White Matter Abnormalities in Different Neurodevelopmental Psychiatric Disorders

Essay
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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
ورَسُولُهُ والْمُؤْمِنُونَ

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List of Abbreviations

Abb.	Meaning
ACC	Anterior Cingulate
ADC	Apparent Diffusion Coefficient
ADHD	Attention Deficit Hyperactivity Disorder
ARND	Alcohol-Related Neurodevelopmental Disorder
BD	Bipolar Disorder
CADASIL	Cerebral Autosomal Dominant Arteriopathy With Subcorticial Infarcts And Leukoencephalopathy
CC	Corpus Callosum
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CY-BOCS	The children'syale- Brown obsessive- compulsive scale.
DSM-IV:	Diagnostic and statistical manual of mental disorders IV
DTI	Diffusion Tensor Imaging
EOS	Early-Onset Schizophrenia
FA	Fractional Anisotropy
FLAIR	Fluid-Attenuated Inversion Recovery
GM	Gray Matter
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
MTR	Magnetization Transfer Ratio
NMDA	N-methyl – D- aspartate
OCD	Obsessive–Compulsive Disorder
OFC	Orbitofrontal Cortex
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
PET	Positron Emission Tomography
PKU	Phenylketonuria
ROI	Region-Of-Interest
SCZ	Schizophrenia
sgACG	Subgenual Anterior Cingulate Gyrus
VBM	Voxel-Based Morphometry
WM	White Matter
WMH	White Matter Hyper-Intensities

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Introduction

White matter comprises over half the human brain, a far greater proportion than in other animals **(Fields, 2008).**

Only vertebrates have myelin, which greatly increases the speed and power of nervous system function. Recently, unanticipated changes in myelin genes and alterations in white matter structure have been observed in a wide range of psychiatric disorders. Together with new data showing that white matter structure is dynamic and myelin can be regulated by impulse activity, these new findings implicate myelin in cognitive function beyond pathology, and illuminate an underappreciated role of myelin in information processing and learning **(Ishibashi et al., 2006).**

A surprisingly diverse range of psychiatric and nervous system disorders are accompanied by changes in white matter structure or abnormalities in myelin genes. Polymorphisms for several myelin genes have emerged as unexpected risk factors for schizophrenia, depression and obsessive-compulsive disorder. Post mortem examination of brain tissue from patients suffering schizophrenia, major depression and bipolar disorder reveals reduced abundance of several mRNA transcripts of myelin genes or genes regulating differentiation and survival of myelin-forming cells (oligodendrocytes) **(Stewart et al., 2007).**

Neurodevelopmental psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), early-onset schizophrenia (EOS) and major depression, are major causes of severe behavioral and cognitive impairment and social exclusion in childhood which persist into adult life and in some cases become aggravated in adulthood **(Rubia, 2002).**

Complex biological and non-biological mechanisms are thought to underlie neurodevelopmental psychiatric disorders such as environmental adversities, genetic predisposition, the complex interaction between both, neurotransmitter imbalance, and structural and functional brain abnormalities. Evidence exists for close causal interconnections between these different biological and social systems. Specific genetic abnormalities, for example, have been shown to sometimes manifest only in their interaction with specific environmental adversities. Highly complex interactions between all these different potential causal pathways make the understanding of the aetio-pathophysiology of psychiatric disorders extremely difficult **(Bradshaw and Sheppard, 2000).**

Early detection and intervention of neurodevelopmental disorders is crucial to ameliorate the behavioral symptoms, prevent academic mal-achievement and improve social integration. The development of targeted treatment such as pharmacological or behavioral intervention is, however, possible only if the behavioral and anatomical correlates of these disorders are fully understood **(Rubia et al., 2000).**

Investigating normative changes in brain anatomy during childhood is important to understand the substrates of cognitive, behavioral and emotional maturation. Such knowledge may also aid in the assessment of aberrations in developmental trajectories that are associated with increased susceptibility for various cognitive and psychiatric disorders. For instance, alterations in brain morphology are associated with neuropsychiatric (depression, schizophrenia, anxiety disorders) and neurodevelopmental (autism, ADHD) disorders **(Verhoeven et al., 2010).**

Identical brain regions appear to be sensitive to a wide range of developmental abnormalities, in particular prefrontal cortex, parietal lobes, the basal ganglia, thalamus and the cerebellum **(Rubia, 2002).**

However, specific differences between the different psychiatric disorders have emerged in either the development of these brain abnormalities (progressive decline in Schizophrenia, non-progressive changes in Attention Deficit/Hyperactivity Disorder. The exact localization (abnormalities in predominantly orbitofrontal cortex in Paediatric Obsessive-Compulsive Disorder. In inferior prefrontal cortex in Attention Deficiet/Hyperactivity Disorder, in dorsolateral prefrontal cortex in Early-Onset Schizophernia, and in anterior cingulate in Depression. The laterality of abnormalities (predominantly right hemispheric abnormalities in ADHD, bilateral abnormalities in OCD, left predominance of abnormalities in depression and schizophrenia) or the sign of the functional abnormalities (increased fronto-striatal brain activation during symptoms or rest in OCD, reduced frontal-striatal activation in ADHD) **(Rosso et al., 2005).**

Rationale

White matter abnormalities in different neuro-developmental disorders are not yet fully understood. Recent studies show abnormalities in structural and functional connectivity have been reported in autism spectrum disorders across wide range. However, developmental changes in White matter microstructure are poorly understood.

Although, findings of abnormal brain structure and function cannot inform us about the causal pathways of mental disorders, yet it can give us information on which brain regions are correlated with specific behavioral abnormalities. Knowledge of the precise behavioral and biological correlates of the disorder can, however, be used to develop targeted treatment in the form of either behavioral or pharmacological intervention.

Aim of The Work

1. To review the available literature on white matter abnormalities in different neurodevelopmental disorders.
2. To highlight the importance of recent techniques to overview the different abnormalities in white matter.
3. To highlight points in this topic need to be clarified in further researches.

Chapter (1):

Neurodevelopmental disorders and the White Matter

A. Neurodevelopmental disorders in brief:

Introduction :

Neurodevelopmental disorders are impairments of the growth and development of the brain or central nervous system. A narrower use of the term refers to a disorder of brain function that affects emotion, learning ability and memory and that unfolds as the individual grows. The term is sometimes erroneously used as an exclusive synonym for autism and autism spectrum disorders. Neuro developmental disorders are associated with widely varying degrees of difficulty, which may have significant mental, emotional, physical, and economic consequences for individuals, and in turn their families and society in general **(Goldstein and Reynolds, 2010).**

The term used in DSM-V instead of disorder usually first diagnosed in infancy,childhood & or adolescents,include:

- Intellectual disabilities.
- Communication disorders,including stuttering.
- Autism spectrum disorder (ASD).
- Attention deficit hyperactivity disorder (ADHD).
- Specific learning disorder,including dyslexia & mathematical disorder.
- Motor disorders including Tics.
- Others psychiatric disorders of neurodevelopmental theory in etiology including (EOS, OCD &Bipolar disorder).

(American psychiatric association,2013).

Causes :

There are many causes of neurodevelopmental disorder, which can range from deprivation, genetic and metabolic diseases, immune disorders, infectious diseases, nutritional factors, physical trauma, and toxic and environmental factors. Some neurodevelopmental disorders—such as autism and other pervasive developmental disorders—are considered multifactorial syndromes (with many causes but more specific neurodevelopmental manifestation). However, other multifactorial syndromes such as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) are presently thought to have a more specific primary causation as well as a specific neurodevelopmental manifestation **(Samaco et al., 2005).**

1. Deprivation :

Infants and children require loving emotional nurture from caregivers—there is a spectrum of problems arising from the lack of it. The most severe deprivation disorder, hospitalism, was described in 1897 as a wasting away to the point of death **(Crandall, 1897).**

A sublethal form, anaclitic depression was first described by René Spitz in the 1940s. It occurred in infants over the age of six months who suffered the loss of their mothers, who then became depressed and showed behavioral retardation (delay in reaching developmental milestones, especially as related to social behaviors). Behavioral retardation, as in the reactive attachment disorders, has been observed in emotionally deprived children living with their families. However, prominent modern thought attributes other causative mechanisms to autism and autistic spectrum disorders **(Newman and Mares, 2007).**

However, nurture is not the only cause of deprivation that leads to neurodevelopmental sequellae. A common example of sensory deprivation due to biologic factors is blindness. Blind infants are at risk for poor developmental outcomes that if left untreated can lead to severe, autistic-like behaviors. Despite its biologic basis, caregivers can ameliorate blindness-related sensory deprivation.

This can lead to positive neurodevelopmental outcome, as in the cases of author Helen Keller, who was trained in the use of tactile sign language, and musicians such as Arthel "Doc" Watson and Ray Charles who remained emotionally connected to others via their sense of hearing **(Sonksen and Dale, 2002).**

2. Genetic disorders:

A prominent example of a genetically determined neurodevelopmental disorder is Trisomy 21, also known as Down syndrome. This disorder usually results from an extra chromosome 21, although in uncommon instances it is related to other chromosomal abnormalities such as translocation of the genetic material. It is characterized by short stature, epicanthal (eyelid) folds, abnormal fingerprints, and palm prints, heart defects, poor muscle tone (delay of neurological development) and mental retardation (delay of intellectual development) **(National Association for Down Syndrome, 2014).**

Less commonly known genetically determined neurodevelopmental disorders include Fragile X syndrome, Rett syndrome, and Williams syndrome. Fragile X syndrome was first described in 1943 by J.P. Martin and J. Bell, studying persons with family history of sex-linked "mental defects". Rett syndrome, another X-linked disorder, produces severe functional limitations. Williams's syndrome is caused by small deletions of genetic material from chromosome 7 **(Merla et al., 2006).**

3. Immune dysfunction:

Immune reactions during pregnancy, both maternal and of the developing child can produce neurodevelopmental disorders. One typical immune reaction in infants and children is PANDAS, or Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection produce abnormal movements of the body, emotional disturbance and obsessive compulsive disorder symptoms. Another disorder is Sydenham's chorea, which results in more abnormal movements of the body and fewer psychological sequellae. Both are immune reactions against brain tissue that follow infection by Streptococcus bacteria. (Susceptibility to these immune diseases may be genetically determined, so sometimes several family members may suffer from one or both of them following an epidemic of Strep infection) **(Dale et al., 2005).**

4. Infectious diseases:

A number of infectious diseases can be transmitted either congenitally or in early childhood, and can cause serious neurodevelopmental disorders, such as schizophrenia. Congenital toxoplasmosis may result in formation of cysts in the brain and other organs, causing a variety of neurological deficits. Congenital syphilis may progress to neurosyphilis if it remains untreated. Measles can progress to subacute sclerosing panencephalitis. Congenital rubella syndrome can produce schizophrenia in addition to multiple other symptoms **(Pavone et al., 2004).**

5. Metabolic disorders:

Metabolic disorders, present in either the mother or the child, can cause neurodevelopmental disorders. Two examples are diabetes mellitus (a multifactorial disorder) and phenylketonuria (an inborn error of metabolism). Many such inherited diseases may directly affect the child's metabolism

and neural development but less commonly, they can indirectly affect the child during gestation **(Richardson and Ross, 2000).**

In the child, type 1 diabetes can produce neurodevelopmental damage by the effects of excessive or insufficient glucose. The problems continue and may worsen throughout childhood if the diabetes is not well controlled. Type 2 diabetes may be preceded in its onset by impaired cognitive functioning **(Olsson et al., 2008).**

However, a non-diabetic fetus can also be subjected to glucose effects if its mother has undetected gestational diabetes. Maternal diabetes causes excessive birth size, making it harder for the infant to pass through the birth canal without injury or it can directly produce early neurodevelopmental deficits. However usually the neurodevelopmental symptoms decrease in later childhood **(Ornoy et al., 1999).**

Phenylketonuria, also known as PKU is an inborn error of metabolism that can induce neurodevelopmental disorders in children. Children with PKU require a strict diet to prevent mental retardation and other disorders. In the maternal form of PKU, excessive maternal phenylalanine can be absorbed by the fetus even if the fetus has not inherited the disease. This can produce mental retardation and other disorders **(Lee et al., 2005).**

6. Nutrition:

Nutritional deficits may cause neurodevelopmental disorders, such as spina bifida, which is common, and anencephaly, which is rare. Both disorders are neural tube defects with malformation and dysfunction of the nervous system and its supporting structures, leading to serious physical disability as well as its emotional sequellae. The most common nutritional cause of neural tube defects is maternal