Treatment of Neurodevelopmental Disorders:

Targeting Neurobiological Mechanisms.

Edited by Randi Hagerman and Robert Hendren, Oxford University Publication, 2014

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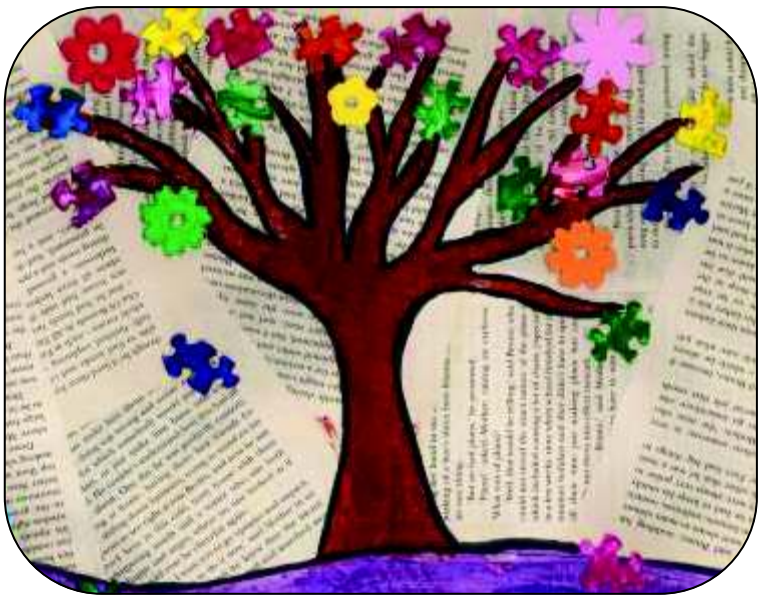
Randi Hagerman is a regular visitor to Australia and has an international reputation as a clinician, researcher and lecturer in the Fragile X field. This book represents a new phase in her career as the director of the MIND Institute at the University of California Davis. As such it represents a new frontier in approaches to and research in developmental and psychiatric disorders.

Targeted for both psychiatric and paediatric audiences: it reinforces that symptoms of neurodevelopental disorders need to be described in the context of brain developmental trajectory which in turn improves our understanding and capacity to address them. It also attempts to link the advances in neuroscience research to clinical practice, calling for an interactive partnership between clinicians, researchers and families for the ongoing success in the management of neurodevelopental disorders. This book captures advances in molecular biology and targeted treatments for major psychiatric and neurodevelopental disorders over thirteen chapters.

The overview describes the process of neurodevelopmental formulation which forms the basis of the therapeutic interventions. These interventions can enhance developmental progression, improve environmental interactions, reverse neurobiological dysfunction and prevent sensitisation. The imbalance of the neurotransmitters GABA and glutamate, and their complex neuroanatomical pathways is the background to explain the pathogenesis and treatment strategies. Newer techniques as WES (whole exome sequencing) and WGS (whole genome sequencing) have been used to trace mutations, deletions and duplications which are seen in more than half of the patients of autism with intellectual disability. The identification of pathways that are affected by these mutations gives insights into understanding major psychiatric and neurodevelopmental processes. The neurodevelopmental process is explained in terms of synaptogenesis and myelination, whilst epigenetics explain the influence of environment on gene expression. For example changes in epigenetic markers such as histone acetylation and DNA methylation secondary to environmental exposure to smoke, air pollutants, metals, and organic chemicals results in conditions such as cancer, asthma and metabolic disorders. More detailed description of epigenetic processes follows, described under different subheadings including immune etiology of neurodevelopmental disorders, oxidative stresses and mitochondrial dysfunction. High levels of cytokines even during intrauterine periods are associated with schizophrenia and major depressive disorders. Similarly there is a link between oxidative stress or mitochondrial dysfunction and disorders like Downs syndrome, Alzheimer disease, Fragile X, schizophrenia, depression, ASD etc. The description of biomarkers in diagnosis of disease risk, targeted treatment and their outcomes is interesting although the examples feel repetitive at times. These aetiologies do not follow a sequence to highlight broader framework but come across as disjointed and fragmented. The theory of mind and developmental sequencing seems to be lost at times in complex descriptive genetic processes.



The major disorders as Autism, schizophrenia, depression, ADHD, Rett syndrome, Cardio-facio-cutaneous syndrome, Tuberous sclerosis, Fragile X, Angelman's syndrome, Down syndrome, Phenylketonuria, muscular dystrophies are described in the next thirteen chap-

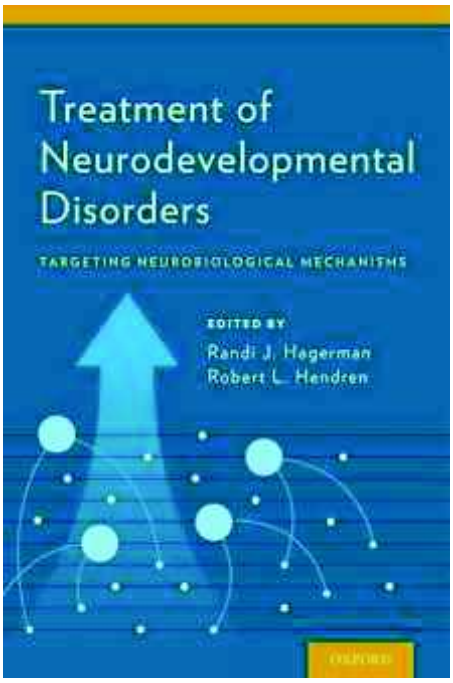
> "Behavioural phenotypes provide important models for understanding the biology of mental mechanisms"

ters. Each topic starts with an introduction of prevalence and clinical features. The neurobiological abnormalities and epigenetics are highlighted followed by use of biomarkers in the diagnosis. The associated comorbidities are mentioned in these contexts. The management is described under current available options, followed by newer targeted treatments and future prospects. There is a useful, comprehensive and relevant summary at the end of each topic. All available treatment options including non pharmacological options are discussed for each disorder. References are current and relevant to the text. Of interest, Mazurek et al (2013) reported aggression in 53% of cases of ASD at some time which is higher if there are associated medical co morbidities highlighting the need of comprehensive screening to look for associated issues.

In the last chapter, the authors bring forward the novel concept of merging current research into clinical practice. The translation of advances in understanding of the neuroanatomical and neurochemical basis of major psychiatric and neurodevelopmental disorders anticipate a new area of targeted treatment options which are currently being successfully trialled in animal models and human cohort studies. It also touches on a few promising potential areas for the future such as stem cell therapy.

While emphasising the potential of newer options to reverse the neurobiological dysregulation caused by mutations, the authors don't minimise the role of advances in educational technology and digital aids in providing comprehensive patient care. This is important for strengthening partnerships with the families in optimising care. It also summarises common abnormalities that occur across different disorders. At the end of the last chapter, all the important concepts that can be translated into clinical practice are summarised.

This book is of interest to paediatricians, allied health, geneticists and child psychiatrists, in fact all involved with disability services as the concepts discussed are viable and relevant across different faculties. The ethical, legal and political implications of such new therapies will need to be worked through, as well as more clinical studies and trials. The authors emphasise the



importance of clinician support to enable the potential of such therapies to become a reality. In the absence of any local experience, most of the targeted treatments which have promising results in animal models raise ethical issues for their suitability for current patient cohorts. Further studies will also need to look at long term safety profiles before they are suitable and applicable to clinical practice.

This book aims to bring current neuroscience to understanding and treating neurodevelopmental and psychiatric disorders. With the presentation of so much detailed research observations it is difficult to find a coherent story. It raises the question as to whether risk markers could ever become the basis of treatment and a substitute for, or significant contribution to diagnostic classification.

There is no doubt that behavioural phenotypes provide important models for understanding the biology of the mental mechanisms. I recently saw a 12 year old boy with temporal lobe epilepsy, severe ADHD, some features of ASD, mixed emotional and conduct problems, motor coordination disorder, encopresis, and specific learning difficulties. Such a multidimensional disorder is not so unusual, but the next time I met him, he had been diagnosed with 16p.11.2 microdeletion, and the behavioural phenotype, which was first described in 2010, fitted my clinical description remarkably. The biological marker added meaning and coherence to this clinical picture. It may be that by collecting different biological mechanisms that each new behavioural phenotype will accumulate understanding of mechanisms of the mind which could create a whole new biology of mental development and disorder. We have to accept that this book represents 'a work in progress' and as such an interesting, novel and potentially important approach to keep informed about.