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Review Article

Essential Metals in the Brain and the Application of Laser Ablation-Inductively Coupled Plasma-Mass Spectrometry for their Detection

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Summary: Metals are natural component of the ecosystem present throughout the layers of atmosphere; their abundant expression in the brain indicates their importance in the central nervous system (CNS). Within the brain tissue, their distribution is highly compartmentalized, the pattern of which is determined by their primary roles. Bio-imaging of the brain to reveal spatial distribution of metals within specific regions has provided a unique understanding of brain biochemistry and architecture, linking both the structures and the functions through several metal-mediated activities. Bioavailability of essential trace metal is needed for normal brain function. However, disrupted metal homeostasis can influence several biochemical pathways in different fields of metabolism and cause characteristic neurological disorders with a typical disease process usually linked with aberrant metal accumulations. In this review we give a brief overview of roles of key essential metals (Iron, Copper and Zinc) including their molecular mechanisms and bio-distribution in the brain as well as their possible involvement in the pathogenesis of related neurodegenerative diseases. In addition, we also reviewed recent applications of Laser Ablation Inductively Couple Plasma Mass Spectrophotometry (LA-ICP-MS) in the detection of both toxic and essential metal dyshomeostasis in neuroscience research and other related brain diseases.

Keywords*: Metal dyshomeostasis, Bio-imaging, LA-ICP-MS, Neurodegenerative diseases, Essential metals, CNS*

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INTRODUCTION

Metals are found ubiquitously in the environment, they are present in air, land, water and various parts of the earth crust (Chen *et al.*, 2016). They form the major parts of the CNS and their critical role in several pathophysiological processes has been of keen interest to several researchers (Flora and Pachauri, 2010). Metals are categorized into essential and toxic metals based on their biological functions (Chen *et al*., 2016). Essential metals include copper (Cu), zinc (Zn), iron (Fe), manganese (Mn), lithium (Li), nickel (Ni), chromium (Cr), selenium (Se), and cobalt (Co). These trace metals are required in an adequate amount and are the key regulatory factors for many cellular activities and brain physiological processes (Lee *et al*., 2008; Becker *et al*., 2010; Chen *et al*., 2016; DeBenedictis *et al*., 2020). Although they are needed for normal brain activities, their deficit or excess through genetic, environmental or nutritional disposition may be linked with several neurological diseases. Their quantitative determination is of growing interest in brain research and biosciences and is relevant for studying many neurological diseases (Becker *et al*., 2007; Becker *et al*., 2010; Chen *et al*., 2016). Out of the aforementioned essential trace metals found in the brain, Zinc, Iron and Copper are the most significant players in both neurophysiology and neuropathology, particularly with regard to aging and neurodegenerative diseases, they constitute the major component of various proteins and enzymes essential for normal brain function and also connected to specialized brain activities (Que *et al*., 2008; Prashanth *et al*., 2015).On the other hand, toxic metals such as vanadium, arsenic, cadmium, lead, mercury, uranium and nickel are ubiquitous in nature, they are found freely in water, food and in green vegetation (Becker *et al*., 2007; Pohl *et al*., 2011; Tchounwou *et al*., 2012; Bhat, 2017; Bhat, 2019). Sources are also through some human activities such as heavy metal mining, crude oil processing, chemicals and toxic waste disposal as well as emission from industrial and electricity-generating (particularly coal-burning) activities (Arruti *et al*., 2010; Sträter *et al*., 2010; Pohl *et al*., 2011; Iqbal and Ahmed, 2019).

Toxic metals possess no functional role in human homeostasis and constitute a risk for most of the chronic neurodegenerative diseases (they elicit severe damages as they easily transverse the brain barrier, bind brain tissue to induce oxidative stress, block aquaporins, interfere with normal endocrine activities and displace essential cations such as zinc and magnesium (Chen *et al*., 2016; Becker *et al*., 2010). In addition, toxic metal exposure early in life pose the risk of lifelong behavioural, intellectual and physical impairment as well as accelerated brain ageing in young adults and children (Pohl *et al*., 2011; Calderón-Garcidueñas *et al*., 2012). Several age-related neurological disorders are strongly linked with disrupted metal homeostasis, thus, brain metal content and their spatial

distribution in the diseased brain is usually obtained and compared with that of controls. Therefore, besides the analysis of food, beverages and environmental samples, the study of elemental distribution in brain and biological tissues is of great importance (Becker *et al*., 2008; Becker *et al*., 2010). This will give a clue to the overall diagnosis of individuals with a metal poisoning symptomatology or dyshomeostasis. It will also inspire newer therapeutic strategies in the diagnosis and potential treatment of several metal induced neurological diseases.

Molecular Biology of Trace Metals in The Brain and Their Roles in Brain Function: Trace metals are micronutrients usually found in relatively small amount but highly needed for proper growth and function of a biological system (Zecca *et al*., 2004; Anderson *et al*., 2011). Being the major part of most vitamins and enzymes, they participate in key oxidative-reduction reactions that control several other cellular metabolic activities (Bartzokis *et al*., 2007; Que *et al*., 2008). In the CNS trace metals such as cobalt, copper, iodine, iron, manganese, molybdenum, selenium, and zinc combine with specific enzymes to catalyze several activities involved in various neurological processes e.g. Iodine is bound to thyrosine, colbat is a component of vitamin B12 and zinc has a special function in zinc metalloenzymes (Que *et al*., 2008). Although, trace metals are needed for proper brain development, their balances and transportation within the CNS is essential and strictly controlled by a complicated barrier system involving the blood-brain barrier (BBB), choroidal blood-cerebrospinal fluid barrier, blood-cerebrospinal fluid (CSF) barrier, and even CSF-brain barrier (Takeda *et al*., 2004; Strazielle and Ghersi-Egea, 2013; Hladky and Barrand, 2016). Since some essential trace metals need to be obtained from the environment in adequate amounts to optimize cellular metabolism, their homeostasis within the brain is dependent on the control of processes such as absorption, distribution, biotransformation, and excretion (Zheng and Monnot 2012; Fu *et al*., 2014). However, their excess or deficit as well as impaired homeostatic metabolic mechanism often generate oxidative stress with deleterious effects on the neurons and glia resulting in neurodegeneration and neurological dysfunction (Garza-Lombo *et al*., 2018). For example, low iron content has been related with brain disabilities such as pediatric stroke, pseudo-tumor cerebri, and cranial nerve palsy (Yager and Hartfield, 2002; Rangarajan and D'Souza, 2007), while aberrant iron, zinc, copper and calcium accumulation was associated with Alzheimer's disease brain (Leskovjan *et al*., 2009, 2011; Li *et al*., 2017; Grochowski *et al*., 2019), highly concentrated iron in neuro-melanin is implicated in dopaminergic mal-function in Parkinson's disease (Sian-Hülsmann *et al*., 2011; Depboylu *et al*., 2007), deficiencies in copper-binding proteins was also linked with neurological disorders such as Menkes and Wilson diseases (Squitti *et al*., 2012; Squitti *et al*., 2013; Strausak *et al*., 2001). The chemical reactivity, spatial distribution as well as biological functions of each essential trace element is quite variable within the CNS, iodine for example is low in content and less distributed, relative to elements such as iron and selenium which are enormous in volume and fairly evenly distributed in all regions of the brain. Others such as copper and zinc are also found to be highly enriched in some regions and nuclei (Bartzokis *et al*., 2007).

Molecular Biology, Bio-Distribution And Roles Of Copper: Copper is one of the essential transition metals needed by the brain. It is rated as the third most abundant trace metal in the CNS; it has an average neural concentration in order of 0.1 Mm (Linder and Hazegh-Azam, 1996; Stöckel *et al*., 1998; Gaggelli *et al*., 2006). It is unevenly distributed in different parts of the brain with higher accumulation in the grey matter when compared with the white matter (Dobrowolska *et al*., 2008). Additionally, high concentration of copper was specifically reported in some brain regions such as substantia nigra, locus coeruleus, dentate nucleus, basal ganglia, hippocampus, and cerebellum (Madsen and Gitlin, 2007; Becker *et al*., 2007b, Popescu *et al*., 2009a, Davies *et al*., 2013). The highest level of copper was found in the basal ganglia, while in glia cells, it was double fold higher in concentration when compared to that of the neuron, especially at the ventricular regions (Madsen and Gitlin, 2007; Becker and Salber, 2010).

Transportation of copper within the CNS is highly dependent on its oxidation state which enables it to be readily involved in several redox activities (Macreadie, 2008). The reduced form of copper is mostly transported and is found in higher concentration within the intracellular environment such as the neurons and glia cells, in contrast to the oxidized forms which are less in abundance and found mostly in extracellular spaces such as the blood serum, CSF and synaptic cleft (Macreadie 2008; Que *et al*., 2008). In the peripheral blood, copper ions are usually transported as free ions which transverses the BBB into the brain parenchyma from where it is utilized for several redox activities and subsequently released into the CSF. Choroid epithelial cells absorb copper from the CSF, and thus facilitate its clearance from the brain to maintain normal brain copper balance (Zheng and Monnot, 2012). Effective cellular copper transportation and homeostatic control is achieved by binding with specific protein transporters and a subset of intracellular proteins known as Cu chaperones which enhances its delivery for specific targets involved in biochemical activities. Upon entering the cell, the fate of copper ions includes; (1) entering into Cu-metallothionein storage pool, (2) incorporation into cytochrome c oxidase in mitochondria for energy generation (3) incorporation into cytoplasmic Cu/Zn SOD for antioxidation; and (4) conveyed to a P-type ATPase in the trans-Golgi network for secretion (Que *et al*., 2008; Zheng and Monnot, 2012; Grochowski *et al*., 2019). The membrane-associated Cu transporters include copper transporter-1 (CTR1), DMT1, and Cu exporter ATPases (ATP7A and ATP7B). The chaperones include antioxidant protein-1 (ATOX1), cytochrome oxidase enzyme complex (COX17), and Cu chaperone for SOD (CCS) (Harris, 2001). Current scientific research has demonstrated the existence of several of these protein transporters, in the Blood Brain Barrier (BBB) and Blood Cerebrospinal Fluid Barrier (BCB) where they facilitate the entering of copper ions into brain tissue (Choi and Zheng, 2009).

ATOX1 (formerly HAH1) is a copper chaperone belonging to a larger family of metallochaperone proteins that binds copper and convey it in a specific pathway manner within the CNS. In addition to their intracellular

copper ions delivery, they also play the additional role of preventing toxicity through removal of unused free copper ions in the brain. ATOX1 associates with the Cu-ATPases located in the trans-Golgi network to perform intracellular copper trafficking and also found widely distributed in the choroid plexus and brain capillary endothelial cells (Nishihara *et al*., 1998; Hamza *et al*., 2001; Hamza *et al*., 2003; Zheng and Monnot, 2012). COX17 is another copper chaperone widely distributed in the neuronal cells, but its existence is not yet confirmed in the BBB or BCB. COX17 mediates the delivery of cytosolic copper to cytochrome c oxidase of mitochondrion for energy metabolism (Kaler, 2011; Hamza and Gitlin, 2002). CCS is a chaperone required for the incorporation of Cu into Cu–Zn SOD in mammals for antioxidant defence (Culotta *et al*., 2006; Que *et al*., 2008; Grochowski *et al*., 2019). Metallothionein (MT) are cysteine-rich copper binding cytoplasmic proteins that chelate excess free copper ions due to much larger Cu-MT binding affinity relative to affinity for other metals such as zinc (Nishimura *et al*., 1992; Que *et al*., 2008; Ba *et al*., 2009). MT was reported to be widely expressed in BB and BCB and plays additional role of regulating intracellular Cu storage by binding Cu ions at the brain barriers (Que *et al*., 2008). ATP7A and ATP7B, variants of P-type ATPases are also copper chaperones that regulate cellular copper homeostasis, through the removal of excess copper ions within the brain cells via the trans-Golgi network secretory pathway (Zheng and Monnot, 2012). They also regulate the release of copper ions to cuproenzymes during neurotransmitter formation and metabolism and mediate uptake of copper ions into the brain from plasma through the BBB and CSF- brain barrier system (Grochowski *et al*., 2019; Zheng and Monnot, 2012). ATP7B specifically play essential role in excreting excess copper ions in the biliary system. While ATP7A is expressed ubiquitously in several brain regions such as the cerebellum and hippocampus, as well as the BBB endothelium, ATP7B are found mostly in the liver cells and in a specific few brain cells such as Purkinje neurons (Madsen and Gitlin, 2007; Zheng and Monno,t 2012), However, both ATP7A and ATP7B was reported to be well expressed in the apical membrane of the gut enterocytes, choroid plexus ependymocytes and capillary endothelium (Mercer et al., 2001; Choi and Zheng 2009; Merle *et al*., 2016). Copper transporter-1 (Ctr-1) is a representative member of copper transport protein family that is expressed widely in many tissues including the brain, specifically within BBB endothelium where they mediate copper uptake into the brain tissue from plasma (Que *et al*., 2008; Madsen and Gitlin, 2007; Zheng and Monnot, 2012). Their expression is usually upregulated in perinatal copper deficiency, however, in a situation of high cellular copper level, Ctr-1 becomes inactive and totally degraded (Madsen and Gitlin, 2007). Amyloid precursor protein (APP), DMT-1 and prion protein (PrP) are other abundant copper transporter proteins in the brain that are essential for the uptake and efflux of copper ions, thereby maintaining normal neural copper homeostasis (Madsen and Gitlin, 2007).

Copper as a redox active nutrient is required in optimal level to cope with high oxygen capacity and oxidative metabolism of brain tissue. As a main component or co-factor for various enzymes, it is essential for a series of protein/enzyme regulated biological functions including energy metabolism involving mitochondrial cytochrome c oxidase, protection against oxidative damage involving Cu/Zn superoxide dismutase (SOD1), modulation and biosynthesis of neuropeptide, regulator of iron metabolism as well as neurotransmitter and intracellular release of copper ion from mobile storage during neural activities (Scheiber and Dringen, 2013; Scheiber *et al*., 2014; Kozlowski *et al*., 2012; Sheykhansari *et al*., 2018).

Copper dyshomeostasis and neurodegenerative diseases: Copper is a redox metal that co-ordinates several biological activities, its accumulation in the brain may be toxic to the body cells if its homeostatic mechanism is not accurately regulated (Kozlowski *et al*., 2012; Emwas *et al*., 2013). Failure of well refined copper homeostatic control can lead to a number of neurodegenerative diseases such as Parkinson's disease (PD), Menkes disease, Alzheimer's disease (AD), familial amyotrophic lateral sclerosis (fALS), Prion diseases, and Wilson disease. In addition to this, higher ability of copper to bind ligands within the cells can also trigger unregulated cellular reactions leading to severed cell impairment and death (Kozlowski *et al*., 2012).

Involvement of copper ion in pathogenesis of Alzheimer's disease is attributed to abnormal binding of Cu ions with APP and the product of its cleavage (β amyloids) which lead to formation of intermediate metalloproteins (copper-amyloid complex) that triggers fenton-type reaction and rapid generation of highly reactive free radical such as hydroxyl radical (OH-) and hydrogen peroxide (H_2O_2) which mediate a number of repeated oxidative stress cycle that ultimately promote repeated plaque formation with subsequent accumulation in the brain including the extracellular fluids (Parthasarathy *et al*., 2014). In a number of studies, high level of copper and zinc were seen in the amyloid plaque and CSF from AD patients (Bolognin *et al*., 2011; Huzumi *et al*., 2011; Cardoso *et al*., 2013).

Prion disease is another neurodegenerative disorder that has been linked with copper ion dyshomeostasis, prion proteins are cell surface copper binding glycoprotein that has six attachment domains for copper ions (Nadal *et al*., 2009). Scientific evidence is available for the possible involvement of prion proteins in the regulation of brain copper metabolism including cellular signaling, anti-oxidation and buffering activities (Walter, 2009; Nadal *et al*., 2009). Studies have also revealed that, higher affinity of cellular form of prion proteins (PrPC) for free Mn^{2+} ions than Cu^{2+} ions may facilitate its modification into a typical toxic, pathological isoform (PrP- Sc), the resultant free unbound Cu^{2+} ions may further aggravate the disease pathogenesis through free radical generation and oxidative damage (Kozlowski *et al*., 2010). However, there are discrepancies in the physiological function of copper in the etiology of prion protein diseases, and thus makes the phenomenon not to be completely understood (Kozlowski et al., 2010; Thakur *et al*., 2011).

Parkinson's disease is a debilitating motor disorder characterized by progressive degeneration of dopaminergic neurons of the substantia nigra and intracellular deposition of lewy bodies, a misfolded form of α-synuclein protein (Paik *et al*., 1999; Uversky *et al*., 2001). Fibrillation of α-synuclein into a misfolded form is facilitated by its binding with several toxic and trace metals in the brain which promote free radical generation and oxidative stress. Self-

oligomerization of alpha synuclein was reported to be initiated by copper binding in the presence of toxic radicals such as H_2O_2 (Paik *et al*., 1999; Uversky *et al.*, 200). Paik *et al*. (1999) also reported copper II induced self-oligomerization of α-synuclein in the presence of coupling reagents such as dicyclohexylcarbodi-imide. Studies have reported that oligomer species of α-synuclein requires association with copper ions to induce neuronal death (Paik *et al*., 1999; Wright *et al*., 2009; Brown, 2009; Wang *et al*., 2010).

Familial amyotrophic lateral sclerosis (fALS) is genetically linked disorder which majorly affects motor neurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord (Rowland *et al*., 2001; Wijesekera and Leigh, 2009). fALS is believed to be either caused by gain of a novel toxic function of the protein or by mutation of essential gene encoding cytosolic Cu/Zn binding superoxide dismutase SOD, a metalloprotein that catalyzes the conversion of toxic superoxide anion radical O^- into hydrogen peroxide (Shibata *et al*., 2000; Shibata, 2001; Howland *et al*., 2002; Valentine *et al*., 2005), and is responsible for 20% of the inherited form of the disease (Deng *et al*., 1993; Goto *et al*., 2000).

Menkes and Wilson diseases are genetic disorders associated with the dysregulation of copper homeostasis (Llanos and Mercer, 2002; Polishchuk *et al*., 2019; Hartwig *et al*., 2019; Weiskirchen *et al*., 2019). It is caused by mutation in the Cu-transporter ATPase7B gene that encodes a protein responsible for the biliary efflux of copper ions, (Boaru *et al*., 2014). ATPase7B are involved in sequestration of excess Cu into bile, and CSF for excretion. They also incorporate excess copper into ceruplasmin apoproteins to avoid systemic toxicity (Boaru *et al*., 2014; Merle *et al*., 2016). Genetically defected ATPase7B copper (Cu) efflux pump resulted in impaired Cu excretion and gradual accumulation in the body organs (liver, brain and kidney) (Merle *et al*., 2016); excessive copper overload in the brain and liver ultimately resulted into clinical manifestation such as liver cancer and severe psychiatric and neurologic symptoms which are without specific therapy (Weiskirchen *et al*., 2019). Menkes disease is a storage copper disorder characterized by high accumulation of copper in non-hepatic tissue but deficit in the liver, the brain and the blood, due to mutation in the Menke- ATP7A gene encoding for Cu-transport protein, failure in ATP7A is responsible for the resulting systemic brain copper deficiency and reduced copper-containing enzymes (cuproenzyme) activity (Vulpe *et al*., 1993; Tumer 2013). In Menkes disease various ATP7A mutation induced deficiency in transportation of copper across the placenta, blood-brain barrier and gastrointestinal tract (Waggoner 1999; Strausak *et al*., 2001; Weiskirchen *et al*., 2019).

Molecular biology, bio-distribution and roles of Zinc in the brain: Zinc is a trace nutrient needed for normal brain function and maturation; it is rated as the 2nd most abundant trace element in the brain (Sensi *et al*., 2009; Kambe *et al*., 2015). It is a structural part of many proteins and co-factor of more than 300 enzymes involved in numerous cellular signaling pathways and functions, Zinc is found to be irregularly distributed in the brain but highly concentrated in some regions such as amygdala, neocortex, olfactory bulb, hippocampus, gray matter of the cortex and neurons (Takeda, 2000; Frederickson *et al*., 2001). In the brain, zinc exists in two forms; the most abundant static form (Zn^{2+}), constitutes up to 90% of the neuronal zinc and is usually tightly bound with numerous metalloproteins. The static or chelatable form plays structural roles in protein as well as structural and catalytic roles in enzymes; the labile or ionic form, constituting up to 10% are widely distributed within the presynaptic vesicles of zinc-dependent glutamatergic neurons (Que *et al*., 2008). The glutamate and zinc-releasing neuronal system forms the cortical–limbic associational network that unites limbic and cerebrocortical functions, and contains a vast number of glutamate- and zinc-releasing neurons with their cell bodies scattered within the cerebral cortex and limbic structures (Frederickson *et al*., 2001; Kozlowski *et al*., 2012). During neuronal activity the co-release of labile zinc at micromolar level with some classical neurotransmitter from the glutamatergic presynaptic vesicle resulted into modulation of their postsynaptic activity, for example Zn^{2+} has an inhibitory effect on N-methyl-D-aspartate (NMDA), $GABA_A$ and glycine inotropic receptors but highly activate α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) glutamate receptors and a specific metabotropic Zn^{2+}-sensing receptor GPR39 (Smart *et al*., 2004; Besser *et al*., 2009). The neuroprotective effect of zinc at physiological concentration have been reported, however deficit concentrations exceeding the physiological level was found to be highly neurotoxic, effective zinc transportation and homeostatic control is therefore required, to avoid brain cytotoxicity and damage (Fukada *et al*., 2011; Szewczyk, 2013; Maywald *et al*., 2017). Zinc transportation is usually mediated by a numerous number of zinc homeostatic regulatory proteins distributed widely in the brain tissue, they are classified into three major groups; ZnTs belonging to a larger family of SLC30 is a membrane bound protein that excretes cystosolic zinc from the cell or influx zinc ions from extracellular space into intracellular compartment or organelles (Huang *et al*., 2013; Kambe *et al*., 2015; Portbury and Adlard, 2017). The second group are the ZIP a member of zinc and iron-regulatory transporter proteins (SLC39 family) that are widely distributed in the brain and responsible for trafficking of zinc from the extracellular space or from intracellular vesicles to the cytoplasm (Cousins *et al*., 2006; Kambe *et al*., 2015). About 10 and 14 variants of ZnTs and ZIP that control zinc transportation in mammalian system have been identified (Cousins *et al*., 2006). The third group is the Metallothioneins (MT), low molecular weight proteins that have affinity for zinc metals.

Zinc dyshomeostasis and neurodegenerative diseases: The role of zinc as essential nutrients for normal brain function is being increasingly appreciated; however, studies have shown that zinc overdose resulting from defective homeostasis is linked with the pathophysiology of many neuropsychiatric diseases (Szewczyk *et al*., 2013; Portbury and Adlard, 2017). Clinical conditions such as epilepsy and stroke are associated with excessive influx of zinc into neurons that ultimately leads to excitotoxic neuronal death. On the other hand, zinc deficiency has been implicated to affect neurogenesis which triggers neuronal apoptosis and consequently leads to learning and memory impairment (Frederickson *et al*., 2005; Szewczyk *et al*., 2013). Effective transportation and homeostatic control to maintain

intracellular and extracellular zinc concentration at nontoxic level is achieved by a number of regulating proteins which includes membrane Zn^{2+} transporters proteins (ZnT and Zip), and metallothioneins (Sensi *et al*., 2009; Szewczyk *et al*., 2013; Portbury and Adlard, 2017). Alteration in any of these proteins have been implicated in the etiology of ageing and age related neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and Alzheimer's disease (AD) (Frederickson *et al*., 2004; Szewczyk *et al*., 2013; Portbury and Adlard, 2017). Recently, alteration in ZnT and MT was implicated in ageing and progression of Alzheimer's disease (AD) (Yu *et al*., 2001; Wong *et al*., 2013).

Alzheimer's disease (AD) is one of the age related neurodegenerative diseases associated with Zinc dyshomeostasis. It is characterized by extracellular deposition of amyloid plaques and intracellular accumulation of Neurofibrillary tangles (NFT), the pathological hallmarks of the disease (Bolognin *et al*., 2011; Portbury and Adlard, 2017). Defective zinc homeostasis may contribute to pathogenesis of AD by promoting protein aggregation and deposition (Szewczyk *et al*., 2013), several lines of evidences have shown that zinc upregulation to toxic concentration (above 300 nM) in extracellular fluids can promote plaque formation in AD (Bush *et al*., 1994; Ha *et al*., 2007; Noy *et al*., 2008). Amyloid precursor proteins (APP) are abundantly distributed in the plasma membrane of neurons, with their functions virtually unknown, however their proteolytic cleavage yield Aβ peptides. Zinc availability is essential for APP function and metabolism especially in the regulation of its formation and processing (Grilli *et al*., 1996; Lee *et al*., 2009), located on the APP ectodomain is the cysteine-rich regions that constitute the binding site for Zn ions (Bush *et al*., 1994b; Que *et al*., 2008). The processing of APP also depends on activities of enzymes secretases (α, β and γ). The common route by which APP is processed in the brain is through the cleavage by α-secretase, within the Aβ region, producing sAPP (soluble amyloid precursor peptide) (Ling *et al*., 2003). Aberrant binding of zinc ions to APP may prevent the activities of α- secretases, to yield non-amyloidogenic peptide (soluble amyloid precursor peptide); further reduction in α-secretase activity facilitates the formation of defective Aβ peptides by its β and γ secretases counterparts (Wilquet and De, 2004). Several studies have highlighted the contribution of zinc dyshomeostasis in amyloid pathology of AD; a research study using ZnT3 knockout mice showed reduced vulnerability toward amyloid plaque deposition (Ritchie *et al*., 2003), while administration of copper-zinc chelator clioquinol was shown to prevent or ameliorate amyloid plaque aggregation in an additional study (Regland *et al*., 2001; Ritchie *et al*., 2003). Oxidative stress has also been suggested as another risk factor contributing to AD pathology (Butterfield *et al*., 2001; Jomova *et al*., 2010) ROS such as NO and peroxynitrate or exogenous oxidant could mediate mobilization of zinc ion from extracellular metallothioneins (MT) and zinc transporters (ZnT) which further upregulate intracellular zinc concentration to toxic level that triggers general tissue damage such as mitochondrion dysfunction and further promote ROS formation (Aizenman *et al*., 2000; Burdette and Lippard, 2003; Sensi *et al*., 2003; Bossy-Wetzel *et al*., 2004). Sensi *et al*. (2008) indicate ROS mediated Z^{2+} upregulation in AD neurons expressing mutant APP, presenilin-1 (PS-1) and tau. Another pathway through which zinc could be implicated in AD pathology is through hyperphosphorylation of tau proteins to generate neurofibrilary tangles another hallmark of AD. Studies have shown that zinc at micromolar concentration can promote NFT formation (Bjorkdahl *et al*., 2005; Pei *et al*., 2006; Mo *et al*., 2009) and the use of appropriate zinc chelator can effectively block hyperphosphorylation of tau (Sun *et al*., 2012).

Amyotrophic lateral sclerosis (ALS) is a chronic disorder characterized by the selective death of motor neurons (Rowland and Shneider, 2001). It is both familiar and sporadic in nature with the sporadic form constituting about 90% of the cases and 10%, the familiar form (Portbury and Adlard, 2017). Mutation in the gene encoding copper, zinc superoxide dismutase (SOD1) is responsible for about 20% of the inherited form of the disease. Mounting evidences are available, suggesting the involvement of zinc dyshomeostasis in the pathogenesis of ALS (Frederickson *et al*., 2005). Studies have shown that mutation of SOD genes result in loss of zinc from its active site and toxic gain of function in motor neurons (Frederickson *et al*., 2005; Roberts *et al*., 2007). Loss of zinc from SOD mutants has been reported to triggers peroxynitrate induced protein nitration, a toxic reaction presumes to contribute to selective death of motor neurons in ALS disease (Crow *et al*., 1997). In another study, deficiency of zinc in SOD mutant was observed to promote nitric oxide induced motor neuron degeneration in ALS disease (Estevez *et al*., 1999). In addition to SOD mutation, several studies have reported the involvement of metallothioneins (MTs) and zinc transporters (ZnTs) in the progression of ALS; a recent study has discovered downregulation of ZnT3 and ZnT6 in the spinal cord of ALS patient (Kaneko *et al*., 2015). Another study also recorded reduced expression of zinc metallothionein RNAs in the spinal cord of patient with sporadic form of ALS (Ishigaki *et al*., 2002; Hozumi *et al*., 2008b). In a study using a mutant SOD transgenic mouse, deficiency of MT1, MT2 or MT3 was shown to exacerbate ALS expression (Nagano *et al*., 2001; Puttaparthi *et al*., 2003). All these together have suggested the possible involvement of zinc dyshomeostasis in ALS disease pathogenesis.

Parkinson's disease is a chronic progressive neurological disease associated with defective motor system. Clinical symptoms develop gradually over time and include tremor, rigidity, postural instability, paucity of movement, behavioural and learning deficit and dementia which is associated with the late phase of the disease. Zinc deficiency has been detected in patients presenting with PD and the efficacy of appropriate zinc supplementation to reverse zinc shortage in animal model of PD has been demonstrated (Forsleff *et al*., 1999; Brewer *et al*., 2010). In addition, accumulation of zinc in specific brain regions associated with PD pathology such as substantia nigra, lateral putamen and caudate nucleus in patients expressing PD have been demonstrated (Dexter *et al*., 1991). Also Drosophila parkin mutants, a PD disease model expressing human PD phenotype with deficits such as, severely shorten life span and locomotor defect due to degenerated flight muscles were restored back to normal through zinc supplementation (Saini *et al*., 2010). Together all these

evidences have indicated the contributory role of zinc dyshomeostasis in the pathogenesis of PD.

Molecular biology, bio-distribution and roles of Iron in the brain: Iron is the most prevalent transition metal in the brain (Que *et al*., 2008; Beard *et al*., 2009). The brain being the organ with the highest rate of cellular metabolism requires iron as a major constituent of enzymes to carry out the process of oxygen transportation and metabolism (Cammack *et al*., 1990). Within the brain, iron is homogeneously distributed with the highest concentration found in the basal ganglia, thus suggesting basal ganglia as the major iron storage and distribution in the brain (Beard *et al*., 2009; Anderson and Erikson, 2011). In a cohort study conducted by Aoki et al. (1989), magnetic resonance imaging (MRI) of the brains of children and adolescents confirmed the substantia nigra, caudate nucleus, globus pallidus and putamen as the brain regions with highest iron concentration while the concentration remained relatively low in the cerebellum and cortex. Studies have also confirmed white matter as the major site of iron concentration within the brain with maximum influx occurring during rapid brain growth at the peak of myelinogenesis (Taylor and Morgan, 1990). Iron is also widely distributed in all cell types of the CNS including, microglia, oligodendrocytes, astrocytes and neurons, with oligodendrocytes having the highest concentration (Que *et al*., 2008). In the biological tissue, iron exists in two common oxidative states namely: +2 (ferrous) and +3 (ferric) oxidation states, other higher redox states are generated through several enzymatic catalytic cycles occurring in the cell (Que *et al*., 2008). With regard to the brain, iron participates in several neurological activities which includes involvement in the function and biosynthesis of neurotransmitters (Youdim, 1990; Loeffler *et al*., 1995), myelin formation (Beard *et al*., 1993; Que *et al*., 2008; Anderson and Erikson, 2011), cofactor for a variety of metalloenzymes and an essential role in neuronal function (Beard *et al*., 1993; Anderson and Erikson, 2011). Despite high need of iron in the brain, only a small quantity, about 5-10% is expected to be used for iron-dependent processes (Sigel *et al*., 2006), while the large portion of the unused (about 33-90%) is stored in ferritin. Due to abundance of iron in the brain and its high redox activities, tight homeostatic regulation is required to prevent oxidative damage to the cells by unlimited iron dependent Fenton reactions (Beard *et al*., 1993; Que *et al*., 2008). To avoid iron toxicity and deficiency, an elegant homeostatic system comprising transferrin, transferrin receptors, and ferritin are in place to ensure effective storage and well-timed release of iron to the cells. The mechanism of transportation of iron in the CNS is not fully comprehended, however both the transferrin-mediated and axoplasmic flow have been described as the most common pathway of iron into the neurons and grey matter (Dwork *et al*., 1990).

Iron initially absorbed from the gastrointestinal tract is integrated into ferritin and plasma transferrin for systemic storage and transportation. Influx of iron into the brain across the blood-brain barrier (BBB) is mediated through a general pathways involving transferrin (Tf), the transferrin receptor (TfR) localized on brain endothelial cells. Iron in oxidized state is incorporated into transferrin (Tf) and bound with transferrin receptor (TfR) to form TfFe2-TfR complex that is translocated across the BBB into the brain. Once in the brain, the influx of iron into the cell occurs through a few major pathways the choice of which is dependent on the cell type and brain region involved. Within the brain the resulting TfFe2-TfR complex is endocytosed into the cell through clathrin-coated endosomes, which undergoes acidification to liberate Fe3+ from transferrin, Fe3+ is further reduced to Fe2+ by an unknown mechanism and subsequently transported into mitochondria through mitoferrin by a mechanism mediated by divalent metal transporter-1 (DMT1), a mitochondrial iron transporter abundantly expressed in astrocytes. Within the mitochondrion, transported Fe^{2+} is utilized for the synthesis of heme and iron-sulfur clusters, while the remaining left over is incorporated into ferritin for storage. Other alternative pathway employed for iron uptake into brain cells include ferritin and ferritin receptors (FtR) (occurring in white matter in oligodendrocytes (Hulet *et al*., 1999; Hulet *et al*., 2000) the transferrin / transferrin receptor pathway (Hulet *et al*., 2000), lactoferrin mediated pathway which involves importing of iron into neuromelanin cells (Zecca *et al*., 2004) and divalent metal transporter-1 (DMT1) abundantly expressed in astrocytes.

Intracellularly iron homeostatic regulation is controlled through translational level with iron responsive elements (IREs) and iron regulatory proteins (IRPs) (Hentze and Kühn, 1996; Eisenstein, 2000). The nucleotide sequences of IREs are fully expressed on mRNA. The expression and the activities of TfR, Ft, and other iron metabolic regulatory proteins is controlled by IRP/IRE interactions. During intracellular iron depletion, the cell put up compensatory action and initiate: binding of IREs of TfR mRNA and Ft mRNA to IRPs to boost intracellular iron level by preventing iron degradation and reduce the population of iron stores in ferritin, while in the case of excess intracellular iron, conformational alteration in IRPs is initiated to prevent IRE binding and increase ferritin level required for excess iron sequestration or initiate TfR mRNA degradation to reduce subsequent iron influx into the cell. Other iron regulatory proteins whose expression is regulated by the IRP/IRE system include DMT1 and ferroportin-1 (FPN1) (Abbou and Haile, 2000; Dunn *et al*., 2007). FPN1 is an iron regulatory protein that controls efflux of iron from the cell. It is abundantly expressed in the brain (Abbou and Haile, 2000; Donovan *et al*., 2000; Burdo *et al*., 2001) and its over expression has been reported to result in intracellular iron deficiency (Abbou and Haile, 2000).

Iron dyshomeostasis and neurodegenerative diseases: Iron is an indispensable metal that is essential for several life processes and cellular functions, its level rises with age. Aberrant iron accumulation in the brain due to mis-regulated homeostasis is a characteristic of several neurological disorder such as Alzheimer's disease (AD) (Que *et al*., 2008; Li and Reichmann, 2016; Bjørklund *et al*., 2019). As a redox active element, iron is involved in several cellular activities, which if unregulated, may result in oxidative damage to macromolecule and cellular dysfunction (Belaidi *et al*., 2016; Eid *et al* 2017; Masaldan *et al*., 2018), evidences are available in the literature which show that abnormal iron accumulation in the brain promote protein aggregation through Fenton- type oxidation of

macromolecules (Zecca *et al*., 2004; Madsen and Gitlin, 2007; Que *et al*., 2008).

Parkinson's disease (PD) is a debilitating disease of the brain characterized by the accumulation of α-synuclein and degeneration of substantia nigra (SN) neurons (Que *et al*., 2008; Li and Reichmann, 2016; Costa-Mallen *et al*., 2017; Bjørklund et al., 2019). It affects about 2% of human population globally especially in ages well above 65 years (De Rijk *et al*., 1997). Clinical symptoms for PD include tremor, muscle rigidity, bradykinesia (slow movements), and deterioration of cognitive functions (Rinne *et al*., 2000). Both the genetic and the environmental factor have been strongly implicated in the etiology of PD, and several research studies have highlighted the role of environmental factors in the disease pathogenesis such as induction of parkinsonism in rats by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) exposure. Exposure to different environmental toxicant, exposure to toxic metals (Pb, V, Hg) as well as the essential trace element dyshomeostasis (iron, copper, manganese, zinc) have also contributed to the development of PD (Bjørklund *et al*., 2019). Evidences are available supporting impaired iron homeostasis as a function of elevated iron accumulation observed in PD, studies done on post mortem brain iron content using MRI and LA-ICP-MS bio-imaging revealed massive accumulation of iron in the SN of brain tissues obtained from various forms of PD (Li and Reichmann, 2016; Costa-Mallen *et al*., 2017; Bjørklund *et al*., 2019). *In-vivo* measurements of brain iron by magnetic resonance imaging (MRI) also confirmed the presence of increased iron deposition in the SN (Wallis *et al*., 2008; Rossi *et al*., 2013). Another study also detected reduction in the level of ferritin and neuromelanin (iron binding proteins) in the SN of PD individuals when compared with normal individuals (Connor *et al*., 1995; Zecca *et al*., 2002; Que *et al*., 2008). Further studies also found abnormally elevated iron accumulation in oligodendrocytes, astrocytes, microglia, and pigmented neurons and in the rim of Lewy bodies in PD patients. All these evidences confirm the association of disrupted iron homeostasis with the pathogenesis of PD. So far, the primary mechanism that is responsible for excessive iron accumulation in PD is insufficiently defined, however, disrupted BBB, α-synuclein aggregation, oxidative stress, mitochondrial dysfunction and iron dyshomeostasis have been suggested to be involved (Que *et al*., 2008; Li and Reichmann, 2016). Moreover, these factors together with iron accumulation constitute the process leading to neuro-inflammation and neuro-degeneration. In PD pathology the vicious cycle of mitochondrial injury, oxidative stress, iron dyshomeostasis and neuro-inflammation are closely interrelated with several other factors in PD (Li and Reichmann, 2016).

Interactions between excess Fe ions and various molecules in the brain are implicated in the pathology of PD. For example, the interaction of electrophilic ferric iron with dopamine in SN could be a major factor associated with neurotoxicity and neurodegeneration in PD (Que *et al*., 2008; Li and Reichmann, 2016). In the presence of elevated ferric iron, dopamine interacts with molecular oxygen to yield quinones and free oxygen radicals (ROS) which appeared to be toxic to SN cells (Zucca *et al*., 2014). Dopamine can be polymerized and oxidized directly to form a characteristic coloured neuromelanin or its other multiple toxic metabolites (Miyazaki *et al*., 2008; Zucca *et al*., 2014). The free reactive radical (ROS) generated promote protein carbonylation which subsequently triggers α-synuclein aggregation and Lewy body formation (Munch *et al*., 2000). Excess iron in SN may directly interact with α-synuclein and catalyse its aggregation into α-synuclein oligomer, while α-synuclein in excess may induce massive iron accumulation, excessive aggregated α-synuclein generated further exacerbate oxidative stress, mitochondrion impairment and iron dyshomeostasis (Devi *et al*., 2008; Que *et al*., 2008; Davies *et al*., 2011; Funke *et al*., 2013). Another example is the interaction of excess ferric ion with neuromelanin pigment, the end product of dopamine metabolism to form neuromelanin iron complex (NM-Fe^{3+}), which is seen in the degenerating neurons of the SN of PD patients (Jellinger *et al*., 1992; Zecca *et al*., 1996). Fe^{3+} stored in degenerating neurons of SN is released into extracellular environment where it interacts with microglia and trigger the release of neurotoxin that mediate neuro-inflammatory cascade. The release of NM-Fe^{3+} complex from degenerating neurons further triggers a cascade of events leading to neuronal death through microglial activation (Wilms *et al*., 2003; Zucca *et al*., 2014). Disrupted iron homeostasis seen in PD has also been attributed to mis-regulation of normal brain iron regulatory system, studies have shown changes in brain iron level in different forms of PD while the serum iron remain largely unaltered (Logroscino *et al*., 1997; Tórsdóttir *et al*., 1999; Costa-Mallen *et al*., 2015; Costa-Mallen *et al*., 2017). In addition, increase in the level of ferritin iron saturation as well as the level of lactoferrin and lactoferrin receptors, which are the potential source of iron storage in the brain, were detected in SN of PD patient in comparison with normal individual (Faucheux *et al*., 1995; Leveugle *et al*., 1996).

Alzheimer's disease (AD) is another degenerative disease of the brain strongly linked with dysfunctional iron homeostasis, and evidences are available showing association of aberrant iron accumulation with AD pathology (Connor *et al*., 1992; Smith *et al*., 2007; Bulk *et al*., 2018; Everett *et al*., 2018). Amyloid plaque and neurofibrillary tangles (NFT) which are pathology hallmarks of the disease were also found with high iron deposits (Connor *et al*., 1992). Studies on postmortem brain from AD patients revealed high iron accumulation especially in the hippocampus (Connor *et al*., 1992; Deibel *et al*., 1996). In addition to this, iron may also directly trigger β amyloid formation and aggregation through several pathway including oxidative stress which is built up in the cell by the activities of other redox metals (Zn, Cu) and thus promote oxidation and subsequent crosslinking of β amyloid species (Huang *et al*., 1999; Bush *et al*., 2003; Que *et al*., 2008; Jomova *et al*., 2010). Alteration of iron regulatory proteins involved in the removal of excess iron from the brain to prevent iron overload has also been implicated in promoting iron dyshomeostasis in AD (Connor *et al*., 1993; Guerreiro *et al*., 2015; Wan *et al*., 2011). This is further confirmed in an analysis on iron transportation and storage which revealed reduced iron mobilization in AD compared to normal individuals (Connor, 2018), the level of Divalent Metal Transporter 1 (DMT1) an iron importer is increased, while the level of ferroportin 1 (FPN1) and Ceruloplasmin (CP) cellular iron exporters were relatively low in AD brain (Connor *et al*., 1993; Wan *et al*., 2011; Guerreiro *et al*.,

2015). Intracellular iron distribution and accumulation may also affect the formation and processing of amyloid precursor protein (APP). The expression of iron responsive element (IRE) identified on the 5' end of APP mRNA, is suggestive of the role of iron in the regulation of APP formation and processing (Connor *et al*., 1993; Que *et al*., 2008; Ward *et al*., 2014), for example excess iron accumulation, has been reported to promote APP formation (Bodovitz *et al*., 1995). In addition, iron responsive element (IRE) on APP mRNA is involved in the translational processing of amyloid precursor protein (APP). Excess iron overload may trigger aberrant binding of iron responsive element and subsequently promote β amyloids formation and aggregation (Bodovitz *et al*., 1995; Rogers *et al*., 2002; Crichton *et al*., 2008; Caldwell *et al*., 2013). The common route of APP processing is non amyloidogenic pathway that involves proteolytic cleavage of APP by α and γ secretases to yield a neuroprotective extracellular soluble A β peptide, (Ling *et al*., 2003) and prevent the formation of β-amyloids however, in AD, APP cleavage by β and γ secreatases produced amyloidogenic fragments of β amyloid which subsequently aggregate to form plaque (Bodovitz et al., 1995; Silvestri. and Camaschella, 2008; Ward *et al*., 2014). Furthermore, the processing of APP is regulated by iron through furin (Hwang et al., 2006). Furin is a calcium-dependent proconvertase, produced in the endoplasmic reticulum (ER) and largely involves in promoting α-secretases cleavage of amyloid protein precursor (APP) to yield the sAPP neuroprotective form. However, excessive iron accumulation has been reported to decrease furin expression and enhanced β amyloids accumulation and aggregation in the brain (Bodovitz *et al*., 1995; Silvestri and Camaschella, 2008). Additionally, accumulated iron in neurofibrillary tangles (NFT) can mediate tau phosphorylation and aggregation (Yamamoto *et al*., 2002; Lovell *et al*., 2004; Chan and Shea, 2006; Castellani *et al*., 2012).

Amyotrophic lateral sclerosis (ALS) is another neurodegenerative disorder associated with aberrant iron trafficking and distribution, it is a debilitating progressive CNS disease characterized by gradual degeneration of motor neurons in the cerebral cortex, brain stem and the spinal cord. ALS affects mostly growing population with global incidence of up to 1/100,000 (Carrì *et al*., 2003; Goodall *et al*., 2008). ALS is categorized into familiar and the sporadic form, but both with similar clinical symptoms and pathological process (Portbury and Adlard, 2017; Sheykhansari *et al*., 2018). Iron as a cofactor is essential for various enzymatic catalyzed reactions in the brain (Hametner *et al*., 2013). A balanced brain iron homeostasis is essential to prevent deleterious effect on cell functions due to high accumulation, mis-regulation of iron may promote neuro-inflammation, mitochondrial impairment and oxidative stress (Carrì *et al*., 2003; Goodall *et al*., 2008; Hadzhieva *et al*., 2013; Tokuda *et al*., 2016), although the involvement of iron in the etiology of ALS is unclearly defined, however, redox capacity of iron to generate ROS has been proposed as one of the factors that initiate ALS pathology (Hametner *et al*., 2013). Moreover, mutation of the gene encoding copper-zinc dismutase (SOD), that constitutes about 20% of the familiar form of the disease has also been implicated in the pathogenesis of the disease (Yoshida *et al*., 2010). In normal conditions SOD is responsible for the catalytic conversion of toxic superoxide anion radical O^- into hydrogen peroxide through dismutation reactions (Shibata *et al*., 2000; Shibata, 2001; Howland *et al*., 2002;Valentine *et al*., 2005). SOD impairment result to reduction in dismutation activities and toxic accumulation of superoxide radicals that subsequently generates oxidative stress. Studies have demonstrated the ability of excess superoxide radicals O^- to remove iron from iron bearing proteins such as ferritin (Jeong *et al*., 2009; Jomova *et al*., 2010), the extracted iron is further incorporated into Fenton and Haber Weiss reactions to generate more free radicals such as OH^- and O_2^- which are toxic to brain cells (Wang *et al*., 2004; Jeong *et al*., 2009; Jomova *et al*., 2011). Furthermore, mutation of the genes controlling appropriate cellular iron homeostasis has been proposed as one of the predisposing factors to ALS (Zamboni *et al*., 2005). Mutation in Hfe with the associated hemochromatosis and decrease in Cu/Zn SOD1 activities have been implicated in ALS (Zamboni *et al*., 2005; Gemmati *et al*., 2006; Singh *et al*., 2010; Gemmati *et al*., 2012). There are several indications showing the involvement of aberrant iron homeostasis in the pathophysiology of ALS; assessment of iron state levels in ALS patient revealed high ferritin level associated with worsened muscle degeneration and shortened patients' survival (Goodall *et al*., 2008; Veyrat-Durebex *et al*., 2014; Nadjar, *et al*., 2012; Ikeda *et al*., 2012), abnormal iron accumulation has also been detected in the spinal cord of ALS patients (Yasui *et al*., 1993; Ince *et al*., 1994; Kasarskis *et al*., 1995; Markesbery *et al*., 1995), Furthermore, high iron concentration has been reported in the CSF of ALS patients (Hozumi et al., 2011). Using animal model of ALS, motor neuron degeneration due to aberrant iron deposition was reported in SOD transgenic mice (Winkler *et al*., 2014), The use of appriopriate iron chelator therapy to alleviate aberrant iron accumulation in a G93A-SOD1 murine model of ALS, resulted in neuroprotection and long life survival (Kupershmidt *et al*., 2009; Wang *et al*., 2011).

Multiple Sclerosis (MS) is a type of demyelinating CNS disorder associated with mis-regulated iron homeostasis. It is characterized by general disruption of iron regulatory mechanism controlled by oligodendrocytes. Oligodendrocytes are responsible for maintenance and myelin production, alteration in this regulatory process could lead to aberrant iron accumulation within the cell that triggers oxidative damage (Beard *et al*., 1993; Sheykhansari *et al*., 2018). Aberrant iron accumulation in the brain and associated oxidative stress is a component of MS pathology (Ferreira *et al*., 2017; Iranmanesh *et al*., 2013; Hametner *et al*., 2013). Studies have reported alteration in the normal cellular pattern of iron and transferrin due to cellular iron dyshomeostasis (Craelius *et al*., 1982; LeVine *et al*., 1997). Age related increase in iron accumulation was also seen in the white matter of MS subject (Hametner *et al*., 2013), Moreover, extensive glial degeneration including iron rich oligodendrocytes and myelin has been reported in MS lesion, the free iron liberated further exacerbates oxidative stress and leads to neurodegeneration (Uttara et al., 2009; Khare *et al*., 2014; Raymond *et al*., 2017), on the other hand, reduced iron accumulation with upregulated oxidative stress has been found in MS disease (Visconti *et al*., 2005; Crichton *et al*., 2008). Several studies have used experimental animal models to investigate the

pathophysiology of MS and their report have been documented, destructive blood brain barrier with excessive iron accumulation have been reported in animal model of experimental allergic encephalomyelitis (EAE) which is one of the clinical condition of MS (Forge *et al.*, 1998). In addition to this, endogenous administration of appropriate antioxidant has proven to reverse the clinical and pathological symptoms linked with experimental autoimmune neuritis in animal model of autoimmune demyelination (Hartung *et al*., 1988).

Methods of metal detection in the brain: Elemental or molecular mapping in biological tissue is of growing interest in different areas of biomedical research (Sussulini and Berker, 2015; Wu *et al*., 2011), in brain research it is mostly used for the detection of spatial element distribution and quantification in the brain. It is relevant in the study of neurodegenerative diseases (Hutchinson *et al*., 2005; Hare *et al*., 2009; Wang *et al*., 2010; Becker *et al*., 2010; Hare *et al*., 2010; Hare *et al*., 2014), proteomics (Wind *et al*., 2003; Becker *et al*., 2004; Feng *et al*., 2015) as well as aging and oncogenic research (Becker, 2005; Zoriy *et al*., 2006; Salber *et al*., 2007; Seuma *et al*., 2008; Fu *et al*., 2015). It also detects changes in metal distribution, homeostasis and contents within brain anatomical structures (Hare *et al*., 2017; Becker *et al*., 2012; Hare *et al*., 2012).

Presently, there are several analytical techniques available for detecting metals in biological system for the purpose of medical investigations, these include non-photometric techniques such as histochemical techniques (Wang *et al*., 2010; Hare *et al*., 2016), fluorescent method (Majumdar *et al*., 2012; Hare *et al*., 2015) and autoradiography (Wang *et al*., 2010; Becker and Salber, 2010); photometric methods such as flame photometry (Meloni *et al*., 2007; Elseweidy et al., 2008) and Atomic absorption spectroscopy (AAS) (Andrási *et al*., 1999; Grochowski *et al*., 2019) other surface analytical techniques include; X-ray spectroscopic techniques (e.g. X-ray photoelectron spectroscopy (XPS)(Briggs and Grant, 2012), scanning electron microscopy with energy dispersive X-ray analysis (SEM-EDX) (Lohrke *et al*., 2017;Pánik *et al*., 2018), proton-induced X-ray emission (PIXE) (Carmona *et al*., 2008; Nakazato *et al*., 2008), and imaging mass spectrometry such as secondary ion mass spectrometry (SIMS) (Chandra *et al*., 2016), and MALDI-MS (matrix assisted laser desorption/ionization mass spectrometry) (Seeley *et al*., 2011). However, these methods have a number of limitations such as non-multi-elemental capability, poor detection limits, poor lateral resolution, lower sensitivity for trace analysis and non-availability of quantification procedure when compared with spectrometry based method such as Laser ablation - inductively coupled plasma - mass spectrometry (LA-ICP-MS) a modern powerful micro-analytical technique with relatively lower matrix effect, high sensitivity, low detection limit and easy quantification and preparative procedure (Hattendorf *et al*., 2003; Hare *et al*., 2010). LA-ICP-MS imaging is a modern method applicable for measuring most of the biological relevant metals and their tissue concentration. The major goal of this review is to highlight the role of some essential metals in the brain and recent applications of LA-ICP-MS imaging in neuroscience, including brain diseases.

Mechanism of LA-ICP-MS: LA-ICP-MS is the most sensitive and widely used technique for *in situ* analysis of metals in cross sections of biological tissue (Becker and Jakubowski, 2009). It is of significant diagnostic importance in brain research, where it allows for the detection of absolute concentration and micro spatial and regional distribution of elements (metals, non-metals and metalloids) within the affected brain tissue. It is also essential for measuring the relative concentration of element within a large number of metals and metalloids (Mokgalaka and Gardea-Torresdey, 2006). A classical Laser ablation system is made up of three key components namely; (A) A high energy ultraviolet laser beam, (B) easily adjustable ablation stage, and (C) a detection system comprising of inductively coupled plasma mass spectrophotometer (ICP-MS). The detection system is of varied types depending on the type of mass analyzer used. However, the most widely used is the quadrupole (Q) based type consisting of a quadrupole mass filter (Potter 2008) with exceptional quality of high sensitivity and less design complexity when compared with the other types such as time of flight (TOF) and double – focusing sector-field (SF). A laser stage consists of a lens, an ablation chamber or cell, and adjustable platform to which is attached an optical microscope equipped with a charged coupled device (CCD) camera from where the cell can be effectively monitored and the material of interest concisely visualized. The mechanism of LA-ICP-MS involves the use of quadrupole (Q) or double-focusing sector field (SF) based mass spectrophotometer coupled with ultraviolet laser beam to vaporize materials from the surface of biological sample. A thin sliced section mounted on a glass slide is obtained and fixed into a sample holder located in a closed ablation chamber or cell. A high energy laser beam is focused unto the area of interest within the section, to generate ablated particulates which are transported in a continuous flow of inert carrier gas such as argon or helium into the inductively coupled plasma (ICP). With the extremely high thermal temperature and pressure of the ICP, the particles, through electromagnetic induction dissociated into ions, which was further extracted and directed into a high vacuum mass analyzer, from where ions are separated into different ones based on their mass - to - charge ratios (m/z). Finally, highly sensitive detection and quantification of the transmitted ions take place (Plates.1a and1b), (Durrant and Ward 2005; Mokgalaka and Gardea-Torresdey, 2006; Weiskirchen *et al*., 2019).

LA-ICP-MS Bio-imaging of normal brain : LA-ICP-MS metal bio-imaging is a unique technique that has provided a new insight in the study of several pathophysiological processes in brain research. Hare *et al*. (2016) used LA-ICP-MS bio-imaging to produce a three-dimensional atlas showing the distribution of Zinc (Zn), Copper (Cu) and Iron (Fe) by using aligned quantified images of these metals obtained from cerebrum and brainstem sections of a mouse brain. This atlas has thus contributed to the better understanding of these essential elements in the brain and further clarifies their function in neurobiology. Becker *et al*. (2005) also employed LA-ICP-MS imaging to produce spatial distribution of trace elements such as Zn and Cu in different layers of human hippocampus.

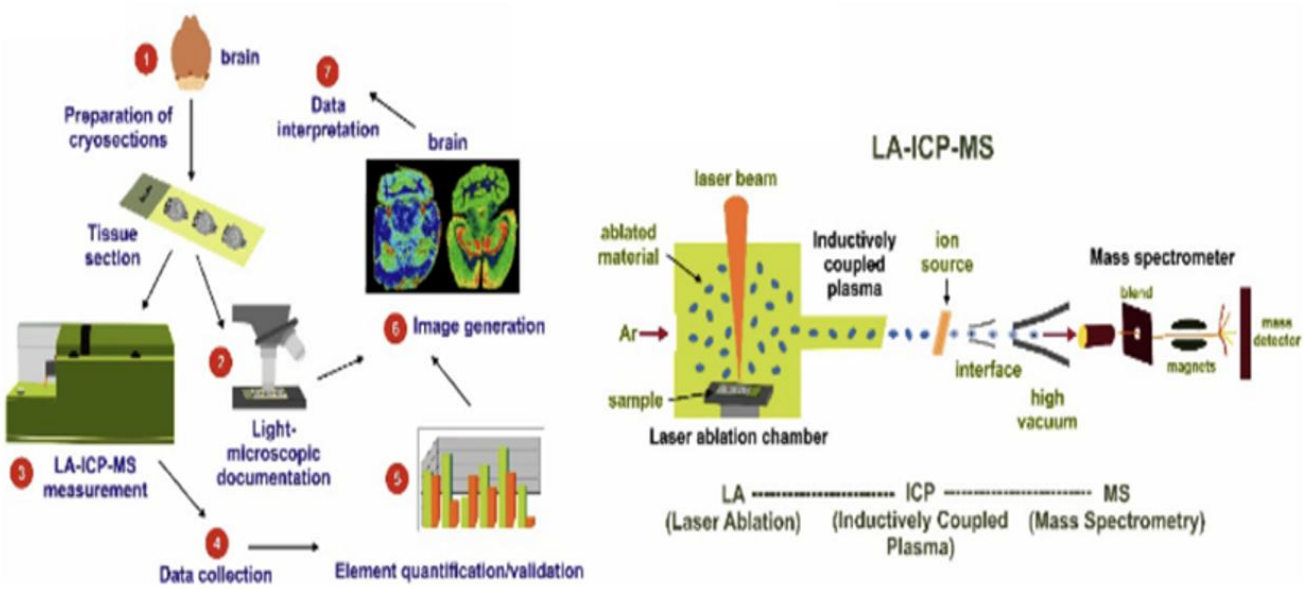

Plate 1 (a and b): Experimental workflow of bioimaging of elements in a brain section leading to a quantitative image: (Adapted from Weiskirchen *et al*., 2019).

In several research experiments, LA-ICP-MS techniques have been adopted to produce standard analytical methods required for data calibration, mostly used in two-dimensional mapping and quantitative assessment of essential trace elements and metals in sections of brain tissue (Becker *et al*., 2003; Becker *et al*., 2005; Zoriy *et al*., 2006; Pickhardt *et al*., 2006). In another follow up study, LA-ICP-MS was employed to reproduce series of quantitative data and images of Zn, Cu and Pb distribution in a numbers of measurements on adjacent sections and several other representative brain regions such as insula, central cortex and hippocampus from rat brain (Dobrowolska *et al*., 2008)

LA-ICP-MS Bio-imaging in Aging study: Metal dyshomeostasis or mis-regulation play essential role in brain aging and neurodegenerative disorders, in the context of ageing, complimentary potential of LA-ICP-MS with immunohistochemistry and autoradiography was used to study age related changes in copper distribution and the activities of cytoplasmic Cu-SOD in the brain of young (2-months), (7-9 months) and aged mouse (14-months). The analysis showed a progressive depletion of copper concentration, noticeable in the striatum and ventral cortex in the aged brain relative to the young brains, the regions with reduced Cu concentration also corresponded to the brain regions with reduced cytoplasmic Cu-SOD contents in the aged mouse. They concluded that decreased Cu content and SOD level may contribute to vulnerability of the aged brain to oxidative damage and neurodegeneration (Wang et al., 2010). In an additional study LA-ICP-MS bioimaging was employed to study the relative distribution of metals (Zn and Cu) in the brain of young (2-months) and old (14-months) mice. The analysis revealed massive accumulation of iron in the substantial nigra, the thalamus and the hippocampal CA 1 region of the older brain when compared to the young brain, while the zinc concentration largely appeared constant. This indicates that cerebral iron accumulation with age may contribute to age related neurodegeneration since iron catalyzes the formation of ROS; zinc enrichment observed in hippocampal CA3 of the young mice indicated the role of zinc in synaptic transmission (Becker *et al*., 2010).

Application of LA-ICP-MS in detecting brain metal dyshomeostasis

Bioavailability of essential trace metal is needed for normal brain function. However, abnormal distribution can influence several biochemical pathways in different fields of metabolism and cause characteristic neurological diseases (Hare *et al*., 2017). Involvement of metals in several neurophysiological and neuropathological events has prompted the study of their bio-distribution In most neurodegenerative disorders, the disease process is strongly linked with abnormal metal accumulations, with several evidences correlating aberrant metal deposition and neurodegeneration (Frederickson et al., 2004; Szewczyk *et al*., 2013; Portbury and Adlard, 2017). Metal overload or deficiency sometimes may result from usage of metal containing drugs such as lithium compounds or cisplatin as a cytostatic drug against some neurological conditions like depression and epilepsy or depletion of metal from therapy to reduce oxidative stress (e.g. in brain after stroke). Quantitative metal bio-imaging is therefore essential for the determination of proper brain function and prevention of certain neurological diseases. This field has therefore provided a unique understanding of brain biochemical architecture linking neuroanatomy, metal mediated processes, changes in metal homeostasis and disease formation (Hare *et al*., 2010; Grochowski *et al*., 2019).

In a study conducted by Boaru *et al*. (2014), (Plate .2) LA-ICP-MS was used to investigate cerebral metal accumulation in the brains of 10-24 months old ATP7B deficient mice, (animal model of experimental Wilson disease) and age matched wild types. Brain sections obtained from the respective animals were comparatively assessed for the multi-elemental distribution of Na, P, Mn, Fe, Cu and Zn. The analysis revealed insignificant difference in the level of Na and P, however, there was an

increased accumulation of Cu throughout the brain parenchyma but reduced deposition in the periventricular region, noticeable from 11 months of age. Also observed was upregulation of Zn concentration in brain regions with copper enrichment while Fe and Mn concentration remained relatively constant. Excessive Cu accumulation in specialized brain area of the ATP7B null mice is indicative of cognitive impairment and the deposition may be due to differential regional affinity to Cu within the brain. The reduced copper accumulation in the perivascular region is in line with the view that the perivascular region is an efflux compartment with low copper contents due to active transportation of Cu into CSF.

In another experiment, Matusch *et al*. (2010), studied multi-elemental distribution in the brain of mice sub-chronically intoxicated with MPTTP as a model for Parkinson's disease, 2 h, 7 d and 28 d post treatments, respective animals were sacrificed and subjected to investigation. The result showed massive depletion of Cu at the periventricular zone and fascia dentate at 2 h, 7 d. A recovery effect was observed at 28d post injury, indicated by increase in Cu concentration in affected brain regions. Also observed was an increase in Fe concentration in interpeduncular nucleus, but not in the substantia nigra, while the level of Zn and Mn were similar to that of the control. However, the level of C, P, and S. remained relatively unchanged at all the time points of treatment. This result confirmed the differential Cu and Fe regulation as well as their roles in Parkinson's disease.

Uerling *et al*. (2018) used LA-ICP-MS imaging to detect beneficial effect of adeno-associated virus (AAV) gene therapy to correct Cu dyshomeostasis using a mouse model of Wilson' disease (ATP7B transgenic mouse and untreated litter mates). After 14 weeks of treatment with AAV-AAT-co-miATP7B therapeutic agent, animals were sacrificed and together with the untreated litter mates were subjected to investigation. The result revealed marked reduction in the level of Cu in some brain regions including the cerebellar cortex, cerebellar white tract, corpus callosum, 3rd and 4th ventricles, and basal ganglia of the treated transgenic mice when compared with the untreated litter mates.

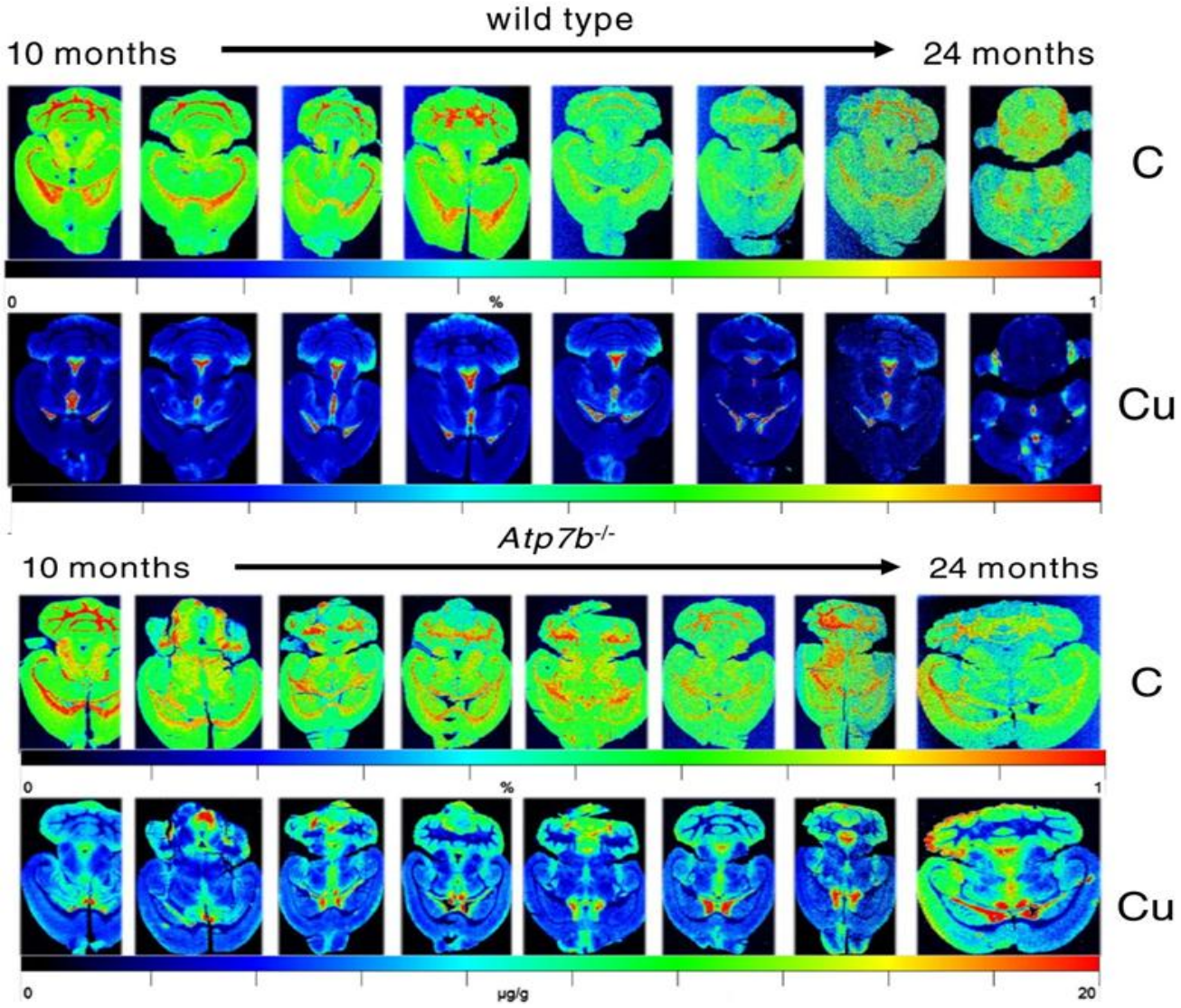

Plate 2:
Comparative assessment of Age-dependent cerebral copper accumulation (10-24 months) in Atp7b deficient mice and age-matched wild type as demonstrated by LA-ICP-MS. (Boaru *et al*., 2014).

Also observed was an unaltered content and distribution of other elements such as the Fe, Zn, Mn and Mg. The study suggested AAV gene therapy as an effective therapy for the treatment of cerebral copper overload in Wilson disease

A further advance of application of LA-ICP-MS in the study of neurodegenerative diseases was seen in a research conducted by Hutchinson *et al.* (2005) who employed the combination of LA-ICP-MS imaging and metal immunolabelling for the detection of β-amyloid distribution in the brain of aged TASTPM transgenic mice (model for Alzheimer) previously tagged with metal (europium) labeled secondary antibodies. The study detected a correlation between the β-amyloid deposits and the trace element content in the brain, this has provided a new insight into the study of metal tagged antibodies for imaging protein distribution one of such is seen in a study to detect neuronal susceptibility to pathological changes observed in Parkinsonism. In the study the effect of 6-hydroxydopamine (6-OHDA) neurotoxin on iron level and dopamine distribution is investigated in a wild-type C57BL/6 mouse by using antibodies previously tagged with gold particles (Hare *et al*., 2014; Ayton *et al.*, 2015).

Another innovative application of LA-ICP-MS is employed in the identification of metals complexed with proteins (metalloproteins) such as phosphoproteins. The combination of LA-ICP-MS technique with proteome analysis through advanced biomolecular mass spectrometry techniques such as electrospray ionization mass spectrometry (ESI-MS) or Matrix-assisted laser desorption/ionization- mass spectrometry (MALDI) has provided a new opportunity for the identification of the detailed structure of metals bound to proteins (metal protein complexes) as well as detection of protein modification associated with several pathophysiological processes (Becker *et al*., 2010). An example of such is employed in the study of protein expression in animal model of Parkinson's disease unilaterally injected with 6-hydroxydopamine, the study revealed accelerated protein acetylation with changes in the striatum protein concentration in dopamine depleted animal when compared with the controls (Pierson *et al*., 2004). It is also useful in the identification of Zn-containing protein such as ATP synthase b-chain identification- in an Alzheimer's brain sample (Becker *et al*., 2006). In another interesting application by the Julich group, pulse from LA-ICP-MS was used for the identification of protein containing Cu, Zn and Fe in human brain tissue (Becker *et al*., 2005).

LA-ICP-MS Bio-imaging in toxic metal study; LA-ICP-MS imaging has also proven to be useful in toxicological study; toxic metals have no functional role in normal brain homeostasis but gradually accumulate in the brain tissue to elicit severe damage leading to chronic degenerative diseases. Lead (Pb) and other divalent cations have been shown to be involved in the damage of calcium- channel proteins which affect neuronal axons and synaptic release of neuro-transmitter (Marchetti, 2003), Pb and Mn have also been implicated in amyloid plaque aggregation (Yegambaram et al., 2015). The knowledge of toxic metal distribution in the brain is essential in both health and medical research where it provide relevant information needed for the study of pathophysiology and potential therapeutic treatment, In a recent study LA-ICP-MS imaging was used to show the distribution of Lead (Pb) and Uranium (U) in human glioblastoma multiform brain tumour (Zoriy *et al*., 2006), Berker *et al.* (2008) also used laser imaging to study the distribution of Uranium and Neodymium in post mortem rat brain tissue previously treated with these metals . The study showed high affinity of Uranium and neodymium for white matter fibres in contrast to its low binding with the grey matter as well as higher binding of these metals to the striatum than the cortex. This result is suggestive of myelinotoxic effect of these metals on the white tract and striatum neurons.

A time-course study (Plate 3) also used LA-ICP-MS imaging to study the distribution of vanadium metal a neuro-toxicant in the brain of mice following chronic exposure. The mass spectrometric analysis revealed gradual influx and accumulation of vanadium metal in several brain regions with an affinity for the olfactory bulb, brain stem and cerebellum and progressive clearance from the brain after withdrawal from the initial exposure. However, the molecular pathway involved in its clearance is unknown and needs to be further investigated. The author concluded that the brain regions with higher vanadium deposition correspond to the regions where distinct pathologies have been earlier reported in the literature (Folarin *et al*., 2017).

LA-ICP-MS bio-imaging in Neurodegenerative diseases and brain lesions: The use of LA-ICP-MS imaging techniques has been employed in the study of metal and elemental dyshomeostasis, diseases pathogenesis and the potential treatment of metal associated neurodegenerative diseases such as Alzheimer's, Parkinson's and Wilson's diseases (Berker *et al*., 2010). In an attempt to provide a novel approach for the assessment of white and grey matter iron accumulation in Alzheimer's diseases, a pilot study was conducted using LA-ICP-MS for the comparative analysis of white and grey matter iron level in an AD brain and control subject. The study detected intrusion of iron into grey matter of Alzheimer's brain when compared with the control. Upregulation of iron level observed in grey matter of the AD brain may be indicative of dysregulated iron homeostasis in vulnerable brain region or inflammatory response to chronic neurodegeneration (Hare *et al*., 2016).
LA-ICP-MS bio imaging techniques has a wide application in the study for detecting metal dyshomeostasis in brain lesions. In 2005, Becker and colleagues first conducted brain tumour study by using LA-ICP-MS for quantitative imaging and spatial distribution of copper, zinc, phosphorus and sulfur in the brain of rat (F344 Fisher rat) injected with F98 giloblastoma cells; the study demonstrated an association between the selected metals and the brain tumour growth. In another experiment by Becker and Salber, (2010), LA-ICP-MS bio-imaging was combined with immuno-histochemical and autoradiographic techniques to study elemental distribution and response of several brain cells to brain thrombosis induced by intense light, using a rat model for stroke. Result revealed massive accumulation of metals (iron, zinc and copper) at the thrombotic lesion as well as reactive gliosis and active neurogenesis at the region surrounding the lesion site.

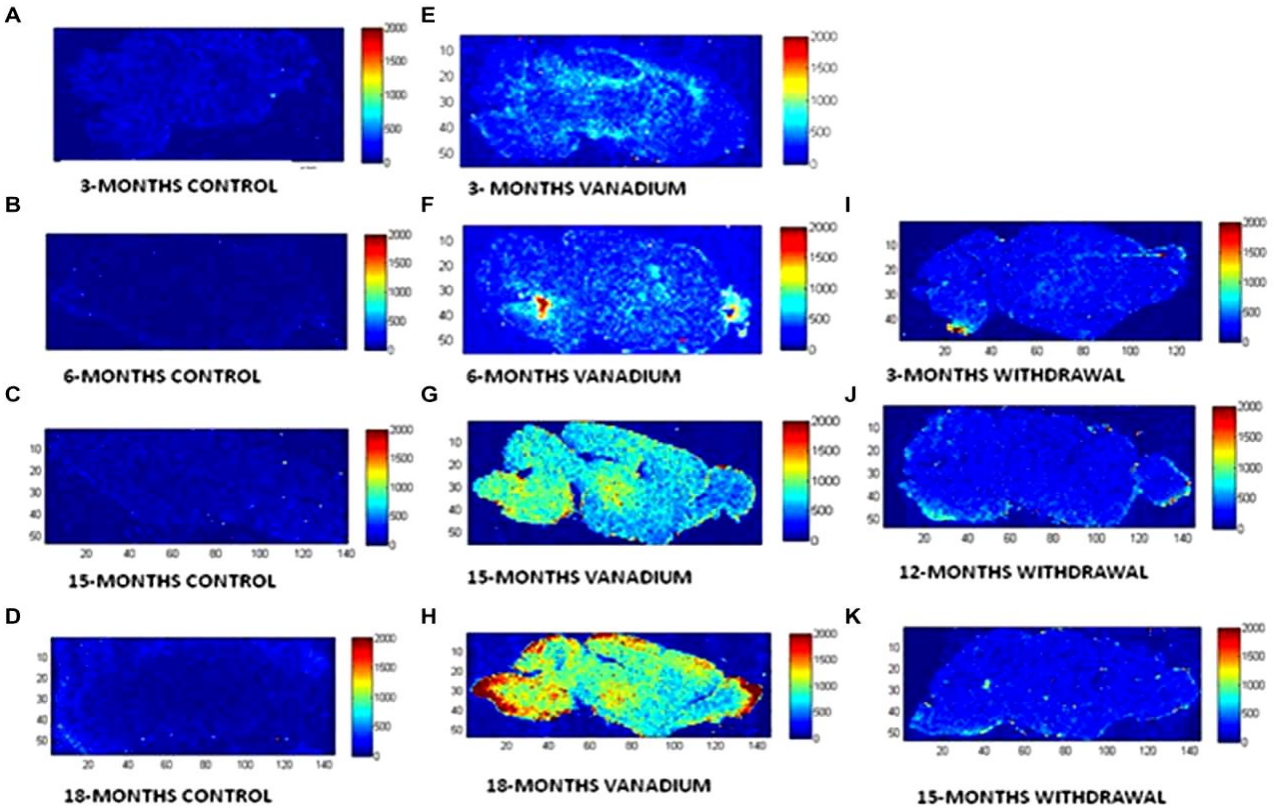

Plate 3:
Laser ablation-inductively coupled plasma-mass spectrometry (LA–ICP–MS) revealed the regional distribution and clearance of vanadium metal from mouse brain after chronic exposure and withdrawal from the initial exposure. (Folarin *et al.*, 2017).

A follow up study was also conducted by Zoriy *et al.* (2006) to examine the level of Zn, Pb and U in human glioblastoma Multiform brain sections. This study employed the complementary potential of LA-ICP-MS brain imaging and autoradiography imaging technique. Additional study by Becker *et al.* (2005) on small-sized brain tumors, also detected mark depletions of Cu and Zn around the tumor area indicating the pathophysiological role of these element in the tumour growth. Further study on comparative imaging of P, S, Fe, Cu, Zn and C was conducted by Zoriy *et al.* (2007) on thin sections of rat brain tumour, the analysis detected the relationship between the tumour boundaries and the regional elemental concentration and distribution.

LA-ICP-MS Bio-imaging in other neurological diseases: Application of LA-ICP-MS bio-imaging is also extended to the study of non neurodegenerative disorders. In an experiment using a mouse model of hypoxia, LA-ICP-MS imaging revealed massive accumulation of cobalt in the exposed brains when compared with the control, the elevated cobalt concentration strongly correlated with endoplasmic reticulum stress, myelin loss, axonal injury as well as vitamin B12 enrichment of the brain (Veasey *et al.*, 2013). Also using mouse model of traumatic brain injury LA-ICP-MS imaging of mouse brain subjected to a controlled cortical impact revealed immediate increase in the level of iron, copper and zinc which was extended till 28-days post injury (Portbury *et al.*, 2016). In another experiment, using animal model of post-traumatic stress disorder, changes in the zinc concentration and dyshomeostasis were detected using LA-ICP-MS bio-imaging. The result showed massive accumulation of Zn in the hippocampus and dentate gyrus of the stress exposed brains relative to the control, stress induced zinc accumulation in the hippocampus could be responsible for the physiological and behavioral deficit observed in this disorder (Sela *et al.*, 2017). LA-ICP-MS imaging of metals in the spinal cord has provided a new insight in the study of pathogenesis and development of target drugs for treating motor disorders such as amyotrophic lateral sclerosis (Robert *et al.*, 2014).

Conclusions and Perspectives: Over the years, LA-ICP-MS bio-imaging technique has gained global recognition and has been consistently employed in different areas of brain research due to its numerous outstanding features when compared with other metal bio-imaging methods. In addition, large list of recent references cited in this review has confirmed the wide application of LA-ICP-MS in several metal bio-imaging researches. Despite its wide use, LA-ICP-MS technique still has a major limitation with respect to calibration, which prevents it from being a front line analytical technique for achieving fast, precise and sensitive metal quantification. The following are the concluding remarks:

1. Sample preparation is a fundamental issue that must be highly considered when designing new experiments. Appropriate protocol must be put in place to prevent leaching of metal ions from brain sections that may likely occur during tissue storage and preparation

2. Formalin fixation a crucial process in any histochemical staining protocol usually results in chemical alteration as well as marked redistribution of trace element and metals in cut tissue section. This change may alter accurate interpretation of imaging data. Further study is needed to evaluate the likely effect of sample preparation on metal distribution; minimal sample handling is also recommended to avoid the chance of chemical alteration in the brain tissue.
3. Preparation of appropriate biological standard for matrix analysis and better understanding of fractionation and matrix effect is required for effective LA- ICP-MS bio-imaging analysis.
4. Comparative analysis of imaging data obtained from LA-ICP-MS technique and other metal bio- imaging method such as a synchrotron-based X-ray fluorescence microscopy (XFM) could improve data accuracy.
5. The study of cellular organelles and their biochemical processes could be enhanced by using higher spatial resolution instrument such as laser microdissection inductively coupled plasma mass spectrophotometry (LMD ICP-MS).
6. Complimentary potential of LA-ICP-MS bio-imaging techniques with other established biomedical imaging techniques such as magnetic resonance imaging (MRI) and metallomics has allowed for identification, quantification and better knowledge of the essential role of metalloproteins in health and in the pathophysiology of several neurological diseases.

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