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Volumetric, Neurochemical and Oxidative Implication of Neurological Disorders: A Focus on Subcortical, Frontal and Occipital Regions

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Abstract*— The human brain utilizes a large amount of oxygen, a requirement it avails via oxidative phosphorylation. With an imbalance in the required and utilized oxygen levels, the brain's environment undergoes the formation of reactive oxygen species (ROS), which are free radicals containing oxygen such as superoxide ($O_2^{\cdot-}$) and hydroxyl radical (·OH). The glutathione (GSH) antioxidant system plays a major role in modulating the ROS levels. If there is a depletion in GSH concentration, the ROS levels increase due to which the brain experiences stresses arising from metabolic dysregulation, cell apoptosis, protein aggregation and neurotransmitter and neurochemical connection impairment. Due to these stresses, neurological disorders may arise and result in attributes such as anatomical atrophies, and progressive neuronal cell apoptosis that may have roots in molecular and neurochemical level imbalances. The repercussions can be seen in the form of deficits encompassing, pyramidal or extra-pyramidal symptoms, cognitive decline, emotional processing dysfunction, visual and auditory hallucinations, and fear triggering common to brain disorders. A structural and neurochemical analysis with the aid of neuroimaging modalities can help in the new age theragnostic approach of brain disorder study and treatment.

***Index Terms*— Glutathione, Reactive Oxygen Species, MRS, Neurochemicals, Subcortical regions, Cognition, Volumetric atrophies**

I. INTRODUCTION

The brain is considered as the central functional unit of the human body, how then is the body impacted when this functional unit disfunctions? The answer is a steep deterioration in lifestyle and livelihood(Ayeni et al., 2022). This dysfunction has been seen in the form of neurological disorders, a few listed in Figure1, such as Alzheimer's Disease (AD), Parkinson's Disease (PD), bipolar disorder (BD), and epilepsy. The central nervous system (CNS) in brain disorders is characterised with neuronal cell apoptosis resulting in the cutting of the connection between neurons(Gorman, 2008), deficits in intellect, motor activity and social (Mullin et al., 2013), cognitive and emotional behaviour of an individual(Ladea et al., 2012). Recent studies are looking at the origin of the degradation observed in neurological disorders in the activity of neurochemicals (dopamine, glutamine, glutamate, N-Acetylaspartic acid(NAA))(Teleanu et al., 2022), antioxidants (glutathione (GSH))(Mandal et al., 2022), proteins (β amyloid peptides)(Sun et al., 2015) and stresses (metabolic, oxidative, chronic)(Salim, 2014). How is this multilevel research carried out? It is done by taking a multimodal approach which involves neuroimaging modalities such as magnetic resonance imaging (MRI) which help in the structural study of the anatomical region(Seiler et al., 2021), MR spectroscopy (MRS) which aids in quantifying the neurochemicals to check for any alterations(Lee et al., 2012), functional MRI (fMRI) detects the metabolic activities that are brought about by tasks that the brain carries out(Auer et al., 2008).

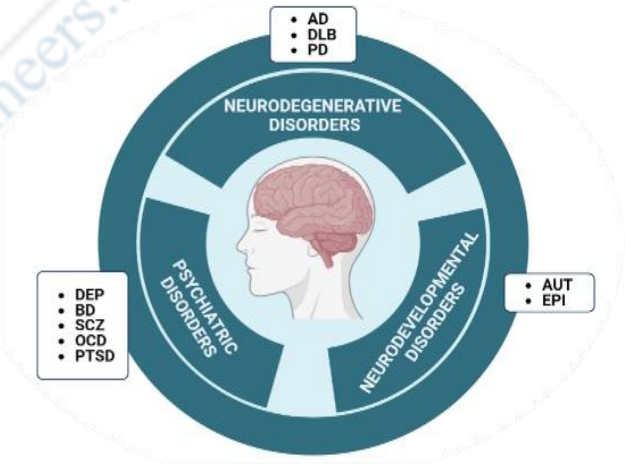

Figure1: The figure highlights the various neurological disorders, neurodegenerative disorder, neurodevelopmental disorder and psychiatric disorder and the disorders under them that are analysed in the article. (Abbreviations: AD-Alzheimer's Disease, DLB-Dementia with Lewy Body, PD- Parkinson's Disease, ASD-Autism Spectrum Disorder, EPI-Epilepsy, DEP-Depression, BD-Bipolar Disorder, SCZ-Schizophrenia, OCD-Obsessive Compulsive Disorder, ANX-Anxiety, PTSD-Post Traumatic Stress Disorder). Figure has been created with BioRender.com.

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II. GLUTATHIONE: AN ANTIOXIDANT WITH IMPLICATION

Glutathione is an antioxidant synthesised in the cytosol of the cell. It can be found in two forms, oxidised as glutathione disulphide (GSSG), and reduced as GSH. Its primary form is the GSH, a tripeptide which is made up of the essential amino acids, glutamic acid, cysteine, and glycine(Mandal et al., 2023). A GSH molecule is formed when cysteine and glutamic acid combine with the aid of glutamate cysteine ligase to form γ-glutamylsyteine which combines with glycine with the help of glutathione synthase to give GSH as the product. In the reduced form, as GSH, glutathione functions as an antioxidant by maintaining redox balance by consuming any radicals and oxygen species which also aids in repairing any DNA damage, works with neurotransmitters and helps cell signalling as it has binding sites for glutamate receptors. The enzyme glutathione reductase helps in generation of the reduced form GSH from its oxidised GSSG form(Iskusnykh et al., 2022). Changes in GSH concentration in some anatomical areas vary according to its availability there. For instance, in the brain the cortex, hippocampus and cerebellum have a higher concentration of GSH in comparison with substantia nigra(Aoyama and Nakaki, 2013). Alteration in the GSH concentration within the region associated with neurological disorders have been observed in 1) psychiatric disorders(schizophrenia, bipolar spectrum disorder, MDD)(Gawryluk et al., 2011), 2) neurodegenerative disorders (Alzheimer's disease, Parkinson's disease)(Aoyama and Nakaki, 2013), 3) neurodevelopmental disorders(ASD, epilepsy)(Bjørklund et al., 2020, Mueller et al., 2001). Via the glutamate receptor of the brain the amino acids which make up the GSH molecule can hinder with signalling between the neurons, which is the cause behind the psychiatric symptoms associated with neurological disorder(Iskusnykh et al., 2022). To keep track of the GSH, and other neurochemical concentration in the different region in various disorders, a spectral peak obtained with the help of magnetic resonance spectroscopy can be quantized via processing(Bottino et al., 2021) through image and data acquisition methods via MRI and MRS as depicted in Figure2.

III. NEUROCHEMICAL AND STRUCTURAL ALTERATIONS IN FRONTAL AND OCCIPITAL BRAIN REGIONS IN BRAIN DISORDERS

a) Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex (DLPFC) region is present in the dorsal portion of the pre-frontal cortex. It forms network with the regions found in the cortical and subcortical regions, which helps, in modulating action and goal directed behaviour and spatial processing(Goldman-Rakic, 1988). DLPFC is also involved in accessing the pleasantness or unpleasantness we associate with an emotional experience (Nejati et al., 2021) showing its involvement in cognition and executive functions such as self-control and planning. Anatomically patients with major depressive disorder (MDD) have shown asymmetry in structure, function, and metabolism in the two hemispheres of DLPFC. This analysed asymmetry and volumetric loss increases with the severity of the depressive symptoms(Liu et al., 2016). Because of its involvement in emotional processing any alterations within it affect the ability of MDD patients to tackle negative emotions (Pulcu et al., 2013). As the earliest structural sign, autism spectrum disorder (ASD), a neurodevelopmental disorder shows an enlarged prefrontal cortex(Hazlett et al., 2011). While in obsessive compulsive disorder (OCD) patients as compared with healthy controls a thinning of the DLPFC region can be observed(Fouche et al., 2017).If discussing neurochemical changes in the DLPFC in neurological disorder a reduction in the NAA levels has been found in DLPFC of adolescents who have been diagnosed with bipolar disorder (BD) or whose parent has a history of it(Chang et al., 2003)and people in their manic stage (Winsberg et al., 2000). N-Acetylaspartic acid(NAA), is a regulator of osmoregulation and nitrogen balance within the brain. This NAA reduction may have a degradative effect on the neuronal function and may indicate at atrophy and malfunctioning of the neurons of the affected area(Moffett et al., 2007). Other neurochemicals such as glutamate also show changes such as a reducing trend in OCD patients (Karthik et al., 2020), it is a chemical which helps the CNS adapt to the stressors and provides the ability of neuroplasticity, while an increase in the levels of myoinositol(Yue et al., 2021), which maintains the osmotic balance in the plasma membrane of glial cells can be seen at the DLPFC region. The antioxidant GSH show a reducing trend in the neurodegenerative disorder AD within the frontal cortex region(Mandal et al., 2015). The pathological protein based contributor to the mentioned depletion of GSH in AD can be the characteristic amyloid beta and neurofibrillary tangles which lead to a rise in oxidative stress(Haass and Selkoe, 2007). The reduction in the GSH levels within the prefrontal region is also characteristic of psychiatric conditions such as schizophrenia, depression, and bipolar disorder, which leads to the damages that the resultant oxidative stress cause(Gawryluk et al., 2011).

b) Primary Visual Cortex

The primary visual cortex (PVC) is a posteriorly situated cortex found in the occipital lobe of the brain. The visual cortex is involved in receiving, merging, and organising the visuals received by the retina(Tran et al., 2019). The visual cortex specifically responds to colour, frequency, orientational and directional signals of edges and lines(Johnson et al., 2008). After the organisation and processing of the visual information at the PVC, the information is relayed to the other parts of the brain for recognition(Gupta et al., 2023). The patients of DLB experience which have been seen to be related to the change in blood flow, synaptic transmission, cell signalling and metabolism alteration in the primary visual

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cortex(PVC)(Erskine et al., 2019). This change in the PVC often lead to individuals not being able to correctly identify and perceive the objects viewed, which may be due to the reduced visual clarity common to dementia with Lewy bodies (DLB)(Mosimann et al., 2004). Another neurological disorder which shows changes in the PVC is epilepsy, where patients undergo seizures, as a result of which it has been observed that their brain GSH levels also undergo reduction around the occipital region(Mueller et al., 2001).

IV. NEUROCHEMICAL AND STRUCTURAL ALTERATION IN SUBCORTICAL BRAIN REGION IN BRAIN DISORDERS

a) Hippocampus

The hippocampus (HP) is found in the temporal region of the brain and makes up the posterior part of the limbic lobe. It is a subcortical region responsible for traits like memory, motivation, pain, imagination, spatial navigation, and pleasure(Anand and Dhikav, 2012). The hippocampus, faces a lot of neuronal cell loss in AD, leading to dysfunction of the synaptic association(Terry et al., 1991) and accumulation of neurofibrillary tangles, which are a result of tau protein increase. The atrophy due to the neuronal cell loss and reduced synaptic density in the hippocampus can be correlated with AD progression(McRae-McKee et al., 2019). In another neurodegenerative disorder, PD, the values obtained via Quantitative Susceptibility Mapping (QSM), a neuroimaging technique, used for quantifying the spatial distribution of magnetic susceptibility within biological tissues, such as those in hippocampus helps in tracking non-motor symptom severity of PD patients and correlate them with scores, such as high iron susceptibility of hippocampus correlating with lowering of cognition. An intermediate structural atrophy in the hippocampus of the DLB patients can also be observed and can be correlated with cognitive decline which can be observed in the form of attentional deficit(Elder et al., 2017). Some studies have correlated the atrophy rate of the hippocampus with the duration of the survival of the DLB patient, with the lower rate correlating with higher atrophy(Graff-Radford et al., 2016). In epileptic patients, the hippocampus, show a loss in grey matter and structural atrophy due to the seizures that occur (Bonilha et al., 2007). These changes combinedly show issues with recollection, attention, and verbal communication of epileptic patients. The reduction in the volume of hippocampus has also been seen in patients with depression and is often seen as an indicator of relapses (Kronmüller et al., 2008). Another psychiatric disorder, schizophrenia utilises the volumetric shrinkage of the hippocampus, as observed in MRI, as an indicator in first episode patients (Bogerts et al., 1990). The changes in the anatomy and function of hippocampus can be because of disturbances in the neurons that project towards it (Anand and Dhikav, 2012). Another factor can be reduction in N-acetylaspartate (NAA) metabolite levels, which function as an indicator of the feasibility of the neurons of a region. As a region involved in negative feedback for inhibitory control on stress response, hippocampus has shown changes in anxiety disorders, in the form of volumetric and neuronal cell loss(Martin et al., 2009). The antioxidant GSH levels within the hippocampal region has shown reduction in AD patients when compared with healthy controls, this reduction can even be traced in mild cognitive impairment (MCI) patients, a preclinical stage of AD(Mandal et al., 2015). While BD patients also show a similar trend in hippocampus, the gene responsible for enzymes involved in GSH synthesis such as glutathione peroxidase, show a lowered expression(Benes et al., 2006)within the region.

b) Substantia Nigra

Substantia Nigra (SN) is situated in the midbrain region, it is one of five the nuclei of basal ganglia and is also its primary input (Young et al., 2023). It is source from which the nerves regulating dopamine originate towards the cerebral hemisphere. The neurotransmitter dopamine produced at the SN is involved in cognitive activities such as the prediction of rewards and errors as a result of an action. The dopamine production responsible region of the SN, substantia nigra's (SN) pars compacta face the issue of neuronal loss in PD pathology. SN with its involvement in motor function, becomes one of the target regions along with cerebellum to be studied and analysed in PD(Sonne et al., 2023). QSM results have also shown traces of iron deposition in the SN of PD patients by employing region of interest and voxel-based study via MRS. Patients with DLB too, show a loss of neurons in this nigrostriatal region. This can be observed in the form of pigmentation loss in the substantia nigra(Wulf et al., 2022). Another region of the SN substantia nigra pars reticulata (SNR) shows damage in epileptic patients. It has been proposed that stimulating the SNR can help regulate the seizures(Inamura et al., 1989), as dopamine, a common neurotransmitter of the SN may have a controlling effect on them. The oxidative stress common to neurodegenerative disorders such as PD can be observed in the form of decrease in the concentration of the GSH levels within the SN. This is observed after the neurons responsible for dopamine production show degeneration(Smeyne and Smeyne, 2013). Another disorder which shows a root in dopamine dysfunction in the SN region is MDD. This is because the sense of loss of pleasure and interest in activities, which is common to depression, can be a result of the lowering of dopamine function, a neurotransmitter responsible for behaviour modulation(Nutt, 2006).

c) Amygdala

The amygdala (AMY) is an almond shaped region found in the temporal lobe of the brain (Ressler, 2010). It plays a role in emotional processing, regulation, and inhibition in domains such as memory, learning, attention, social behaviour, and influence. In fear conditioning, which is a type of emotional learning, the amygdala uses a stimulus from an event and convert it to a defensive behaviour or a

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physiological response(Phelps and LeDoux, 2005). As the earliest structural sign, autism spectrum disorder(ASD), a neurodevelopmental disorder shows an enlarged amygdala(Nordahl et al., 2012), in the post-natal stage. This may be seen in the form of increase head size in children and with its involvement in social behaviour the abnormal amygdala size results in impaired social behaviour of ASD patients. If we talk about effect of amygdala in psychiatric disorder such as major depressive disorder (MDD), there have been reports of an increase in its activation in response to stimulus(Sheline et al., 2001) and response duration to negative stimuli(Stephanou et al., 2017). The amygdala, a region responsible for emotional control has been one of the regions studied in psychiatric disorders. For instance, a study between healthy and bipolar patients, an enlargement in size of amygdala has been observed(Strakowski et al., 1999). The subcortical region, amygdala also plays a role in facial recognition and familiarising this facial expression recognition has been shown to be impaired in people with schizophrenia(Kohler et al., 2010, Haxby et al., 2002). In post-traumatic stress disorder (PTSD) patients the amygdala shows increased activation in comparison of healthy control when exposed to trauma triggering words and pictures(Ressler, 2010). This can be correlated with amygdala's involvement in generation of memories associated with fear for future retrieval(Sun et al., 2020). The amygdala's association with the DLPFC for functions such as attention to stimuli and emotions such as fear often shows impairment in the depressive phase of anxiety disorder patients(Rauch et al., 2000).

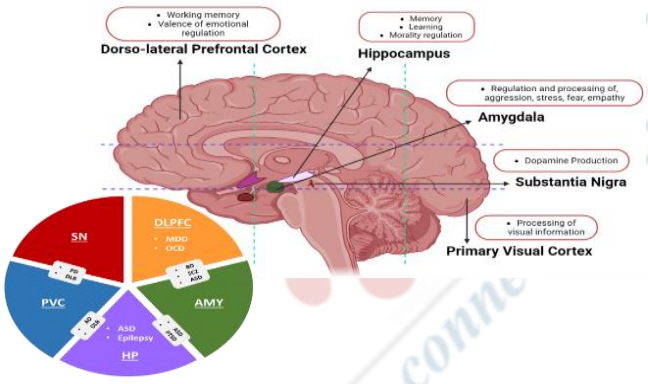

Figure3: Diagrammatic representation of the position of the five areas of interest, DLPFC(dorsolateral prefrontal cortex), HP(hippocampus), AMY(amygdala), SN(substantia nigra,) PVC(primary visual cortex), with a mention of their function and disorders (MDD: major depressive disorder, OCD: obsessive compulsive disorder, BD: bipolar disorder, SCZ: schizophrenia, ASD: autism spectrum disorder, PTSD: post-traumatic stress disorder, DLB: dementia with Lewy body, AD: Alzheimer's disease, PD: Parkinson's disease) associated with any abnormality within one or more of the mentioned regions. Figure has been created with BioRender.com.

V. CONCLUSION

The neurons of the central nervous system (CNS) undergo oxidative phosphorylation to keep up with the high oxygen demand of the brain. Any imbalance in the redox equilibrium within the CNS sends the antioxidant glutathione into action to keep the risen amount of reactive oxygen species (ROS), which are the free radicals, under check. If left unchecked the risen species may lead to degeneration such as cell apoptosis, metabolic dysfunction, protein aggregation, anatomical atrophies, motor irregularities, molecular alterations, behavioural and cognitive deficits. These alterations form the basis of neurological disorders, which affects an individuals' lifestyle. Studies encompassing neuroimaging such as MRI and MRS can help obtain a structural and neurochemical profile of an individual helping us analyse the changes that occur within the brain during the brain disorders and the treatment that can follow after. We present this review paper with the hope of it forming a baseline study into the milestone of theragnostic approach to brain disorders.

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