Early Prevention of Severe Neurodevelopmental Behavior Disorders: An Integration

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Abstract

There is a very substantial literature over the past 50 years on the advantages of early detection and intervention on the cognitive, communicative, and social-emotional development of infants and toddlers at risk for developmental delay due to premature birth or social disadvantage. Most of these studies excluded children with severe delays or other predisposing conditions, such as genetic or brain disorders. Many studies of children with biological or socio-developmental risk suggest that behavior disorders appear as early as three years and persist into adulthood if not effectively treated. By contrast, little is known about the infants and toddlers with established risk for severe delays, who make up a significant proportion of the population with dual diagnoses later in life.

In the past decade, there has been a growing interest in early detection and intervention with children aged birth to three years, e.g. the P.L.99-457, Part C Birth-Three population, who may have disabilities and severe behavior problems, e.g. aggression, self-injury, and repetitive stereotyped behaviors. The available research is scattered in the behavior analytic literature, in the child development literature, as well as in the child mental health and psychiatry literature, the developmental disability literature, the animal modeling literature, and the genetics literature. The goal of this introductory overview is to integrate these literatures, by cross-referencing members of these various groups who have worked in this field, in order to provide the reader with an integrated picture of what is known and of future directions that need more research.

Keywords

severe aggression; self-injurious behavior; stereotyped behavior; early prevention; young children; intellectual disabilities

Neurodevelopmental behavior disorders (NBD), especially aggression, self-injury (SIB) and their related counterpart, stereotyped behavior, are some of the most devastating severe behavior problems of people with disabilities. They sometimes occur alone, but often overlap, providing a major barrier to social integration in the family and the community (see Rojahn, Schroeder, & Hoch, 2008 for an extensive review).

SIB, aggression, and stereotyped behavior each have a distinctive history of research, both among human models and among a variety of animal models. In the past two decades more attention has been given to early identification and intervention. The literature is scattered among several streams of research which often have developed independently of one

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another with little cross-reference. There appear to be six main streams: 1. infant mental health and psychiatry; 2. child development of infants and toddlers at sociocultural and/or biological risk for developmental delays; 3. psychometric assessment of at risk dimensions of psychopathology among young children and those with established disabilities, e.g. severe developmental, genetic, and neurobiological disorders; 4. behavioral studies of individuals with socially mediated behavior problems and disabilities using direct observations of behavior and single-subject designs; 5. animal models of SIB, aggression, and stereotyped behavior; and 6. genetic and neurobiological factors related to severe behavior problems. Each of these topics has been reviewed independently and frequently over the past 40 years, but they rarely have been integrated into a cohesive body of knowledge in which one informs the other.

Our goal in the introduction to this special issue on early identification and early intervention of SIB, aggression, and stereotyped behavior is to integrate past authoritative reviews with recent advances in research on gene-brain-behavior relationships involved in their emergence and intervention, and to trace the contributions of each to our current state of knowledge.

Research on Infant Mental Health and Psychiatry

A recent history in a special issue of the American Psychologist by Egger & Emde (2011) gives an excellent historical view of the field of infant mental health. They point out the limited empirical base for this area, although much progress has been made recently in devising developmentally sensitive diagnostic criteria for mental health disorders in early childhood. There have been basically two approaches i.e. descriptive and dimensional. The former is modeled after DSM IV (APA, 1994), where a panel of experts described criteria based upon their experience and knowledge of the literature. Another revision, DSM V, is expected in 2013, which may contain some changes in diagnostic categories, but the multiaxial diagnostic system is expected to remain essentially intact. In order to cover the diagnoses of children from 0–3 ages that would stream into DSM IV and ICD-10 (WHO, 1994) criteria, several diagnostic systems have been devised: the Research Diagnostic Criteria-Preschool Age (RDC-PA, Scheeringa, 2003), Early Childhood Symptom Inventory-4 (Gadow & Sprafkin, 2000), which goes down to age two, and the Diagnostic Criteria 0–3 and its updated revision, DC:0-3R (Zero to Three, 2005). The most popular, DC:0-3R, is a multiaxial system with five axes patterned after DSM IV. Axis I covers clinical disorders of affect, adjustment, and regulation. Axis II covers personality disorders. Axis III covers medical and developmental disorders and conditions, but little is done to address the definitions of SIB, aggression, and stereotyped behavior, perhaps because they appear to be rarer disorders. Axis IV covers psychosocial and environmental problems. Axis V covers global assessment of functioning.

DC: 0-3 diagnoses are not yet included in the DSM IV system, so crossing over from one system to the other is difficult. There is a growing prevalence of pediatric psychopharmacology emerging to treat DC: 0-3 disorders (e.g. Luby & Riddle, 2009). However, cautions about the possible effects of such medications on a child’s growth and development at this early age are necessary. Longitudinal studies, especially in the birth-three ages, are lacking. Follow-up into later childhood and adulthood, as has been done for children at sociocultural risk (e.g. Ramey & Ramey, 1999), still remains to be done.
Research on Infants and Toddlers at Sociocultural and Biological Risk for Developmental Delay

This area of research has a long and distinguished history in the literature on Child Development for the past 40 years and has been summarized in many handbooks since then. For instance, see an early anthology by Tjossem (1976) already. Sociocultural risk factors have focused on the effects of prematurity, poverty, parental education, the home caregiving environment and their interrelationships. They form the basis of current early intervention programs such as Birth-to-Three (Part C) programs, Head Start, and others. Ground-breaking analyses by Sameroff and Chandler (1975) and Sameroff (2009) have had a major impact on establishing the effectiveness of early identification and intervention programs (Guralnick, 2005). Most of these studies were directed at promoting cognitive, social, and emotional competence of children with mild delays, and they excluded children with severe disabilities with severe behavior problems of the type currently of interest because they did not have adequately standardized assessment instruments for this population.

In their early days, there was a great controversy on whether people with severe disabilities were essentially different or just developmentally delayed, compared to typically developing children (Zigler & Balla, 1982). This controversy has been rendered moot by the development of appropriate instruments that now cover a wide range of psychopathology for these populations (see Matson, 2007 for a review) and by the advances in genetics and neurobiology which have elucidated a multitude the similarities and differences among different behavior phenotypes (Dykens, Hodapp & Finucane, 2000).

The paper by Richman, et al. (this issue) is an example of exploring the relationship among different fears among young autistic children. This area of research has been fertile ground for developing more targeted early intervention programs with these more specialized populations (Wallace & Rogers, 2010). Longitudinal studies of higher functioning intellectually delayed children three years and older suggest that many of these problems begin at a young age and persist into later childhood if untreated (Baker, Blacher, Crnic, & Edelbrock, 2002; Emerson & Einfeld, 2010).

Psychometric Assessment of Young Children with Established Risk of Disabilities and NBD

Psychometric studies present a dimensional approach to the study of behavior problems and psychopathology in intellectual disabilities. The best ones are standardized on the target populations and cut-off scores are usually based upon one, two, or three standard deviations from the mean. Most of the early instruments were validated on higher-functioning populations and specifically excluded lower functioning children with established biological syndromes and brain disorders from their samples. However, a variety of instruments have recently appeared, standardized properly on the target populations, and covering a wide variety of disorders, well defined operationally, so that they could be replicated. A good example of a measure of aggression is the Irritability Subscale of the Aberrant Behavior Checklist (Aman, Singh, Stewart, and Field (1985) has been used widely in over 500 studies. Another excellent measure of aggression, SIB, and stereotyped behavior is the Behavior Problem Inventory (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001) which has proven a sensitive measure in over 30 studies. An excellent measure of stereotyped behavior is The Repetitive Behavior Rating Scale-Revised (Bodfish, Symons, Parker, & Lewis, 2000). Most of these instruments have been standardized on adult populations with disabilities, however. Only recently have they been used in younger children, e.g. Karabekiroglu and Aman (2009), Maclean, Tervo, Hoch, Tervo, and Symons (2010),
Maclean and Dornbush, (this issue), and Mayo, et al. (this issue). For an in-depth review of assessment instruments for the full range of people with intellectual disabilities, the best text is Matson (2007).

Assessment of the first signs of behavior problems in infancy continues to be difficult. However, a new instrument for assessing the Birth-to-Three population by Matson and colleagues shows considerable promise, i.e. the Baby and Infant Screen for Children with Autism Traits (BISCUIT). (Matson, et al. (2009 a, b; 2010 a, b, c) have shown not only that it has good validity and reliability, but it is also the first instrument that shows relationships between severe behavior problems and comorbid symptoms of psychopathology in infants and toddlers. This may be an important area for future research, especially as these children are followed into later childhood and adulthood.

Mass screening for the first signs of aggression, SIB, and stereotyped behavior is discussed in the paper by Mayo, et al. (this issue) Theirs is a two-phase approach to assessment, rather than the use of a convenience sampling procedure used by Matson and colleagues, and it may be more appropriate for large scale screening and a cost effective strategy for multidisciplinary evaluations. The ages of the children included, the methods of sampling, subject ascertainment and the instruments used have all been shown to be important in estimating the prevalence and severity of NBD in the above studies.

Behavioral Studies of NBD in Young Children with Direct Observations and Interventions

The first studies using behavioral assessment and intervention technology for SIB, stereotyped behavior, and aggression were single-subject studies on children with autism by Wolf, Risley, and Mees (1964) and by Lovaas, Freitag, Gold, and Kassorla (1965). Since that time, thousands of studies have been performed on many aspects of functional assessment and intervention, which are reviewed in detail in Rojahn, et al. (2008). Significant contributions from the behavioral approach have been: clear definition of behaviors, valid sampling of the behaviors using direct observation, coding and analysis of actual frequencies, durations, intensities, and sequential dependencies of the target behaviors, as well as functional assessment methods, which are now commonplace in clinical settings for people with disabilities. A good example is the work of Lovaas and colleagues on intensive treatment for children with autism (Lovaas, 1987). This work has been a break-through which has changed our expectations and methods for educating children with autism (National Research Council, 2001).

Two excellent recent reviews of early development of SIB (Symons, Sperry, Dropik, & Bodfish, 2005) and its early interventions (Richman, 2008) attest to the effectiveness of behavioral methods. Richman and Lindauer (2005) and Kurtz, et al. (2003) showed that SIB in young children could be prevented using functional communication training. The paper in this issue by Danov, Tervo, Meyer, and Symon shows how this technology can be applied to studying drug X behavior interaction effects on severe behavior problems in young children with disabilities. Kurtz, et al. (this issue) also have shown that the emergence of SIB can be observed in very young children with developmental delays which then develops into other topographies and behavior problems which may require treatment. The research on development and treatment of severe aggression by young children with developmental disabilities is much sparser, with few well-controlled studies (see Matson, Dixon, & Matson, 2005 for a review).
Animal Models of Aggression, SIB, and Stereotyped Behavior

Animal models permit the experimental investigation of gene-brain-behavior relationships underpinning severe behavior problems that would not be ethically permitted among humans. They can be very useful, as long as appropriate precautions concerning generalization from animal models are observed. The most developed animal models of severe behavior problems explore the genetic and neurobiological sources of SIB. We have recently reviewed these models (Schroeder, Loupe, & Tessel, 2008): 1. SIB can be induced by isolate-rearing in primates; 2. by neonatal lesions in nigrostriatal dopamine pathways in rats, which has been suggested as a model for Lesch-Nyhan syndrome (Breese, et al, 2005); 3. by chemical induction of intact rats with amphetamine or pemoline; 4. in several genetic knock-out mouse models; 5. in a compelling mouse model for stereotyped behavior which can be prevented by environmental enrichment and complexity (Lewis & Kim, 2009); 6. finally, recovery from neonatal lesion-induced SIB in nigrostriatal dopamine pathways in rats shows neuroplasticity and can be improved by systematic operant training.

Animal models of aggression have been known for a long time to vary greatly, depending on the different types of aggression exhibited, i.e. territorial aggression, maternal aggression, inter-male aggression, predatory aggression, fear-induced aggression, operant aggression, and their correlated genetic and neural substrates (Moyer, 1976). There is only one animal rodent model of aggression designed specifically to model severe behavior problems among people with disabilities, i.e. the Kennedy and colleagues mouse model of operant aggression. They have shown that Swiss CFW mice performed operant tasks for the opportunity to aggress an intruder mouse (May & Kennedy, 2009). They have been able to relate these behaviors to dopamine functions in the mesocorticolimbic system, especially the nucleus accumbens, in mice (Couppis & Kennedy, 2008; Couppis, Kennedy, & Stanwood, 2008), as well as to polymorphisms on the MAOA gene (May, Srour, Hedges, Lightfoot, Phillips, Blakely, & Kennedy, 2009) and in a serotonin transporter gene (May, Light-foot, Srour, Kowalchuk, & Kennedy, 2010) in human adults with severe aggression and SIB.

Taken together, these animal models implicate the uncoupling of the HPA-axis and correlated dopamine, serotonergic, GABAergic, and opioid peptide systems (see Rojahn, et al., 2008; Schroeder, et al., 2008 for reviews). Disruption of stereotypic SIB may be primarily the result of malfunction of the D1 and D2 dopamine pathways (Lewis & Kim, 2009), whereas SIB with aggression, as shown in isolate-reared primate models, may be more related to disruption of serotonergic function (Tiefenbacher, Novak, Lutz, & Meyer, 2005). This model seems to be more related to self-aggression and self-mutilation discussed in the Psychiatric literature (Favazza, 1996). All of these systems appear to be connected and to operate in a correlated fashion.

Emergence of Genetic Factors related to Aggression, SIB, and Stereotyped Behavior

The pioneering discovery of the first SIB-related genetic disorder of Lesch-Nyhan syndrome (Lesch & Nyhan, 1964) occurred almost at the same period as the Lovaas, et al. (1965) work on behavioral assessment and intervention for SIB. These two strains of research continued independently for several years until Nyhan (1970) coined the term “behavior phenotype,” and began attempts at behavioral and pharmacological intervention for Lesch-Nyhan cases (see Rojahn, et al., 2008 for a review). Although many of the effects he found at the time were only transient, research on gene-brain-behavior relationships among both human and animal models was begun and has progressed steadily since then. There are now more than 15 genetic syndromes with a high risk of disabilities and severe behavior problems (see Mayo, et al. Table 1, this issue). In addition to those already discussed in the Kennedy
model of aggression, there are also several other gene mutations and polymorphisms associated with SIB in humans, i.e. the pro-opiomelanocortin system, the POMC gene, which is the precursor to beta-endorphin and ACTH (Sandman, Spence, & Smith, 1999), with aggression in mice, i.e. the COMT gene, which is the precursor of the catabolism of dopamine (Gogos, et al. 1998), and with self-aggression in primates, i.e. the TPH-2 gene, which controls the rate-limiting enzyme in the production of serotonin in the brain which in turn impacts mood regulation and obsessive and compulsive behaviors (Chen, et al., 2010).

### Integration and Future Directions

It has long been accepted that severe behavior problems in people with intellectual disabilities are multiply caused and multiply affected (Schroeder, Mulick, & Rojahn, 1980). Therefore, all of the above research streams are interconnected and should not be viewed in isolation. They require interdisciplinary collaboration and expertise if we are to advance our knowledge in this field. Each time we take such a view, we see additional levels of complexity of the questions and answers and new avenues of research. For instance, we now have extensive descriptions of behavior phenotypes of different genetic syndromes involving SIB and aggression, but few explanations as to how they actually interact to produce their end result. Earlier models, e.g. Guess and Carr (1991), stressed only developmental changes resulting from environmental factors, but Rutter, Moffit, and Caspi (2006) have shown that gene-environment interactions play a powerful role in the development of physical and mental health disorders. Langthorne and McGill (2008) have given a specific seven-stage model of how gene-environment interactions may occur in order to develop into SIB for people with disabilities. Rojahn, et al. (2008) have also given a multidimensional model of how SIB may develop over the life span. These models are worth exploring, and, guiding research in the future. They require that we pursue our research efforts in a multimodal and interdisciplinary manner, since they are all part of multiple causes and multiple effects of severe behavior problems among people with disabilities.

### Acknowledgments

Supported by NIH Fogarty International Grant No. HD 060500

### References


