Published in final edited form as:

Psychiatr Clin North Am. 2009 March ; 32(1): 199–211. doi:10.1016/j.psc.2008.11.003.

Towards a Neurodevelopmental Model of Clinical Case Formulation

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Abstract

Rapid advances in molecular genetics and neuroimaging over the last 10–20 years have been a catalyst for research in neurobiology, developmental psychopathology, and translational neuroscience. Methods of study in psychiatry, previously described as “slow maturing,” now are becoming sufficiently sophisticated to more effectively investigate the biology of higher mental processes. Despite these technological advances, the recognition that psychiatric disorders are disorders of neurodevelopment, and the importance of case formulation to clinical practice, a neurodevelopmental model of case formulation has not yet been articulated. The goals of this manuscript, which is organized as a clinical case conference, are to begin to articulate a neurodevelopmental model of case formulation, to illustrate its value, and finally to explore how clinical psychiatric practice might evolve in the future if this model were employed.

Introduction

Rapid advances in molecular genetics and neuroimaging over the last 10–15 years have been a catalyst for research in neurobiology, developmental psychopathology, and translational neuroscience [1]. Methods of study in psychiatry are becoming sufficiently sophisticated to effectively investigate the biology of higher mental processes and complex forms of psychopathology [2]. These advances have the potential to add depth to our understanding of psychiatric symptoms and to facilitate more targeted interventions.

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Rett syndrome and Down syndrome are examples of conditions thought of as being “neurodevelopmental” disorders [3] -- disorders where the interaction of genes and the environment lead to the biochemical processes involved in pathological development of the brain and central nervous system. However, aspects of almost all psychiatric disorders likely involve the interaction of multiple genes with environmental factors. Thus, schizophrenia, autism spectrum disorders (ASDs), attention-deficit hyperactivity disorder (ADHD), Tourette’s disorder and bipolar disorder also can be approached from a perspective emphasizing the importance of neurodevelopment.

Historically, mental health professionals have used heuristic case formulation models to help organize complex information about psychological, interpersonal and behavioral problems, and to guide the development of treatment plans [4]. A biopsychosocial formulation, particularly when applied through a developmental lens for children, can bring a rich perspective to the case. However, some cases lend themselves to an even more specific focus—that of the neurodevelopmental formulation, which also brings to bear genetic and neurological information, which is becoming more readily available to the clinician due to rapidly advancing research in these areas.

A neurodevelopmental model of case formulation has not yet been clearly articulated. This is probably due to the enormous complexity inherent in explaining the relationship between genes and behaviors and our often nascent knowledge base, and skepticism about whether this type of formulation model could improve clinical practice in terms of accuracy, treatment, or cost. The goal of this manuscript, which is written as a clinical case conference, is to begin to articulate a neurodevelopmental model of case formulation; to illustrate its value; and to explore the evolution of clinical psychiatry if this type of case formulation became standard practice.

Towards a Neurodevelopmental Model of Case Formulation: Bridging the Gap Between Genes and Behaviors

Pennington [8] articulated a model of developmental psychopathology that offers an organizing framework for examining critical elements in neurodevelopment. This framework traces four “levels” between genes and behavior. Level 1, Etiology, is concerned with the genetic and environmental influences and the role they play in the development of symptoms and disorders. Level 2, the Brain and Central Nervous System, includes development of the neuroarchitecture of the brain. In this model, Level 3, Neuropsychology, performs a “bridging” function between the internal and external manifestations of psychopathology through the use of non-invasive assays of brain functioning such as neuropsychological tests. Level 4, Symptoms, consists of observable behaviors. During development, interactions between these four levels are continuous, bi-directional, and interactive [9]. In considering schizophrenia research, Tandon, Keshavan, & Nasrallah [10] suggest that pathophysiology including neurochemical alterations in brain regions should be considered as part of Level 2, and that the Symptoms level should be expanded to include treatment. See Figure 1 for a schematic diagram of this model. We propose that the practice of clinical psychiatry can be advanced and enhanced by using diagnostic formulations that consider and organize information using these levels of analysis.

Below we present a case in a Grand Rounds Format to illustrate the application of a neurodevelopmental model of case formulation and the clinical issues it raises. In this case, a neurodevelopmental formulation reveals that a complex constellation of psychiatric and learning problems has arisen from a “single-gene” disorder with a well-described phenotypic presentation. Case materials are presented using the Levels, starting with the presenting Symptoms. This case was chosen because it illustrates how case formulation would be affected when a genetic “cause” can be identified, although there also are many aspects of the case that

conform to the more common situation of disorders related to multiple genes and/or environmental factors or those with no known genetic origin. We have presented similar case materials with a different emphasis previously [11].

Case Presentation 1: “Sarah,” a Girl with Mild Intellectual Disability, Anxiety, Behavioral Dysregulation, and Symptoms of Autism

Dr. Hendren

At level 4, the Symptom level, we evaluate Sarah’s presenting problems, her medical and developmental history, and her medical examination. At age 8, Sarah was referred to us for a multidisciplinary evaluation due to longstanding difficulties with social skills, learning, aggression, and anxiety. She is described as an extroverted and pleasant girl. However, she becomes severely emotionally dysregulated and engages in tantrums, aggression, and self-injury, when she becomes frustrated in academic or social situations. Academic performance is a relative strength, although she has trouble with mathematics.

Sarah was born weighing 7 pounds 2 ounces following an uncomplicated delivery. Motor milestones and language development were within normal limits. Hand flapping, poor eye contact, and tactile defensiveness began during the first year of life. Her preschool years were unremarkable.

She was referred for evaluation at age 6 when kindergarten teachers observed that her play and social skills were delayed. She also demonstrated echolalia, obsessiveness, and intolerance for changes in her routine. In first grade, issues related to inattention, following instructions, and reading comprehension became apparent, and her academic performance was well below average. She began to display behavioral problems including talking out, provoking other children, difficulty transitioning between activities, and tantrumming or sulking when upset. She did not have any friends, and exhibited autistic-like symptoms including poor eye contact, solitary play, sensory hypo- and hyper-responsiveness, and hand flapping.

We hypothesized that Sarah’s emergent behavioral problems were directly related to her frustration and desperation that her academic and social skills were failing to keep pace with environmental demands. Sarah’s behavioral difficulties destabilized the institutional and family systems that supported her, as teachers and parents struggled to respond. Likely, at least initially, Sarah’s problems led to increased anger on the part of her teachers and feelings of guilt and loss in her parents.

She was initially tried on atomoxetine at 18 mg and then later at 40 mg for distractible inattention, impulsivity, hyperactivity and anxiety. She became more irritable and this was discontinued. She was subsequently started on sertraline at 50 mg at which dose she displayed decreased anxiety, fewer emotional outbursts and aggression, and improved behavior at school. Her attentional problems and impulsivity persisted, however, and an additional 36 mg of once-daily methylphenidate was added. This resulted in improved attention and concentration, and further reduction in aggressive behavior.

During her medical examination with us, Sarah presented as an attractive overweight girl. She was appropriately dressed and well groomed. Ear pinna were prominent with significant cupping. Hyperextensible joints and macrocephaly were noted. Her features were mildly dysmorphic-- she had a long face and prominent ears. She made poor eye contact, and had difficulty sitting still during the interview. Her speech was of normal rate, but volume was loud and prosody was monotone and slightly robotic. Her mother reported no evidence of auditory, visual or tactile hallucinations. However, Sarah was reportedly often “in her own world” where

she engaged in self-talk and recited lines from favorite television shows and videos. Thought content was generally appropriate for the interview. She displayed no suicidal ideation.

Discussion

Dr. Hessl

In consideration of Level 1, Etiology, we were impressed by similarities between Sarah's symptom presentation and the neuropsychiatric phenotype of Fragile X Syndrome, and referred her for hi-resolution cytogenetic and fragile X DNA testing. Fragile X DNA testing was positive for the full mutation with 486 to 845 CGG repeats, and fragile X mental retardation 1 (*FMR1*) protein studies demonstrated 48% of normal protein expression. These results documented a full mutation of the fragile X mental retardation 1 (*FMR1*) gene and Sarah was subsequently diagnosed with fragile X syndrome (FXS).

FXS is a "single gene" disorder caused by a trinucleotide repeat expansion (CGG)_n in the 5' untranslated region of the fragile X mental retardation 1 gene (*FMR1*) located on the X chromosome. It is the most common form of inherited mental retardation. The full mutation, as in Sarah's case, occurs when individuals have more than 200 CGG repeats, leading to methylation, subsequent transcriptional silencing of the *FMR1* gene, and absence or deficiency of the FMR1 protein, FMRP [12].

Individuals with FXS demonstrate a behavioral phenotype characterized by hyperarousal, social anxiety and withdrawal, social deficits, abnormalities in communication, unusual responses to sensory stimuli, stereotypic behavior, gaze aversion, inattention, impulsivity, and hyperactivity [13–19]. Autistic disorder is present in 15–33% of individuals with FXS [20–23]. Studies of females with FXS have shown that reduced FMRP expression is associated with internalizing behaviors such as anxiety and social withdrawal [19] and reduction of task specific areas of brain activation during fMRI studies of math calculation [24]. Sophisticated neurogenetic studies have even documented that functional brain activation during arithmetic processing and executive function tasks involving response inhibition in females with FXS are linearly related to FMR1 protein expression [24,25]. Consistent with these research studies, our patient's most prominent referral concerns were anxiety and social withdrawal, math learning problems, and impulsivity.

Our clinical research program has begun to examine secondary genetic factors that might explain why some boys with FXS develop more severe aggression or anxiety symptoms than others [26]. As part of a study protocol approved by the U.C. Davis Institutional Review Board, Sarah's DNA sample also was analyzed for polymorphisms known to be associated with anxiety and aggression in the general population including the serotonin transporter gene and the monoamine oxidase A (MAOA) polymorphism. The functional polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) has been associated with reduced 5-HTT expression and function, increased fear and anxiety-related behaviors, and greater amygdala neuronal activity in response to fearful stimuli [27]. In our study, we found that boys with FXS who were homozygous for the short genotype (S/S) had the least aggression. Those with the long (L/L) genotype had the highest levels of stereotyped behaviors. We also were surprised to observe that individuals in the study taking SSRI or SNRI medication were more likely to have the high activity MAOA-VNTR 4-repeat genotype. Writing about a sample of boys with autism, Brun, Kim, Salt, Leventhal, Lord & Cook [28], found that the short (S/S) and (S/L) genotypes, were associated with the failure to use nonverbal communication to regulate social interaction, whereas the (L/L) phenotype was associated with more severe stereotyped motor mannerisms, and aggression. The probe of Sarah's serotonin transporter gene revealed two copies of the short allele (S/S). Additional empirical studies, and studies specifically about girls, clearly will be needed to confirm that these polymorphisms are

associated with psychiatric symptoms in individuals with FXS. Preliminarily, however, Sarah's aggression symptoms do not conform to our research findings about individuals with the short allele (S/S), however, she does have difficulty using nonverbal communication to regulate social interactions as discussed by Brun et al.

Monoamine oxidase A (MAOA) is a mitochondrial enzyme active in degrading all of the monoamines – namely serotonin, dopamine, and norepinephrine. Although our study did not demonstrate a relationship between MAOA levels and aggression, self-injurious behavior, or stereotypy, in boys with FXS, the 3-repeat allele has been implicated in the pathogenesis of aggression and impulse control disorders [29,30], autism symptom severity [31], conduct/aggression disorders co-morbid with ADHD [32], and unmanageable aggressive behaviors in schizophrenia [33] and Alzheimer's disease [30]. Examination of Sarah's MAOA status showed that she carries one allele with 3.5 repeats and one allele with 3 repeats. Although findings regarding the significance of this are contradictory at the present time, the relationship between Sarah's MAOA status and her behavior may become clearer with future research, and such information may help to better delineate the relative responsibility of genes and environment in Sarah's presentation.

In sum, for this case, knowledge of genetic information about the fragile X phenotype, combined with knowledge about the serotonin transporter gene and MAOA polymorphisms provides the clinician with a richer understanding of factors mediating symptom expression.

Dr. Chiu

At the Brain Level, we can consider what we know about neuronal growth and development in individuals with FXS. Greenough and colleagues [34], have provided strong evidence that FMRP is required for the refinement of dendritic spine morphology -- an important neural correlate of brain changes linked to development and learning. FMRP is expressed in all brain regions of typically developing individuals. Therefore, FXS is characterized by effects on all of brain development and all cognitive domains are likely to have developed at least somewhat atypically [14]. fMRI, neurohistological, and neuropsychological studies, however show that particular brain regions may demonstrate higher FMRP expression and therefore some brain functions such as those subserving sequential information processing [24], visual tracking [27], and inhibitory processes [25] may be especially affected in patients with FXS. Again, knowledge about neurodevelopment associated with the fragile X phenotype, provides a more complete appreciation of the patient and her symptoms given that it enables us to anticipate problem areas of cognitive and adaptive functioning, and vulnerability to psychopathology,

Dr. Solomon

At Level 3, Neuropsychology, we know that the cognitive profile of individuals with FXS is characterized by relative strengths in language, long-term memory, holistic information processing [35], and as mentioned above, relative weaknesses in attention, visuospatial cognition, short-term memory, sequential information processing, and inhibition. Most individuals with FXS exhibit symptoms of ADHD [18,36], and up to one- third meet criteria for autism [22].

On the Kaufman Assessment Battery for Children (K-ABC) [37], Sarah obtained a Mental Processing Component of 72 (borderline range of intellectual functioning), and scales on non-verbal items were significantly depressed to others. Consistent with this pattern, Sarah's academic achievement scores (Woodcock-Johnson Psychoeducational Battery III) [38] ranged from a high of 105 in Reading to 78 in Mathematics. Scores on a developmental examination of visual motor integration revealed that Sarah's scores were below average.

To see whether the atypical language, reciprocal social deficits, and restricted and repetitive behavior symptoms associated with autism were present, we completed the Autism Diagnostic Observation Schedule [39] – Module 3. Sarah showed a wide range of affect on the ADOS. She was able to engage in imaginary play with the examiner. Her speech was odd in its sing-song prosody, and repetitive use of catch phrases. She did not comment on others' emotions, demonstrate true empathy, or engage in perspective taking during the testing. Her score on the ADOS was in the autism spectrum disorder range, but below the cut-off for full autism. Her score on The Social Communication Questionnaire [40], a parent report inventory of items related to the DSM diagnosis of autism, was consistent with this.

Dr. Hendren

For most children presenting in our clinics with a constellation of cognitive, learning, emotional, and social difficulties, the etiology is unknown and somewhat mysterious. In Sarah's case, however, we are fortunate because our neurodevelopmental formulation rests on the foundation of a wealth of genetic, biological, and behavioral knowledge about FXS. At levels 3 and 4, we have a wide range of seemingly disparate symptoms and cognitive strengths and weaknesses, including social deficits, anxiety, and mathematics learning difficulties. Studies have documented that each of these are features of the phenotype of FXS. At levels 1 and 2, the etiological/genetic and brain/pathophysiologic levels, we recognize that many of Sarah's difficulties have been directly linked to the dysfunction of the fragile X gene, *FMRI*, through neuropsychological and neuroimaging studies. Although many of these phenotypic features may be modified by environmental factors [29], Sarah's experience starts from a point of significantly increased genetic susceptibility. In addition to her fragile X status, Sarah carries two additional genetic risk factors: a less efficient serotonin transporter gene, and a MAOA polymorphism predisposing her to aggressive behavior.

Dr. Solomon

We sought to reduce Sarah's anxiety by accentuating her strengths and by bolstering her functioning in problem areas. Psychopharmacologic interventions were used to target her anxiety and attentional problems as previously noted. Sarah's presentation includes aspects of a non-verbal learning disorder profile (NLD) [41] commonly seen in girls with Fragile X Syndrome. Hence, we encouraged teachers and parents to recognize and help her use her excellent rote memory for facts and other information delivered verbally; and to use her relatively strong fund of knowledge to compensate for areas such as abstract reasoning which are more difficult for her. We recommended that teaching methods be tailored to Sarah's sequential information processing problems. We recommended that Sarah receive more assistance in math as this is a relative weakness for her as it is with other individuals with NLD. She has been able to use assistive technology during math class. To help desensitize her to social challenges and to provide extra scaffolding and practice, Sarah attends a social skills group, which includes lessons on stress and anger management.

Hopefully, advances in our understanding of the phenotype of FXS will lead to improved pharmacological and psychosocial interventions targeted to these individuals.

Dr. Hendren

Environmental and psychodynamic factors including those involving adoption and family dynamics play a role in Sarah's experience as does learned behavior. Explanations for her behavioral dysregulation, however, should not over-emphasize the role of her parents or other caregivers. Sarah's emotional dysregulation may be due at least in part to deficits and/or immaturities in inhibitory neural circuits which permit self-soothing, diminution of negative affect, and enhanced emotion regulation [42,43]. It is important to note that Sarah's academic

achievement exceeds what would be expected given her cognitive level, speaking to the ability of her parents to provide a supportive learning environment for her.

Dr. Chiu

This diagnosis has direct genetic counseling implications for Sarah's extended family. The identification of FXS has implications for *FMRI* screening in her siblings and other extended family members. In addition, the recent discovery of fragile X-associated tremor ataxia syndrome (FXTAS) [44], a neurodegenerative disorder occurring in elderly carriers of the *FMRI* premutation, indicates that Sarah's grandfather is at risk for a late-onset disease that arises from an abnormality of the same gene but with completely different phenotypic expression.

The Future

Dr. Hendren

One can imagine a time in the future when it will be the standard of care to draw blood and order several genetic tests to ascertain a patient's vulnerabilities and even make diagnoses. More will be known about the genes involved in schizophrenia, ADHD, autism and bipolar disorder. Single nucleotide polymorphism (SNP) profiles that are characteristic of different disorders will be established. Gene expression profiling with DNA microarrays, which assess the expression of thousands of mRNA transcripts simultaneously using tissue samples, also will come into more widespread use due to the ability to use whole blood [45,46]. Unique gene expression profiles will have been identified for many disorders. For example, a pilot study at the M.I.N.D. Institute has recently demonstrated that there are different gene expression profiles for children with autism with and without symptoms of regression [47]. These genetic information profiles will help clinicians by providing comparative contexts within which to evaluate symptoms, prognoses, and potential efficacy of intervention strategies.

Dr. Hessl

The tremendous challenge of understanding what happens between Levels 1 and 4 can be facilitated by the use of the intermediate "endophenotypes."

Phenotypes represent the full expression of an individual's genes in the environment. They are heterogeneous and potentially include multiple symptoms in the diagnostic category. Endophenotypes are partial "internal phenotypes" or collections of traits [48]. Conceptually, they are closer to the site of genes or primary causative agents than symptoms, and are therefore considered to be more homogeneous. They distinguish individuals with the disorder from a control population; are stable over time; are more prevalent in family members of the affected individual; precede the development of clinical manifestations of the disorder; and are more accurately measured than clinical features. Schizophrenia researchers were the first to suggest this approach 30 years ago [48]. Endophenotypes have received renewed attention, and are being used to study ADHD [50,51], and to a lesser extent, autism [52] and bipolar disorder [53].

Dr. Chiu

While it is too early to attempt to interpret this information, some research programs have begun to collect age- and gender-normed developmental data sets about the size and volume of brain structures for typical and atypical populations [54]. One day it may be possible to chart the growth trajectory of an individual's brain structures relative to established developmental norms. At that point, we may also know more about the pathophysiology resulting in these size patterns, and their relationship to behavioral symptoms. For example, researchers have demonstrated that children and adolescents with autism demonstrate a different trajectory of

amygdala growth than typically developing control subjects [55], and efforts currently are underway to understanding the etiology of these differences and their functional significance.

“Pharmaco fMRI” also is now being used in ADHD research. This work has begun to clarify which forms of the disorder are most responsive to medication [56] and mechanisms of stimulant action on the neural circuitry of individuals with the disorder [57]. Similarly, Diffusion Tensor Imaging (DTI), which is used to measure white matter tracts, and computational modeling will help further our understanding of neural circuits and patterns of regional connectivity.

Dr. Solomon

If cost barriers can be overcome, fMRI may be used more routinely to provide a window into brain activation associated with cognitive and affective processes. This would lead to a merger between the Brain and Neuropsychology Levels as it becomes feasible to study brain function during cognitive testing. Measures of key neural processes will evolve as the result of imaging technology, and developmental norms for these new cognitive science-based measures will be established. Given that these new assays will derive from cognitive neuroscience and fMRI-based investigation, they will relate more closely to endophenotypes than currently available neuropsychological tasks. For example, as mentioned above, measures of context processing have developed this way in schizophrenia research [58,59]. Neuroimaging will also serve as a source of converging evidence in understanding the effects of genes on neural circuitry as genetic testing is more routinely incorporated in fMRI studies, and relationships between genes and neural circuitry activation patterns are investigated.

Dr. Hessler

Some of the biggest potential benefits of a neurodevelopmental model that enhances our understanding of pathophysiology occur at the levels of treatment development and treatment matching. Advances in the field of proteomics are likely to serve as a catalyst for the development of new pharmaceuticals, which may help with cognitive, social, and adaptive functioning. In this case, as a single gene disorder, Fragile X provides a relatively simple model for studying the effects of secondary or tertiary modifying genes because the primary genetic deficit and phenotype are known [26]. It is known that the lack of a fragile X mental retardation 1 gene protein in fragile X leads to dramatic up regulation of the metabotropic glutamate 5 pathway, which affects synaptic plasticity leading to long-term depression and subsequent development of weak and immature synaptic connections [60]. The use of metabotropic glutamate 5 antagonists has been helpful in improving cognition and in decreasing seizures in animal models of fragile X syndrome. Initial Phase I clinical trials in humans are now underway; it is hoped that they may be further developed to play an important clinical role in humans. Neural retraining programs are already used to remediate reading [61], attention [62,63], and face processing [64] problems, as well as general cognition and working memory in schizophrenia [65]. Based on our understanding of the endophenotype of Fragile X Syndrome, it is reasonable to expect that these interventions can also be usefully applied to patients with Fragile X. Once we can reliably augment an individual's phenotypically-derived diagnosis with a neurodevelopmental formulation, we can better establish a well-targeted treatment plan.

Dr. Hendren

Some readers may wonder if we believe there is room for environmental factors, including early childhood experience, in this neurodevelopmental model. The answer to this question is clearly “yes.” Better understanding the origin of Sarah's symptoms enabled those around her to be more helpful and responsive. Sarah's parents were able to stop “blaming” themselves and/or their parenting for many of her problems. They were empowered by knowing more of

what to expect in her development, by having a more elaborated treatment armamentarium to draw upon, and by having a new found supportive community of other families and clinicians dealing with fragile X syndrome. They were able to better educate teachers, service providers, and relatives about how to help Sarah. Sarah was of course a beneficiary of this attuned and responsive environment, which has enabled her to achieve her full potential.

We hope, however, that this neurodevelopmentally focused discussion will encourage more systematic thought about the role of biological factors, which are highly complex as well. Interestingly basic science research using animal models clearly demonstrates the profound impact of early caregiving on an offspring's gene expression related to stress responses, which are critical for survival [66]. In this instance, a neurodevelopmental approach to formulation is consistent with psychodynamic models' emphasis on the critical role of early experience, even if the underlying theory is quite different.

Dr. Chiu

Finally, it should be evident that a neurodevelopmental case formulation model may serve as a catalyst for the development of a taxonomy of mental disorders informed by pathophysiology. Once we possess a better understanding of the genes, endophenotypes, and prodromal symptoms underlying psychiatric disorders, it is likely we will discover unappreciated relationships between symptom clusters. We expect that this will lead to the revision of our conceptualization of many psychiatric disorders.

Acknowledgments

The authors would like to acknowledge Flora Tassone, Ph.D. for providing genetic data information, and Dr. Randi Hagerman for providing helpful comments on prior drafts.

During the preparation of this manuscript, Dr. Solomon was supported by NIH grant K-08 MH-074967; Dr. Hessl was supported by NIH Grant MH-77554;

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Four Levels In A Neurodevelopmental Model

Adapted from Pennington, 2002; Tandon, Keshavan, & Nasrallah, 2008

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