining the axon's electrical potential. Factors like viral infection, hypoxia, immune response and nutritional disorders can play a part in damaging the myelin, and thereby inducing blockade of conduction(A. S. Wang et al., 2018). Oligodendrocytes on the other hand, play a protective role in preventing the contact with the extracellular matrix (Raddassi et al., 2011). Therefore, the death of these oligodendrocytes and any injury to the myelin will lead to the loss of the myelin, decrease in impulse propagation and also in causing severe neurological dysfunctions like the impaired cognitive functions, motor dysfunction, neurodegenerative diseases and psychiatric disorders.

This will ultimately lead to blockade of conduction of neuronal information (Shiryaev et al., 2009). Blockade of the neuronal information conduction is also caused due to the destruction to the neuronal structure (Marty et al., 2002). Therefore, the crucial parameter for the appropriate maintenance and formation of myelin, is the normal differentiation and the proliferation of oligodendrocytes (Landry et al., 1996). Substitution of the oligodendrocyte loss and remyelination of the axons is the major role of the two endogenous cells- Neural progenitor cells (NPCs) and oligodendrocyte precursor cells (OPCs) (Alizadeh et al., 2015). Injury to OPCs lead to death of the oligodendrocytes which ultimately induces axonal demyelination. The mechanism is mentioned in Figure 4.

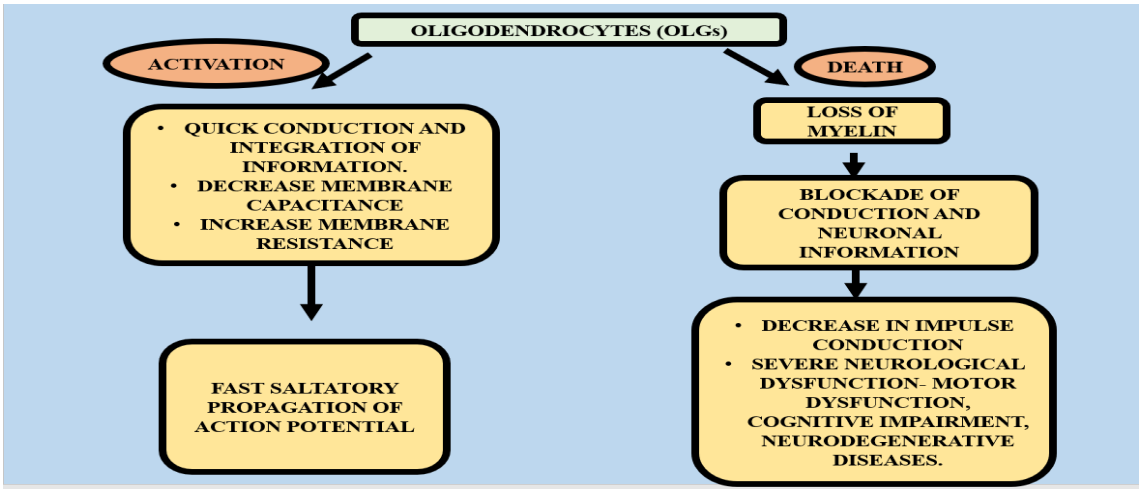

Figure 4: Mechanism of Myelination.

One of the example of neurodegenerative disease is the multiple sclerosis (MS). It is the central nervous system's (CNS) chronic enervating disease described by its demyelinating lesions, found to be an outcome of an

autoimmune response against an unidentified antigen on myelin and the oligodendrocytes that produce and maintain it. The autoimmune attack prompts a disturbance in the axonal function, and eventually, to axonal loss and neuronal death. This axonal loss in the spinal cord and brain is secondary to demyelination and is believed to trigger the slow accumulation of debility met by people with Multiple Sclerosis. Most common symptoms of MS expressed in all types and stages, are the reduced motor and sensory function, speech and vision deficits, cognitive impairment which includes decrease in the speed to process information, impaired long-term episodic memory, compromised attention and reduced executive functioning and disruption of the blood brain barrier (BBB). These symptoms are mainly caused by the demyelination- mediated hippocampal malfunction. This also leads to significant reduction in the hippocampal volume and density of the synaptic sites, disturbance in the excitatory synapse maintenance and in the neuronal signalling pathway activation, which regulates learning and memory. Even in the absence of inflammation, demyelination can cause degeneration of axons and neurons. Mitochondrial malfunctions, loss of energy, oxidative stress also contributes to neurodegeneration. Therefore, remyelination is proving to be a promising therapeutic approach in treating MS, as it takes an effort to re-establish normal axonal function and protects the brain against neuronal loss.

4.3 Autophagy Induction

Neurons in the hippocampus show a presence of autophagosomes (APs), the double-layered vesicles associated with autophagy, have appeared to take shape in the neurotransmitter synapses and along the neuronal processes (Kulkarni et al., 2018; Vijayan & Verstreken, 2017; Y. Wang et al., 2017). Developing information propose that in axonal growth, synaptic assembly, long-term depression (LTD) and release of dopamine, hippocampal autophagy plays an important role in maintaining the neuronal homeostasis (Bartsch & Wulff, 2015; Kulkarni et al., 2018; Shehata et al., 2012; Shen & Ganetzky, 2009; Vijayan & Verstreken, 2017; Y. Wang et al., 2017).

Autophagy is referred to as a catabolic cellular process, wherein the damaged organelles and degraded proteins are engulfed inside the autophagosomes, which are later carried to the lysosomes for the process of degradation (Patricia Boya et al., 2013; Mizushima & Komatsu, 2011). This can be triggered through multiple physiological stimuli as well as by the changes in environmental conditions(Patricia Boya et al., 2013). Multiple ATG (autophagy-related) proteins (like the Fip200, beclin 1, and VPS34) can identify the biogenesis of AP's which are found to be involved in various dynamic membrane complexes (Ktistakis & Tooze, 2016; Lamb et al., 2013; Mizushima et al., 2011). Lipidation of the LC3 protein (LC3-II), is carried out by the ATG5/12/16L1 complex which favours the maturation of the AP at the recruited site of nascent AP (Ktistakis & Tooze, 2016; Lamb et al., 2013; Mizushima et al., 2011). There is presently growing evidence which propose that induction of autophagy is necessary for the regulation of vital physiological functions, such as regulator of appetite, regulation of energy metabolism, and modulation of host defence, by facilitating the cellular adaptive outcomes to new physiological stimuli (Patricia Boya et al., 2013; Galluzzi et al., 2014; Singh & Cuervo, 2011). However, its role is mostly restricted to the brain. In the hippocampus, the neuronal plasticity and the memory, experience fluctuations in organelle turn over and cellular protein homeostasis (Bishop et al., 2010; Bostancikliogl u et al., 2015). This is the place where the neurons in the hippocampus are continuously exposed to various stimulus. Therefore, it leads to a conclusion that in regulating hippocampal-dependent cognitive fitness, autophagy plays a vital functional role (Glatigny et al., 2019).

In numerous cell types autophagy is a noteworthy part of a cell's reaction to stress, upregulated in response to mitochondrial damage, nutrient deprivation, or proteotoxic stress (Maday & Holzbaur, 2016; Maday et al., 2012; Mizushima et al., 2004). It is also known to play a vital role in the pathogenesis of muscular diseases, neurodegenerative diseases, infectious diseases, cancer and immune system diseases. Neurons are found to be very sensitive to the stress caused by misfolded proteins and damaged organelles than somatic cells (Tang et al., 2019). Autophagy are responsible for the removal of these stress factors to maintain the neuronal homeostasis. Cellular dysfunctions are frequently caused by the autophagy failure to eliminate damaged organelles or defective proteins (Tang et al., 2019). An imbalance of body homeostasis is also caused by a deletion of the autophagy- related gene (Atg), ultimately leading to obesity (Meng & Cai, 2011), diabetes (Jung & Lee, 2010), insulin resistance (Yang et al., 2010) and neurodegeneration (Komatsu et al., 2006). Playing an important role in removing the damaged organelles or the degraded proteins (Mizushima et al., 2008), autophagy can now be considered as a therapeutic target in the neurodegenerative disease treatment. Evidence till now, favors a strategy for enhancing the efficacy of autophagy in the neurodegenerative disorders by targeting the specific stages that are disrupted. The advantages of such modulation may include more effective responses to stress, incomplete digested autolysosomal metabolites, suppression of apoptotic cascades and reduced toxic protein aggregates(P Boya & Kroemer, 2008; Ravikumar et al., 2004). It is reported that autophagy plays a protective role in the development of certain human disorders, including cardiovascular diseases, neurodegeneration and cancer(Levine & Kroemer, 2008).

4.4 Role of glial cells in dementia induced brain recovery

Brain is considered an extremely vulnerable organ as it is subjected to a wide array of dangerous stimuli-

hampering its homeostasis both internally and externally. The cascade of reaction, which takes place after the stimulus, is required to promote homeostasis, which is altogether referred as "neuroinflammation". This includes the involvement of mechanisms, both molecular and cellular which plays a role in identifying potential harmful stimulus, alleviates their effect, and repairs any subsequent damage as quickly as possible.

During the initial stages of dementia, microglial cells and astrocytes play an important role in neuroinflammatory reactions which is widely understood; but, in spontaneous recovery, the role of glial cells remains unknown.

Microglia, the essential intrinsic immune cells resident to the brain are considered to be an active member of the neuroinflammatory reactions which express chemokine and cytokine receptors that interact with the peripheral immune cells. In the adult Central Nervous System (CNS) they represent about 10%-20% of the overall population of the cell and play a vital role in protection of the CNS during its lifetime. Being a part of the lineage of mononuclear phagocyte, they are found to be active sensors of instabilities in the environment outside the cell which includes the morphological changes, and can elaborate an extensive range of outcomes to re-establish the tissue homeostasis (Hanisch & Kettenmann, 2007; Kreutzberg, 1996). They are very dynamic and responsive cells in nature which resolve the fluctuations caused by the surrounding signals. Under physiological conditions, microglia, test and examine the neighbouring region and discard the damaged tissue component and accumulated parenchyma of metabolic products (Neumann et al., 2008; Nimmerjahn et al., 2005; Ransohoff & Cardona, 2010). Microglia cells originate from the mesenchymal and migrate into various regions of CNS and distribute through the brain parenchyma and acquire a ramified or "resting" microglia phenotype which in its surveillance state is sustained by signals which are carried by astrocyte-derived factors and neuronal factors (Kierdorf & Prinz, 2013). In the ordinary CNS condition, signals are provided to microglial cells by healthy neurons via secreted and membrane-bound factors, such as CX3CL1, neurotrophins, CD22 and neurotransmitters (Frank et al., 2006; Pocock & Kettenmann, 2007). After continuous stimulus of brain lesions or nervous system dysfunction, these cells actuate explicit reactions that outcome in the slow change of ramified microglia into 'reactive microglia' or 'activated microglia,' which has the ability to release large number of products that is beneficial for the neighbouring cells (Pocock & Kettenmann, 2007). Depending on the nature of the stimulus, these outcomes include inflammation-related genes and altered expression of cell surface markers, amplified capacity of phagocytes, process withdrawal, amoeboid morphology acquisition, site of injury migration, and better proliferation(Kettenmann et al., 2011; Lynch, 2009).

Microglia can be classified into two types based on their outcomes to the surrounding environment- pro-inflammatory phenotype (M1 type) and anti-inflammatory phenotype (M2 type). The former helps in the release of destructive pro- inflammatory cytokines, while the latter produces molecules that take part in the tissue repair and shows anti-inflammatory action (Anttila et al., 2017; Boche et al., 2013; Hu et al., 2015; London et al., 2013). Axonal regeneration, neurogenesis, vascular repair and angiogenesis are some of the useful effects of the M2 type microglia (Hu et al., 2015). Neurons are the only one, which express the chemokine fractalkine (CX3CL1), and its receptor, CX3CR1, and is solely expressed by microglia present in the CNS parenchyma.

Controlling microglia initiation has been proposed as a critical remedial method for different neuroinflammatory issue which leads to dementia, for example, Alzheimer's illness, Parkinson's infection, and Multiple sclerosis. By the secretion of the brain derived neurotrophic factor (BDNF), microglia plays an important role in promoting synaptogenesis(Miyamoto et al., n.d.).

5 Non-Pharmacological Approaches

Modern non- pharmacological approaches for the treatment of dementia have been proposed to quicken the retrieval of motor control and brain function by helping in preventing or retarding dementia. In recent years, researchers have produced many non- pharmacological treatments and therapies which include transcranial magnetic stimulation, music therapy, cognitive behavioural therapy, art therapy, aromatherapy, physical exercise and motor training and acupuncture etc. These therapies provide beneficial effects by activating specific pathways in several parts of the brain including the amygdala, hypothalamus, prefrontal cortex and hippocampus. They also help to increase the levels of neuropeptide and neurotransmitters resulting in increase in repair mechanisms, neuroplasticity and neurogenesis (Farooqui, 2019b).

5.1 Transcranial Magnetic Stimulation

Human brain can be invasively stimulated by a powerful technique called as the Transcranial Magnetic Stimulation (TMS) (Barker et al., 1985). With the help of a coil, the brain receives a strong and time-varying magnetic pulse in the TMS. These coils comprise of an insulating material containing small number of turns of copper wire. An electric field in the cortex is induced by the magnetic pulse produced by the coil, which results in the production of neuronal activation only when the inhibitory interneurons and pyramidal cells are depolarized (Koch et al., 2018; Ridding & Rothwell, 2007). The physical principle of TMS, described by Faraday's law, is based on electromagnetic induction, whereby a changing magnetic field (B) induces an electric field (E). If the magnetic field slowly changes or is static, there is no excitation of the neurons. In TMS, the strength of the magnetic field used is on the order of

1 to 2 T and its rise time is 100 microseconds approximately.

In TMS, the magnetic pulse is produced by passing a current pulse through an induction coil placed over the scalp. Recent evidences indicate the presence of more sophisticated stimulators under development for the stimulation of multiple brain areas. This is because of the only fact that TMS can activate neurons in the cortex rather than deeper parts of the brain. Apart from the activation of the target area, TMS is also shown to activate the brains distant interconnected sites, which are shown to be important for the study of connectivity of the brain (Katila;, 1997). Depending on the location and the shape of the coil, the spatial distribution of the induced electric field is shown to vary in the brain. At the microscopic level, TMS is appeared to drive the free charges in extracellular and intracellular regions to move along the electric field. Stimulation produced by TMS produces possibilities for mapping the human brain, which can prove to be effective in understanding the motor, cognitive, and sensory brain networks. Therefore, combination of TMS with the other neuroimaging techniques, such as functional MRI electroencephalography (EEG) (Bestmann et al., 2005; Katila;, 1997), near-infrared spectroscopy (Näsi et al., 2011), or PET (Paus et al., 1997), acts as an effective tool to investigate human brain functions. Figure 5 clearly depicts the role of TMS in treatment of Dementia.

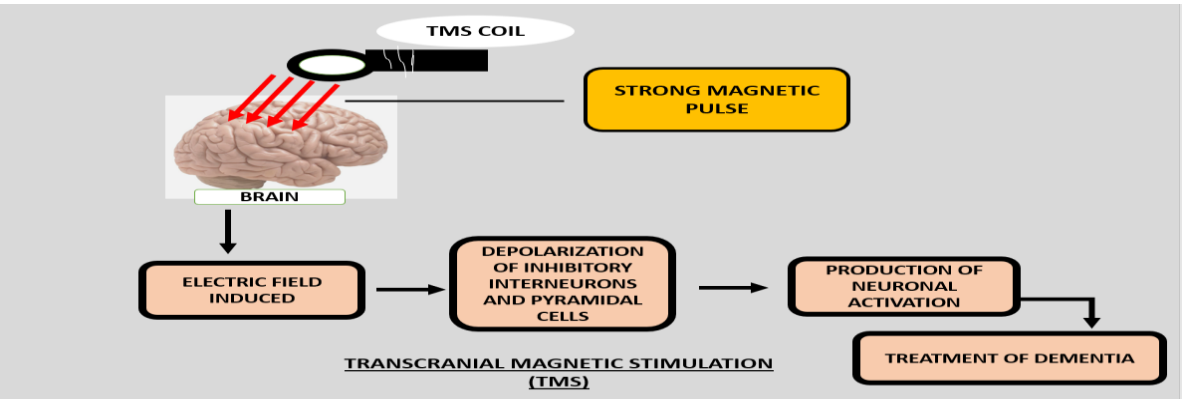

Figure 5: Role of TMS in treatment of Dementia.

When the delivery of the pulses is in a repetitive fashion, the TMS technique is called as Repetitive Transcranial Magnetic Stimulation (rTMS) (Elder & Taylor, 2014). This type of stimulation produces persistent neuronal excitability, resulting in the manipulation of the brain functions. The low intensity of the magnetic stimulation helps in the treatment of depression (Martiny et al., 2010), dementia, stroke and pain (Shupak et al., 2004). It is well recognized until now, that by depolarizing axons close to the stimulation electrode, specific input to a neuron can be activated by the local electrical stimulation. In contrast to local stimulation, rTMS also acts via the depolarization of a specific set of axons(Bosch & Hayashi, 2012), but it also targets other neural structures found to be within the electric field within the stimulated network (up to several cm^3) (Opitz et al., 2011). Recent evidence has shown that rTMS plays a role in counteracting the apoptotic cell death, regulation of microglia and astrocytes and also in reducing the inflammatory responses. Based on the above information, it can be concluded that rTMS provides a therapeutic approach in decreasing the neuroinflammation, reducing the hyper excitability of the neurons, promoting neuronal survival and in altering the permeability of BBB (Cullen & Young, 2016). It is relatively safe and also well-tolerated. High frequency rTMS is shown to increase the expression of NR2B and BDNF in rat hippocampus (Shang et al., 2016; N. Zhang et al., 2015). Moreover, a relative high level of BDNF in the hippocampus results in a higher spine density and better LTP (Kellner et al., 2014; Leal et al., 2014; Panja & Bramham, 2014). It suggests that there is a possibility that rTMS can prove as an efficient approach to reduce the adverse effects of learning and memory.

5.2 Treatment of Dementia with Acupuncture

Acupuncture is an ancient healing technique that treats a disorder by insertion of needles into the skin at specific locations (acupoints) of the body. This technique can be manipulated by heat, electrically, or manually (Shupak et al., 2004). The main principal behind this technique is adjustment of Qi (vital energy) flow which is believed to circulate in a network of 12 primary channels which connects 360 principal acupuncture points(Kavoussi & Ross, 2007; X. Zhang et al., 2015). The stimulation of these points produces psychophysical responses by balancing the Qi energy, as well as blood flow throughout the body(X. Zhang et al., 2015; Y. Zhang et al., 2016). Acupuncture at accurate acupoints activates fibers that send signal to the spinal cord. Acupuncture has been used for the treatment of many neurological disorders including psychiatric and cardiovascular diseases, acute, and chronic pain, Alzheimer's Disease, and behavioural disturbances in vascular dementia (Abraha et al., 2017; Liu et al., 2016; Shi et al., n.d.) However, it is proposed that acupuncture may provide useful effects by regulating the expression of caspase family Bcl-2/Bax, Fas/FasL, Tumor necrosis factor-α

(TNF-α), c-Fos and NFκB, which suppress autophagy and neural cell apoptosis to reduce cell death in different pathological states especially vascular dementia and ischemic stroke(Luo et al., 2017). In Alzheimer's Disease and Parkinson's Disease patients, functional brain imaging verified that acupuncture increases the neuronal activity in the prefrontal lobe and temporal lobe which may contribute to memory formation and learning and in promotion of the maintenance of cognitive function (*Effect and Mechanism of Acupuncture on Alzheimer's Disease*, 2013; Lee et al., 2009; Salvage & Jenner, 2013). It is also shown to increase blood vessel function and synaptic plasticity. Acupuncture retards neuroinflammation, suppresses oxidative damage, improves synaptic plasticity, enhances neurotrophin signalling, decreases the levels of Aβ proteins, and reduces microglial activation in the hippocampus but also improves cognitive function (*Effect and Mechanism of Acupuncture on Alzheimer's Disease*, 2013; Salvage & Jenner, 2013; Ye et al., 2017). Neurological disorders contributing to the brain damage, activate neurogenesis which is an endogenous neural repair system. Acupuncture exerts its beneficial effects by facilitating and activating adult neurogenesis via the stimulation of Neural Stem Cells differentiation and proliferation in the brain (Ahn et al., 2016; Kim et al., 2014; Tao et al., 2016). Therefore, the possible mechanism underlying the beneficial effects of acupuncture is the plasticity regulation in the brain. Significantly, acupuncture can also be used in combination with drugs or other therapeutic treatments in stimulating neurogenesis in the neurodegenerative diseases.

5.3 Treatment of Dementia With Music Therapy

Music, a universal art form that exists in every culture around the world, is an integral part of a number of social and courtship activities. People express their thoughts, emotions, cope with their emotional conflicts and increase their self-awareness through a mode of music. It is observed that specific pathways in several brain areas such as the hippocampus, hypothalamus, insular and cingulate cortex, prefrontal cortex and amygdala, which are associated with emotional behaviours, can be activated by a simple musical stimulus. Music therapy finds its use as a clinical management and treatment of many neuropsychiatric and behavioural symptoms of depression, schizophrenia, dementia, and autism. In addition, neurochemical studies have suggested that several biochemical mediators, such as endorphins, endocannabinoids, dopamine and nitric oxide, may play a role in the musical experience (Farooqui, 2019c). Many studies have demonstrated that music can improve multiple domains of cognitions in AD patients, including attention, orientation, memory, psychomotor speed, and executive functions. It is also seen that 6 weeks of music therapy can help to decrease anxiety and depression in an AD patient (Gómez Gallego & Gómez García, 2017). It is also seen to promote the calming of the emotional expression and behavioural symptoms of dementia. In music therapy, a trained and registered music therapist treats dementia patients with a program of musical engagement, thereby improving their motor skills and enhancing one's self-esteem. Listening to music facilitates the neurogenesis, the regeneration, and repair of cerebral nerves by adjusting and optimizing the secretion of steroid hormones, leading to an increase in neuroplasticity (*Neurophysiology and Neurobiology of the Musical Experience - PubMed*, n.d.).

5.4 Treatment of Dementia with Cognitive Therapy

Significant functional impairment is produced by the cognitive deficits of Alzheimer's disease (AD) in its early stages. Such as impairments in visuospatial functioning, attention, language, reasoning, and executive functioning are common, along with personality changes and behavioural disturbances. Alternative or supplemental treatments to pharmacological interventions include psychosocial treatments targeting cognition, such as cognitive training (CT) for AD patients in the mild to moderate stages of the disease. CT refers to any non-pharmacologic intervention designed to improve cognitive functioning, regardless of mechanism of action. They mainly focus on cognitively mediated domains of functioning, such as basic and instrumental activities of daily living, social skills, and behavioral disturbances. They also focus on specific domain of cognitive functioning like the attention, memory and problem solving abilities (Sitzer et al., 2006b).

Cognitive training strategies can be divided into two basic categories: compensatory and restorative. Compensatory strategies aim to teach new ways of performing cognitive tasks by working around cognitive deficits like organizing information by visualizing or categorizing information to be remembered, encoding through multiple sensory channels, asking questions during learning, and focusing on a single task; external strategies such as memory notebooks, and calendars, environmental cues. Restorative strategies attempt to improve functioning in specific domains with the ultimate goal of returning functioning in those domains to premorbid levels. It requires the patients to perform drills thereby engaging their memory and attention skills, telling them to recall information over a long period of time, reality orientation therapy where the information such as a patient's name, date, time, location, weather, and current events, is continually presented (Mahendra, 2001; Sitzer et al., 2006a).

6 CONCLUSION

Dementia is any decline in cognition that is significant enough to affect the independent and daily functioning of an individual. Considering the threat of growing dementia demand, It has now become the primary goal of all the worldwide researchers to find new approaches, trials in treating the dementia. It is common for multiple diseases to contribute to any one patient's dementia syndrome. Dementia is known to be caused by some diseases like Alzheimer's disease, Parkinson's disease,

vascular dementia, Traumatic brain injury, Huntington's disease etc. Dementia not only causes decrease in cognitive function but also reduces the quality of life. This brief review has focused on the need to enhance the endogenous capacity of the dementia-induced brain. By stimulating the endogenous parameters like the brain plasticity, enhancement of the process of myelination, induction of autophagy and the presence of glial cells prove to be effective in acting as a neuroprotective and aid in neuronal repair and enhancement of the enzymes or the substrates which helps in treatment of the memory as well as the learning impairment. Some of the non-pharmacological treatments of dementia have been used to treat dementia, improve cognitive impairment and quality of life without little if any side effects. Among non-pharmacological treatments, acupuncture, and repetitive Transcranial Magnetic Stimulation have shown to play a role in improving the cognitive function by modulating the signaling pathways involved in neuronal survival and function, specifically, through enhancing neurotrophin signalling, promoting glutamatergic neural transmissions and cholinergic dopaminergic, attenuating apoptosis, reducing microglial activation and suppressing oxidative stress. The non-pharmacological treatments have shown to have beneficial effects in dementia and more studies are therefore required on pharmacological and non-pharmacological treatments of dementia.

7 Conflict of Interests Statement

The authors declared that they have no conflicts of interest with respect to the authorship or publication of this article.

8 REFERENCES

1. Abraha, I., Rimland, J. M., Trotta, F. M., Dell'Aquila, G., Cruz-Jentoft, A., Petrovic, M., Gudmundsson, A., Soiza, R., O'Mahony, D., Guaita, A., & Cherubini, A. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. *BMJ Open*, 2017; *7*(3): e012759. https://doi.org/10.1136/bmjopen-2016-012759.
2. Ahn, S. M., Kim, Y. R., Kim, H. N., Shin, Y.-I., Shin, H. K., & Choi, B. T. Electroacupuncture ameliorates memory impairments by enhancing oligodendrocyte regeneration in a mouse model of prolonged cerebral hypoperfusion. *Scientific Reports*, 2016; *6*(1): 28646. https://doi.org/10.1038/srep28646.
3. Aldana, B. I. Microglia-Specific Metabolic Changes in Neurodegeneration. *Journal of Molecular Biology*, 2019; *431*(9): 1830–1842. https://doi.org/10.1016/J.JMB.2019.03.006.
4. Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. Myelin damage and repair in pathologic CNS: challenges and prospects. *Frontiers in Molecular Neuroscience*, 2015; *8*: 35. https://doi.org/10.3389/fnmol.2015.00035
5. Alle, H., Roth, A., & Geiger, J. R. P. Energy-Efficient Action Potentials in Hippocampal Mossy Fibers. *Science*, 2009; *325*(5946): 1405–1408. https://doi.org/10.1126/science.1174331.
6. Anttila, J. E., Whitaker, K. W., Wires, E. S., Harvey, B. K., & Airavaara, M. Role of microglia in ischemic focal stroke and recovery: focus on Toll-like receptors. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 2017; *79*(Pt A): 3–14. https://doi.org/10.1016/j.pnpbp.2016.07.003.
7. Article, R. *Do children really recover better ? Neurobehavioural plasticity after early brain insult*. https://doi.org/10.1093/brain/awr103, 2011.
8. Attwell, D., & Laughlin, S. B. An Energy Budget for Signaling in the Grey Matter of the Brain. *Journal of Cerebral Blood Flow & Metabolism*, 2001; *21*(10): 1133–1145. https://doi.org/10.1097/00004647-200110000-00001.
9. Bailey, C. H., & Kandel, E. R. Structural Changes Accompanying Memory Storage. *Annual Review of Physiology*, 1993; *55*(1): 397–426. https://doi.org/10.1146/annurev.ph.55.030193.002145.
10. Barba, A. L., Kelly Changizi, B., Higgins, D. S., Factor, S. A., & Molho, E. S. Dementia. *Parkinson's Disease, Second Edition*, 2012; 413–433. https://doi.org/10.1201/b12948.
11. Barker, A. T., Jalinous, R., & Freeston, I. L. NON-INVASIVE MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX. *The Lancet*, 1985; *325*(8437): 1106–1107. https://doi.org/10.1016/S0140-6736(85)92413-4
12. Bartsch, T., & Wulff, P. The hippocampus in aging and disease: From plasticity to vulnerability. *Neuroscience*, 2015; *309*: 1–16. https://doi.org/10.1016/J.NEUROSCIENCE.2015.07.084.
13. Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., & Johns, H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia : A population-based perspective. *Alzheimer's & Dementia*, 2015; *11*(6): 718–726. https://doi.org/10.1016/j.jalz.2015.05.016.
14. Ber, I. L., Guedj, E., Gabelle, A., Verpillat, P., Volteau, M., Thomas-Anterion, C., Decousus, M., Hannequin, D., Vera, P., Lacomblez, L., Camuzat, A., Didic, M., Puel, M., Lotterie, J.-A., Golfier, V., Bernard, A.-M., Vercelletto, M., Magne, C., Sellal, F., … Dubois, B. Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. *Brain*, 2006; *129*(11): 3051–3065. https://doi.org/10.1093/brain/awl288.
15. Bestmann, S., Baudewig, J., Siebner, H. R., Rothwell, J. C., & Frahm, J. BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. *NeuroImage*, 2005; *28*(1): 22–29. https://doi.org/10.1016/J.NEUROIMAGE.2005.05.

027.
16. Bishop, N. A., Lu, T., & Yankner, B. A. Neural mechanisms of ageing and cognitive decline. *Nature*, 2010; *464*(7288): 529–535. https://doi.org/10.1038/nature08983.
17. Boche, D., Perry, V. H., & Nicoll, J. A. R. Review: Activation patterns of microglia and their identification in the human brain. *Neuropathology and Applied Neurobiology*, 2013; *39*(1): 3–18. https://doi.org/10.1111/nan.12011.
18. Bosch, M., & Hayashi, Y. Structural plasticity of dendritic spines. *Current Opinion in Neurobiology*, 2012; *22*(3): 383–388. https://doi.org/10.1016/J.CONB.2011.09.002.
19. Bostanciklioglu, M., Demiryürek, Ş., Cengiz, B., Demir, T., Öztuzcu, S., Aras, M. H., Özsevik, S., Usumez, A., Ergün, S., Özbal, H. K., & Bagci, C. Assessment of the effect of laser irradiations at different wavelengths (660, 810, 980, and 1064 nm) on autophagy in a rat model of mucositis. *Lasers in Medical Science*, 2015; *30*(4): 1289–1295. https://doi.org/10.1007/s10103-015-1727-4.
20. Boya, P, & Kroemer, G. Lysosomal membrane permeabilization in cell death. *Oncogene*, 2008; *27*(50): 6434–6451. https://doi.org/10.1038/onc.2008.310.
21. Boya, Patricia, Reggiori, F., & Codogno, P. Emerging regulation and functions of autophagy. *Nature Cell Biology*, 2013; *15*(7): 713–720. https://doi.org/10.1038/ncb2788.
22. Butnaru, D., & Chapman, J. The impact of self-replicating proteins on inflammation, autoimmunity and neurodegeneration—An untraveled path. *Autoimmunity Reviews*, 2019; *18*(3): 231–240. https://doi.org/10.1016/j.autrev.2018.09.009.
23. Cowan, N. The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioral and Brain Sciences*, 2001; *24*(1): S0140525X01003922. https://doi.org/10.1017/S0140525X01003922
24. Cullen, C. L., & Young, K. M. How Does Transcranial Magnetic Stimulation Influence Glial Cells in the Central Nervous System? *Frontiers in Neural Circuits*, 2016; *10*: 26. https://doi.org/10.3389/fncir.2016.00026.
25. *Dementia statistics | Alzheimer's Disease International*. (n.d.). Retrieved May 7, 2019. from https://www.alz.co.uk/research/statistics
26. Dizdaroglu, M. Base-excision repair of oxidative DNA damage by DNA glycosylases. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 2005; *591*(1–2): 45–59. https://doi.org/10.1016/J.MRFMMM.2005.01.033.
27. *Effect and Mechanism of Acupuncture on Alzheimer's Disease*, 2013; *111*: 181–195. https://doi.org/10.1016/B978-0-12-411545-3.00009-2.
28. Eichenbaum, H. *Hippocampus : Cognitive Processes and Neural Representations that Underlie Declarative Memory The hippocampus serves a critical role in declarative*, 2004; *44*: 109–120.
29. Elder, G. J., & Taylor, J.-P. Transcranial magnetic stimulation and transcranial direct current stimulation: treatments for cognitive and neuropsychiatric symptoms in the neurodegenerative dementias? *Alzheimer's Research & Therapy*, 2014; *6*(5–8): 74. https://doi.org/10.1186/s13195-014-0074-1.
30. Farooqui, A. A. Neurochemical Aspects of Poststroke Dementia. In *Molecular Mechanisms of Dementia*. https://doi.org/10.1016/b978-0-12-816347-4.00002-7, 2019.
31. Farooqui, A. A. Potential Treatment Strategies for Dementia With Pharmacological and Nonpharmac ological Interventions. In *Molecular Mechanisms of Dementia*, 2019; 215–250. Elsevier. https://doi.org/10.1016/B978-0-12-816347-4.00007-6.
32. Farooqui, A. A. Potential Treatment Strategies for Dementia With Pharmacological and Nonpharmacological Interventions. In *Molecular Mechanisms of Dementia*, 2019; 215–250. Elsevier. https://doi.org/10.1016/b978-0-12-816347-4.00007-6.
33. Frank, M. G., Wieseler-Frank, J. L., Watkins, L. R., & Maier, S. F. Rapid isolation of highly enriched and quiescent microglia from adult rat hippocampus: Immunophenotypic and functional characteristics. *Journal of Neuroscience Methods*, 2006; *151*(2): 121–130. https://doi.org/10.1016/j.jneumeth.2005.06.026.
34. Galluzzi, L., Pietrocola, F., Levine, B., & Kroemer, G. Metabolic Control of Autophagy. *Cell*, 2014; *159*(6): 1263–1276. https://doi.org/10.1016/J.CELL.2014.11.006.
35. Glatigny, M., Moriceau, S., Rivagorda, M., Ramos-Brossier, M., Nascimbeni, A. C., Lante, F., Shanley, M. R., Boudarene, N., Rousseaud, A., Friedman, A. K., Settembre, C., Kuperwasser, N., Friedlander, G., Buisson, A., Morel, E., Codogno, P., & Oury, F. Autophagy Is Required for Memory Formation and Reverses Age-Related Memory Decline. *Current Biology*, 2019; *29*(3): 435-448.e8. https://doi.org/10.1016/j.cub.2018.12.021.
36. Gómez Gallego, M., & Gómez García, J. Music therapy and Alzheimer's disease: Cognitive, psychological, and behavioural effects. *Neurología (English Edition)*, 2017; *32*(5): 300–308. https://doi.org/10.1016/j.nrleng.2015.12.001.
37. Hanisch, U.-K., & Kettenmann, H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience*, 2007; *10*(11): 1387–1394. https://doi.org/10.1038/nn1997.
38. Hartline, D. K., & Colman, D. R. Rapid Conduction and the Evolution of Giant Axons and Myelinated Fibers. *Current Biology*, 2007; *17*(1): R29–R35.

https://doi.org/10.1016/j.cub.2006.11.042.
39. Hartline, D. K., & Colman, D. R. Rapid Conduction and the Evolution of Giant Axons and Myelinated Fibers. *Current Biology*, 2007; *17*(1): R29-35. https://doi.org/10.1016/j.cub.2006.11.042.
40. Hu, X., Leak, R. K., Shi, Y., Suenaga, J., Gao, Y., Zheng, P., & Chen, J. Microglial and macrophage polarization—new prospects for brain repair. *Nature Reviews Neurology*, 2015; *11*(1): 56–64. https://doi.org/10.1038/nrneurol.2014.207.
41. Jones, D. L., & Roseman, R. B. Comparing physics and math problems. *AIP Conference Proceedings*, 2013; *1513*(1): 206–209. https://doi.org/10.1063/1.4789688.
42. Jung, H. S., & Lee, M.-S. Role of autophagy in diabetes and mitochondria. *Annals of the New York Academy of Sciences*, 2010; *1201*(1): 79–83. https://doi.org/10.1111/j.1749-6632.2010.05614.x.
43. Katila;, R. I. V. R. K. A. N. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport*, 1997; *8*(16): 3537–3540. https://insights.ovid.com/crossref?an=00001756-199711100-00024.
44. Kavoussi, B., & Ross, B. E. The Neuroimmune Basis of Anti-inflammatory Acupuncture. *Integrative Cancer Therapies*, 2007; *6*(3): 251–257. https://doi.org/10.1177/1534735407305892.
45. Kellner, Y., Gödecke, N., Dierkes, T., Thieme, N., Zagrebelsky, M., & Korte, M. The BDNF effects on dendritic spines of mature hippocampal neurons depend on neuronal activity. *Frontiers in Synaptic Neuroscience*, 2014; *6*: 5. https://doi.org/10.3389/fnsyn.2014.00005.
46. Kettenmann, H., Hanisch, U.-K., Noda, M., & Verkhratsky, A. Physiology of Microglia. *Physiological Reviews*, 2011; *91*(2): 461–553. https://doi.org/10.1152/physrev.00011.2010.
47. Kierdorf, K., & Prinz, M. Factors regulating microglia activation. *Frontiers in Cellular Neuroscience*, 2013; *7*: 44. https://doi.org/10.3389/fncel.2013.00044.
48. Kim, Y. R., Kim, H. N., Ahn, S. M., Choi, Y. H., Shin, H. K., & Choi, B. T. Electroacupuncture Promotes Post-Stroke Functional Recovery via Enhancing Endogenous Neurogenesis in Mouse Focal Cerebral Ischemia. *PLoS ONE*, 2014; *9*(2): e90000. https://doi.org/10.1371/journal. pone. 0090000.
49. Kjølhede, D., Bohr, V. A., & Stevnsner, T. *Progress in Neurobiology DNA repair deficiency in neurodegeneration*, 2011; *94*: 166–200. https://doi.org/10.1016/j.pneurobio.2011.04.013.
50. Koch, G., Bonnì, S., Pellicciari, M. C., Casula, E. P., Mancini, M., Esposito, R., Ponzo, V., Picazio, S., Di Lorenzo, F., Serra, L., Motta, C., Maiella, M., Marra, C., Cercignani, M., Martorana, A., Caltagirone, C., & Bozzali, M. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. *NeuroImage*, 2018; *169*: 302–311. https://doi.org/10.1016/J.NEUROIMAGE.2017.12.048.
51. Komatsu, M., Waguri, S., Chiba, T., Murata, S., Iwata, J., Tanida, I., Ueno, T., Koike, M., Uchiyama, Y., Kominami, E., & Tanaka, K. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature*, 2006; *441*(7095): 880–884. https://doi.org/10.1038/nature04723.
52. Kreutzberg, G. W. Microglia: a sensor for pathological events in the CNS. *Trends in Neurosciences*, 1996; *19*(8): 312–318.
53. Ktistakis, N. T., & Tooze, S. A. Digesting the Expanding Mechanisms of Autophagy. *Trends in Cell Biology*, 2016; *26*(8): 624–635. https://doi.org/10.1016/J.TCB.2016.03.006.
54. Kulkarni, A., Chen, J., & Maday, S. Neuronal autophagy and intercellular regulation of homeostasis in the brain. *Current Opinion in Neurobiology*, 2018; *51*: 29–36. https://doi.org/10.1016/J.CONB.2018.02.008.
55. Lamb, C. A., Yoshimori, T., & Tooze, S. A. The autophagosome: origins unknown, biogenesis complex. *Nature Reviews Molecular Cell Biology*, 2013; *14*(12): 759–774. https://doi.org/10.1038/nrm3696.
56. Landry, C. F., Ellison, J. A., Pribyl, T. M., Campagnoni, C., Kampf, K., & Campagnoni, A. T. Myelin basic protein gene expression in neurons: developmental and regional changes in protein targeting within neuronal nuclei, cell bodies, and processes. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 1996; *16*(8): 2452–2462. https://doi.org/10.1523/JNEUROSCI.16-08-02452.1996.
57. Leal, G., Comprido, D., & Duarte, C. B. BDNF-induced local protein synthesis and synaptic plasticity. *Neuropharmacology*, 2014; *76*: 639–656. https://doi.org/10.1016/j.neuropharm.2013.04.005.
58. Lee, M. S., Shin, B.-C., & Ernst, E. Acupuncture for Alzheimer's disease: a systematic review. *International Journal of Clinical Practice*, 2009; *63*(6): 874–879. https://doi.org/10.1111/j.1742-1241.2009.02043.x
59. Leuner, B., & Gould, E. Structural Plasticity and Hippocampal Function. *Annual Review of Psychology*, 2010; *61*(1): 111–140. https://doi.org/10.1146/annurev.psych.093008.100359.
60. Levine, B., & Kroemer, G. Autophagy in the Pathogenesis of Disease. *Cell*, 2008; *132*(1): 27–42. https://doi.org/10.1016/J.CELL.2007.12.018.
61. Lewis, P. A., & Spillane, J. E. Alzheimer's Disease and Dementia. In *The Molecular and Clinical Pathology of Neurodegenerative Disease*, 2019;

25–82. Elsevier. https://doi.org/10.1016/B978-0-12-811069-0.00002-1.
62. Li, J., Park, E., Zhong, L. R., & Chen, L. ScienceDirect Homeostatic synaptic plasticity as a metaplasticity mechanism — a molecular and cellular perspective. *Current Opinion in Neurobiology*, 2019; *54*: 44–53. https://doi.org/10.1016/j.conb.2018.08.010.
63. Lisman, J., Cooper, K., Sehgal, M., & Silva, A. J. Memory formation depends on both synapse-specific modifications of synaptic strength and cell-specific increases in excitability. *Nature Neuroscience*, 2018; *21*(3): 309–314. https://doi.org/10.1038/s41593-018-0076-6.
64. Liu, Q., Wang, X., Zhang, Z., Xue, R., Li, P., & Li, B. Neuroprotection against vascular dementia after acupuncture combined with donepezil hydrochloride: P300 event related potential. *Neural Regeneration Research*, 2016; *11*(3): 460. https://doi.org/10.4103/1673-5374.179059.
65. London, A., Cohen, M., & Schwartz, M. Microglia and monocyte-derived macrophages: functionally distinct populations that act in concert in CNS plasticity and repair. *Frontiers in Cellular Neuroscience*, 2013; *7*: 34. https://doi.org/10.3389/fncel.2013.00034.
66. Luo, D., Chen, R., & Liang, F. Modulation of Acupuncture on Cell Apoptosis and Autophagy. *Evidence-Based Complementary and Alternative Medicine*, *2017*; 1–11. https://doi.org/10.1155/2017/8268736.
67. Lynch, M. A. The Multifaceted Profile of Activated Microglia. *Molecular Neurobiology*, 2009; *40*(2): 139–156. https://doi.org/10.1007/s12035-009-8077-9.
68. Maday, S., & Holzbaur, E. L. F. Compartment-Specific Regulation of Autophagy in Primary Neurons. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 2016; *36*(22): 5933–5945. https://doi.org/10.1523/JNEUROSCI.4401-15.2016.
69. Maday, S., Wallace, K. E., & Holzbaur, E. L. F. Autophagosomes initiate distally and mature during transport toward the cell soma in primary neurons. *The Journal of Cell Biology*, 2012; *196*(4): 407–417. https://doi.org/10.1083/jcb.201106120.
70. Mahendra, N. Direct interventions for improving the performance of individuals with Alzheimer's disease. *Seminars in Speech and Language*, 2001; *22*(4): 291–303. https://doi.org/10.1055/s-2001-17427.
71. Manuscript, A. *Mechanisms of Memory Enhancement*, 2014; *5*(1): 37–53. https://doi.org/10.1002/wsbm.1196.Mechanisms.
72. Martiny, K., Lunde, M., & Bech, P. Transcranial Low Voltage Pulsed Electromagnetic Fields in Patients with Treatment-Resistant Depression. *Biological Psychiatry*, 2010; *68*(2): 163–169. https://doi.org/10.1016/j.biopsych.2010.02.017.
73. Marty, M. C., Alliot, F., Rutin, J., Fritz, R., Trisler, D., & Pessac, B. The myelin basic protein gene is expressed in differentiated blood cell lineages and in hemopoietic progenitors. *Proceedings of the National Academy of Sciences*, 2002; *99*(13): 8856–8861. https://doi.org/10.1073/pnas.122079599.
74. Massenzio, F., Peña-Altamira, E., Petralla, S., Virgili, M., Zuccheri, G., Miti, A., Polazzi, E., Mengoni, I., Piffaretti, D., & Monti, B. Microglial overexpression of fALS-linked mutant SOD1 induces SOD1 processing impairment, activation and neurotoxicity and is counteracted by the autophagy inducer trehalose. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 2018; *1864*(12): 3771–3785. https://doi.org/10.1016/J.BBADIS.2018.10.013.
75. Mcleod, F., & Salinas, P. C. (n.d.). ScienceDirect Wnt proteins as modulators of synaptic plasticity. *Current Opinion in Neurobiology*, *53*: 90–95. https://doi.org/10.1016/j.conb.2018.06.003.
76. Meng, Q., & Cai, D. Defective Hypothalamic Autophagy Directs the Central Pathogenesis of Obesity via the IκB Kinase β (IKKβ)/NF-κB Pathway. *Journal of Biological Chemistry*, 2011; *286*(37): 32324–32332. https://doi.org/10.1074/jbc.M111.254417.
77. Miss, S., C.P., F., D., A., E., A., M., G., Y., H., K.S., J., A.T., J., J.J.L., R., G.R., P., M.C., R., A., S., A.L., S., J., W., T., Z., & M., P. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. In *The Lancet*. https://doi.org/http://dx.doi.org/10.1016/S0140-6736%2809%2961829-8, 2009.
78. Miyamoto, A., Wake, H., Ishikawa, A., … K. E.-N., & undefined. (n.d.). Microglia contact induces synapse formation in developing somatosensory cortex. *Nature.Com*. Retrieved May 11, 2019. from https://www.nature.com/articles/ncomms12540.
79. Mizushima, N., & Komatsu, M. Autophagy: Renovation of Cells and Tissues. *Cell*, *147*(4): 728–741. https://doi.org/10.1016/J.CELL.2011.10.026, 2011.
80. Mizushima, N., Levine, B., Cuervo, A. M., & Klionsky, D. J. Autophagy fights disease through cellular self-digestion. *Nature*, 2008; *451*(7182): 1069–1075. https://doi.org/10.1038/nature06639.
81. Mizushima, N., Yamamoto, A., Matsui, M., Yoshimori, T., & Ohsumi, Y. In Vivo Analysis of Autophagy in Response to Nutrient Starvation Using Transgenic Mice Expressing a Fluorescent Autophagosome Marker. *Molecular Biology of the Cell*, 2004; *15*(3): 1101–1111. https://doi.org/10.1091/mbc.e03-09-0704.
82. Mizushima, N., Yoshimori, T., & Ohsumi, Y. The Role of Atg Proteins in Autophagosome Formation. *Annual Review of Cell and Developmental Biology*, 2011; *27*(1): 107–132.

https://doi.org/10.1146/annurev-cellbio-092910-154005.

83. Näsi, T., Mäki, H., Kotilahti, K., Nissilä, I., Haapalahti, P., & Ilmoniemi, R. J. Magnetic-Stimulation-Related Physiological Artifacts in Hemodynamic Near-Infrared Spectroscopy Signals. *PLoS ONE*, 2011; *6*(8): e24002. https://doi.org/10.1371/journal.pone.0024002.
84. Neumann, H., Kotter, M. R., & Franklin, R. J. M. Debris clearance by microglia: an essential link between degeneration and regeneration. *Brain*, 2008; *132*(2): 288–295. https://doi.org/10.1093/brain/awn109.
85. *Neurophysiology and Neurobiology of the Musical Experience - PubMed*. (n.d.). Retrieved June 8, 2020. from https://pubmed.ncbi.nlm.nih.gov/17367577/.
86. Nimmerjahn, A., Kirchhoff, F., & Helmchen, F. Resting Microglial Cells Are Highly Dynamic Surveillants of Brain Parenchyma in Vivo. *Science*, 2005; *308*(5726): 1314–1318. https://doi.org/10.1126/science.1110647.
87. Opitz, A., Windhoff, M., Heidemann, R. M., Turner, R., & Thielscher, A. How the brain tissue shapes the electric field induced by transcranial magnetic stimulation. *NeuroImage*, 2011; *58*(3): 849–859. https://doi.org/10.1016/J.NEUROIMAGE.2011.06.069.
88. Palacios-Filardo, J., & Mellor, J. R. Neuromodulation of hippocampal long-term synaptic plasticity. *Current Opinion in Neurobiology*, 2019; *54*: 37–43. https://doi.org/10.1016/j.conb.2018.08.009.
89. Panja, D., & Bramham, C. R. BDNF mechanisms in late LTP formation: A synthesis and breakdown. *Neuropharmacology*, 2014; *76*: 664–676. https://doi.org/10.1016/j.neuropharm.2013.06.024.
90. Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., & Evans, A. C. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 1997; *17*(9): 3178–3184. http://www.ncbi.nlm.nih.gov/pubmed/9096152.
91. Pocock, J. M., & Kettenmann, H. Neurotransmitter receptors on microglia. *Trends in Neurosciences*, 2007; *30*(10): 527–535. https://doi.org/10.1016/j.tins.2007.07.007.
92. Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. The global prevalence of dementia : A systematic review and metaanalysis. *Alzheimer's & Dementia*, 2013; *9*(1): 63-75.e2. https://doi.org/10.1016/j.jalz.2012.11.007.
93. Raddassi, K., Kent, S. C., Yang, J., Bourcier, K., Bradshaw, E. M., Seyfert-Margolis, V., Nepom, G. T., Kwok, W. W., & Hafler, D. A. Increased Frequencies of Myelin Oligodendrocyte Glycoprotein/MHC Class II-Binding CD4 Cells in Patients with Multiple Sclerosis. *The Journal of Immunology*, 2011; *187*(2): 1039–1046. https://doi.org/10.4049/jimmunol.1001543.
94. Ransohoff, R. M., & Cardona, A. E. The myeloid cells of the central nervous system parenchyma. *Nature*, 2010; *468*(7321): 253–262. https://doi.org/10.1038/nature09615.
95. Ravikumar, B., Vacher, C., Berger, Z., Davies, J. E., Luo, S., Oroz, L. G., Scaravilli, F., Easton, D. F., Duden, R., O'Kane, C. J., & Rubinsztein, D. C. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nature Genetics*, 2004; *36*(6): 585–595. https://doi.org/10.1038/ng1362.
96. Ridding, M. C., & Rothwell, J. C. Is there a future for therapeutic use of transcranial magnetic stimulation? *Nature Reviews Neuroscience*, 2007; *8*(7): 559–567. https://doi.org/10.1038/nrn2169.
97. Salvage, S., & Jenner, P. Current Development of Acupuncture Research in Parkinson's Disease. *International Review of Neurobiology*, 2013; *111*: 141–158. https://doi.org/10.1016/B978-0-12-411545-3.00007-9
98. Schneider, J. A., Arvanitakis, Z., Bang, W., & Schneider, J. A. *Mixed brain pathologies account for most dementia cases in community- dwelling older persons*. https://doi.org/10.1212/01.wnl.0000271090.28148.24, 2007.
99. Shang, Y., Wang, X., Shang, X., Zhang, H., Liu, Z., Yin, T., & Zhang, T. Repetitive transcranial magnetic stimulation effectively facilitates spatial cognition and synaptic plasticity associated with increasing the levels of BDNF and synaptic proteins in Wistar rats. *Neurobiology of Learning and Memory*, 2016; *134*: 369–378. https://doi.org/10.1016/j.nlm.2016.08.016.
100. Shehata, M., Matsumura, H., Okubo-Suzuki, R., Ohkawa, N., & Inokuchi, K. Neuronal stimulation induces autophagy in hippocampal neurons that is involved in AMPA receptor degradation after chemical long-term depression. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 2012; *32*(30): 10413–10422. https://doi.org/10.1523/JNEUROSCI.4533-11.2012.
101. Shen, W., & Ganetzky, B. Autophagy promotes synapse development in Drosophila. *The Journal of Cell Biology*, 2009; *187*(1): 71–79. https://doi.org/10.1083/jcb.200907109.
102. Shi, G., Liu, C., Guan, W., Wang, Z., Wang, L., Xiao, C., Li, Z., Li, Q., & Wang, L. (n.d.). Effects of acupuncture on Chinese medicine syndromes of vascular dementia. *Chinese Journal of Integrative Medicine*, *20*(9): 661–666. https://doi.org/10.1007/s11655-013-1323-4.
103. Shiryaev, S. A., Savinov, A. Y., Cieplak, P., Ratnikov, B. I., Motamedchaboki, K., Smith, J. W.,

& Strongin, A. Y. Matrix Metalloproteinase Proteolysis of the Myelin Basic Protein Isoforms Is a Source of Immunogenic Peptides in Autoimmune Multiple Sclerosis. *PLoS ONE*, 2009; *4*(3): e4952. https://doi.org/10.1371/journal.pone.0004952.

104. Shupak, N. M., Prato, F. S., & Thomas, A. W. Human exposure to a specific pulsed magnetic field: effects on thermal sensory and pain thresholds. *Neuroscience Letters*, 2004; *363*(2): 157–162. https://doi.org/10.1016/j.neulet.2004.03.069.
105. Singh, R., & Cuervo, A. M. Autophagy in the Cellular Energetic Balance. *Cell Metabolism*, 2011; *13*(5): 495–504. https://doi.org/10.1016/J.CMET.2011.04.004.
106. Sitzer, D. I., Twamley, E. W., & Jeste, D. V. Cognitive training in Alzheimer's disease: A meta-analysis of the literature. *Acta Psychiatrica Scandinavica*, 2006; *114*(2): 75–90. https://doi.org/10.1111/j.1600-0447.2006.00789.x.
107. Sitzer, D. I., Twamley, E. W., & Jeste, D. V. Cognitive training in Alzheimer's disease: A meta-analysis of the literature. In *Acta Psychiatrica Scandinavica*, 2006; 114(2): 75–90. https://doi.org/10.1111/j.1600-0447.2006.00789.x
108. Sperling, G. A Model for Visual Memory Tasks. *Human Factors: The Journal of the Human Factors and Ergonomics Society*, 1963; *5*(1): 19–31. https://doi.org/10.1177/001872086300500103.
109. Squire, L. R., & Zola, S. M. Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National Academy of Sciences*, 1996; *93*(24): 13515–13522. https://doi.org/10.1073/pnas.93.24.13515.
110. Squire, Larry R. Declarative and Nondeclarative Memory: Multiple Brain Systems Supporting Learning and Memory. *Journal of Cognitive Neuroscience*, 1992; *4*(3): 232–243. https://doi.org/10.1162/jocn.1992.4.3.232.
111. Takeda, M. Brain mechanisms of visual long-term memory retrieval in primates. *Neuroscience Research*. https://doi.org/10.1016/j.neures.2018.06.005, 2018.
112. Tang, T., Gao, D., Yang, X., Hua, X., Li, S., & Sun, H. Exogenous Netrin-1 Inhibits Autophagy of Ischemic Brain Tissues and Hypoxic Neurons via PI3K/mTOR Pathway in Ischemic Stroke. *Journal of Stroke and Cerebrovascular Diseases*, 2019; *28*(5): 1338–1345. https://doi.org/10.1016/J.JSTROKECEREBROVASDIS. 2019.01.032
113. Tao, J., Zheng, Y., Liu, W., Yang, S., Huang, J., Xue, X., Shang, G., Wang, X., Lin, R., & Chen, L. Electro-acupuncture at LI11 and ST36 acupoints exerts neuroprotective effects via reactive astrocyte proliferation after ischemia and reperfusion injury in rats. *Brain Research Bulletin*, 2016; *120*: 14–24. https://doi.org/10.1016/J.BRAINRESBULL.2015.10.011
114. Venkat, P., Chopp, M., & Chen, J. Models and mechanisms of vascular dementia. *Experimental Neurology*, 2015; *272*: 97–108. https://doi.org/10.1016/j.expneurol.2015.05.006.
115. Vijayan, V., & Verstreken, P. Autophagy in the presynaptic compartment in health and disease. *The Journal of Cell Biology*, 2017; *216*(7): 1895–1906. https://doi.org/10.1083/jcb.201611113.
116. Wang, A. S., Zhang, Z., Zhu, T., & Wang, S. diseases PT Corresponding author at : Department of Pharmacology , Institute of Materia SC. *Brain Research Bulletin*. https://doi.org/10.1016/j.brainresbull.2018.05.003, 2018.
117. Wang, Y., Lu, C., Yang, G., Chen, Z., & Nie, J. A crosslinked bis(amino)-containing polymer as a remarkable support for heterogeneous palladium-catalyzed Suzuki-Miyaura reaction. *Reactive and Functional Polymers*, 2017; *110*: 38–46. https://doi.org/10.1016/J.REACTFUNCTPOLYM.2016.12.003.
118. Wilson, D. M., & Bohr, V. A. The mechanics of base excision repair, and its relationship to aging and disease. *DNA Repair*, 2007; *6*(4): 544–559. https://doi.org/10.1016/J.DNAREP.2006.10.017.
119. Yang, L., Li, P., Fu, S., Calay, E. S., & Hotamisligil, G. S. Defective Hepatic Autophagy in Obesity Promotes ER Stress and Causes Insulin Resistance. *Cell Metabolism*, 2010; *11*(6): 467–478. https://doi.org/10.1016/j.cmet.2010.04.005.
120. Yao, Y., Wang, F., Yang, X., Zang, D., Yang, J., & Wang, Z. Biomedicine & Pharmacotherapy Bombesin attenuated ischemia-induced spatial cognitive and synaptic plasticity impairment associated with oxidative damage. *Biomedicine & Pharmacotherapy*, 2018; *103*(March): 87–93. https://doi.org/10.1016/j.biopha.2018.03.155.
121. Ye, Y., Zhu, W., Wang, X.-R., Yang, J.-W., Xiao, L.-Y., Liu, Y., Zhang, X., & Liu, C.-Z. Mechanisms of acupuncture on vascular dementia—A review of animal studies. *Neurochemistry International*, 2017; *107*: 204–210. https://doi.org/10.1016/J.NEUINT.2016.12.001.
122. Zhang, N., Xing, M., Wang, Y., Tao, H., & Cheng, Y. Repetitive transcranial magnetic stimulation enhances spatial learning and synaptic plasticity via the VEGF and BDNF–NMDAR pathways in a rat model of vascular dementia. *Neuroscience*, 2015; *311*: 284–291. https://doi.org/10.1016/j.neuroscience.2015.10.038.
123. Zhang, X., Xu, X., Xu, W., Hou, W., Cheng, Y., Li, C., & Ni, G. Acupuncture Therapy for Sudden Sensorineural Hearing Loss: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLOS ONE*, 2015; *10*(4), e0125240. https://doi.org/10.1371/journal.pone.0125240.
124. Zhang, Y., Lin, R., Tao, J., Wu, Y., Chen, B., Yu, K., Chen, J., Li, X., & Chen, L.-D. Electroacupuncture improves cognitive ability following cerebral ischemia reperfusion injury via

CaM-CaMKIV-CREB signaling in the rat hippocampus. *Experimental and Therapeutic Medicine*, 2016; *12*(2): 777–782. https://doi.org/10.3892/etm.2016.3428

125. Zilles, K. Neuronal plasticity as an adaptive property of the central nervous system. *Annals of Anatomy - Anatomischer Anzeiger*, 1992; *174*(5): 383–391. https://doi.org/10.1016/S0940-9602(11)80255-4