THE JOURNAL OF
CHILD PSYCHOLOGY AND PSYCHIATRY
ACAMH
Journal of Child Psychology and Psychiatry 51:4 (2010), pp 333–340 doi:10.1111/j.1469-7610.2010.02226.x

Editorial: Developmental transitions to psychopathology: from genomics and epigenomics to social policy

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'*Prodrome: An early, nonspecific set of symptoms that indicate the onset of disease before specific, diagnosable symptoms occur*' (National Research Council and Institute of Medicine., 2009)

Mental, behavioral, and developmental disorders with childhood onset are a major public-health concern (WHO, 2005). Based on the National Comorbidity Survey Replication study, about half of all Americans will meet the criteria for a DSM-IV disorder sometime in their life, with first onset usually in childhood or adolescence (Kessler et al., 2005). Impulse control and anxiety disorders lead the way with a median age of onset of 11 years of age. It is likely that a majority of mental, behavioral, and developmental disorders begin in childhood and adolescence. Yet the mental health needs in young people are often unmet, even in high-income countries (Leckman & Leventhal, 2008; UNICEF, 2007). Given the stigma associated with mental disorder and the small numbers of trained professionals, there is an urgent need to develop efficacious interventions aimed at prevention or early treatment that can be implemented by non-specialist health workers in primary health care settings (National Research Council and Institute of Medicine, 2009). The focus of this annual review issue is the importance and the current status of prodromal research. As various reformulations of diagnostic criteria are being considered as part of the DSM-V and ICD-11 deliberations, there is an urgent need to highlight the importance of developmental and dimensional processes that contribute to the emergence of full syndromes (Hudziak, Achenbach, Althoff, & Pine, 2007; Pine et al., 2010; Regier et al., (2009); Shaffer, Fischer, & Burke, 2010).

Understanding how best to identify and intervene with individuals at clinical high risk for schizophrenia, for example, is an area with a long history, increasing maturity and sophistication (Correll, Hauser, Auther, and Cornblatt, in press). For other disorders, such as pediatric-onset major depression, the stage is set for a major advance in the years to come (Kovacs & Lopez-Duran, in press). For other conditions, including pediatric-onset bipolar disorder, despite significant progress and potential, progress towards developing efficacious early interventions has just begun (Luby & Navsaria, in press). Finally, for substance use disorders, but indeed for all disorders, the question arises: Is defining a prodrome even possible in the absence of an accurate understanding of developmental pathophysiology underlying the disorder (Costello & Angold, in press; NAMHC Workgroup on Neurodevelopment, 2008)?

Questions abound in this area of research. What is a prodrome? Does the characterization of a disorder-specific prodrome have the potential to provide useful heuristics for early detection and intervention? Can a prodrome even be identified prospectively (Eaton, Badawi, & Melton, 1995)? How does a subclinical form of a disorder relate to the concept of prodrome? To what extent does our need to sort child and adolescent mental disorders (CAMDs) into discrete, reliably identified diagnostic entities create difficulties for this area of research? Will current efforts to make nosological systems more developmental and dimensional be useful in defining prodromal states? How do 'genetic and environmental risk factors' and heritable 'endophenotypes' relate to prodromes? What more do we need to know vis-à-vis specific disorders, or more especially, overlapping groups of disorders, before significant progress can be made?

Despite these questions, certain themes and perspectives recur throughout this issue. Perhaps most prominently, how the child's genetic endowment, prenatal environment, temperamental predisposition, early parenting, peer relationships, and larger social and intergenerational environments shape and mold the child's behavior and the relevant neural pathways over the course of development.

Tremblay (in press) touches on each of these issues as he explores the origins of disruptive behavior problems, reminding us of the evolutionary value of aggressive behavior for our species and that the peak frequency of physical aggression for most humans is 'somewhere between 2 and 4 years of age.' He also points to the critical importance of genes and other features of the child's early life circumstances: 'maternal characteristics – lifestyle – mental health, family characteristics, maternal parenting and child

Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

characteristics' and their potential power in epigenetically shaping aspects of the child's behavioral regulation. The importance of these genetic and early environmental risk factors is amply demonstrated in prospective, longitudinal studies (Odgers et al., 2008). Tremblay also challenges us to study in depth the developmental trajectories not only of children at risk (including their brain development) but to study the developmental trajectories of parenting and the impact of variations in DNA methylation as they relate to the course of disruptive behavior. The major conclusion he draws from five decades of longitudinal studies on disruptive behavior is that the time is right for investments in large collaborative early experimental interventions modeled in part on the work of David Olds and his colleagues (Donelan-McCall, Eckenrode, & Olds, 2009; Olds, Sadler, & Kitzman, 2007). These randomized trials focused on very early interventions for first-time mothers, judged to be at high risk, that were initiated as soon as possible during the pregnancy and that continued through the first two years of life. Finally, in commenting on existing taxonomies, Tremblay concludes that subtypes of disruptive behavior should not be aggregated and that there are two relevant dimensions (overt–covert) and (destructive–nondestructive) that should be embodied in future diagnostic systems.

Many of the same developmental and dimensional themes addressed by Tremblay recur in the Sonuga-Barke and Halperin (in press) review of the developmental phenotypes and causal pathways associated with attention deficit hyperactivity disorder (ADHD). Like other disruptive behavioral disorders, ADHD is perhaps best viewed as a heterogeneous condition that arises from the dynamic interplay of multiple genes and environmental exposures and adversities that affect multiple brain-based developmental processes (Thapar, Langley, Asherson, & Gill, 2007; Thapar et al., 2009). Inattention and impulsivity/hyperactivity appear to be separable dimensions. The onset of the disorder is best viewed as a transition of degree rather than of kind and the degree of impairment can fluctuate and is in part dependent on the child's home and educational environment. In the case of ADHD, prospective longitudinal data are ongoing with regard to brain morphology and cortical thickness (Shaw et al., 2007, 2009a). Compared to typically developing children, children with ADHD show throughout most of the cerebrum a region-specific pattern of delay in attaining peak cortical thickness. In addition, patterns of frontal asymmetries seen in typically developing children are lost in children with ADHD. How these differences are associated with specific genotypes, environmental adversities, and neuropsychological deficits is currently being explored. Preliminary evidence also suggests that some of these neuroanatomic abnormalities seen in adolescence can be slowed or reversed through active treatment with psychostimulants (Shaw et al., 2009b). Similarly, preliminary data support the potential benefits and specificity of neurofeedback training in children with ADHD (Arns et al., 2009; Gevensleben et al., 2009a). While the authors provide evidence that neurofeedback training results in changes in distinct neuronal systems (reduced theta activity in the centro-parietal area) (Gevensleben et al., 2009b), additional well-designed randomized studies are needed to replicate these findings by independent groups of investigators and to determine their duration and long-term clinical significance.

Sonuga-Barke and Halperin also present an ambitious agenda for future research to understand more fully the causal pathways so that *early* preschool cognitive and social interventions can be undertaken that will prevent or moderate the course of the disorder (Sonuga-Barke et al., 2006). Although they acknowledge the possibility that early intervention may not be an effective strategy in ADHD, particularly in terms of its ability to fundamentally redirect developmental pathways, they make a strong case for such research efforts to be thoughtfully undertaken. As a first step, they point to the need to identify subgroups of children that have distinct neuropsychological phenotypes and developmental trajectories and then to test developmentally appropriate and rewarding interventions that can be applied in real-life settings that are specific for each subgroup.

Steady efforts to identify the early signs and symptoms of schizophrenia have been ongoing since at least the 1980s. As documented in the review by Correll et al. (in press), significant progress has been made over the past 15 years as teams of investigators have sought to develop methods to identify individuals at high risk and to test a variety of interventions to prevent conversion to the full syndrome. After recounting the development and validation of assessment tools, the authors provide a comprehensive review of the clinical and biological risk factors associated with being at high risk of developing schizophrenia. They also provide a useful summary of the completed and ongoing clinical trials. They point to the gradual move away from second-generation neuroleptics towards phase-specific interventions with more benign risk–benefit ratios including the increasing use of neuroprotective agents alone or in combination with a broad range of psychosocial interventions such as various forms of cognitive behavioral therapy (CBT). The authors conclude that with the possible exception of the potentially enduring beneficial effects of eicosapentaenoic acid (EPA, an omega-3 fatty acid) (Amminger et al., 2007a, 2008), the benefits from other interventions including active treatment with CBT, low-dose antipsychotic or combined low-dose antipsychotic plus CBT last only as long as patients receive the active treatment. If the EPA findings are replicated, this could be a major advance for the

field. Other multisite trials are under way with EPA and other putative neuroprotective agents including D-serine and sacrosine (see: http://clinicaltrial.gov/ct2/). Based on initial double-blind studies in individuals with first episode schizophrenia, N-acetyl cysteine (NAC) appears to be another agent with real promise (Berk et al., 2008).

Other areas to keep in mind include the advances being made in understanding the genomics, epigenomics, as well as the neurobiological substrates of schizophrenia and how these emerging areas of science undeniably point to the overlap of schizophrenia with multiple other disorders including bipolar disorder and autism spectrum disorders (ASD), among others. On the genomic front, the prevailing view of complex neuropsychiatric disorders being the product of multiple genetic variants, each with a small impact on disease risk, is gradually being replaced by the view that in many instances, schizophrenia is genetically highly heterogeneous and that many predisposing mutations are rare and recent, perhaps occurring just in single cases or families, but that these mutations are highly penetrant (McClellan, Susser, & King, 2007). This 'common disease–rare alleles' hypothesis has led the way to major gene discoveries and a rethinking of the impact of recent mutations including copy number variation (CVN) as well as stochastic epigenetic variation (Feinberg & Irizarry, in press). This innovative stochastic model may provide a new non-Lamarckian theory for how *heritable* epigenetic variations can alter brain development, leading to selectable phenotypic variation within the context of a changing environment. Individuals with schizophrenia may have one *de novo* hit and/or a second or third hit from rare, family-specific, transmitted alleles. This sets the stage for phenotypic variation and the expression of a broad range of disorders (from ASD, to severe intellectual disability, to schizoaffective and bipolar disorder) depending on how and when in development the complex neurodevelopmental pathways associated with CAMDs are altered (Addington & Rapoport, 2009). This viewpoint is consistent with the conclusions reached by Correll et al. (in press) indicating that many of the gray-matter abnormalities seen in prodromal cases (primarily involving the temporal, prefrontal, limbic, and cerebellar regions) may be a consequence rather than the cause of the disorder. It is also abundantly clear that certain types of social adversity and drug exposures can play an important role, leading to biased cognitive appraisal and delusional interpretations of perceptual experiences. In any case, if specific, but rare, syndromic causes of schizophrenia can be identified, this will allow for early screening and intervention.

The review of Yirmiya and Charman (in press) summarizes the status of research on the early manifestation of ASDs. Viewed from a historical perspective, Losche (1990) in a report published in our *Journal* was the first to analyze home videos of children who were later diagnosed with ASDs. Our *Journal* also has a long history of monitoring the early developmental course of children at high risk for autism (Charman & Baird, 2002; Chawarska, Klin, Paul, Macari, & Volkmar, in press).

The most common early signs detected by 18 months are delays in early social communication. Language regression appears to be differentially associated with narrowly defined autism (Baird et al., 2008; Pickles et al., 2009). Some of the other more striking findings include that many high-risk children (siblings of children with autism) also show a specific vulnerability in language development by 24 and 36 months (Yirmiya, Gamliel, Shaked, & Sigman, 2007). However, despite these deficits, many of these high-risk children *do not* go on to develop the full syndrome.

Emerging brain imaging data continues to point to abnormalities in connectivity and volume across specific brain regions including prefrontal regions, the amygdala, superior temporal and fusiform cortices, the thalamus, and the cerebellum (Amaral, Schumann, & Nordahl, 2008; Casanova et al., (2009); Mosconi et al., 2009; Pelphrey & Carter, 2008; Stanfield et al., 2008). We have much to look forward to from imaging studies that begin at the earliest possible age and are longitudinal rather than cross-sectional in design. One has the sense that the secrets of the neuropathology of autism, similar to early-onset schizophrenia, and their interface with recent, but rare genetic mutations have yet to be elucidated (Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009). Although autism does not remit in the majority of children, it is also clear that early intensive behavioral and cognitive interventions can make a real difference in many cases. Therefore, the development of targeted therapies based on pathophysiologically and etiologically defined subtypes of ASD remains an important and achievable goal for our interdisciplinary field. As in schizophrenia, there are also promising developments in the use of neuroprotective agents (Amminger et al., 2007b; Bent, Bertoglio, & Hendren, 2009).

Next, Luby and Navsaria (in press) document that during the past decade, interest in and research on pediatric bipolar disorder (PBD) have increased substantially. Prevalence rates of the disorder have doubled in outpatient settings, and twice as many research articles were published on this topic in the past five years as in the prior decade (Leibenluft & Rich, 2008). Efforts to identify PBD in children as young as preschoolers have been ongoing (Luby, Belden, & Tandon, in press). Leaving aside the diagnostic complexities associated with children and adolescents with severe chronic irritability, hyperarousal, and hyperreactivity, who reflect the population in whom the diagnosis of PBD is most rigorously debated, it is clear that there are promising findings vis-à-vis the prodrome of PBD. For us the most exciting portion of the review was the detailed look at

an ongoing prospective study in an Amish population (Egeland et al., 2003). This population was of great interest given the known high genetic loading for bipolar disorder in this population isolate, the presence of large sibships, stability of family life, and geographic immobility in Amish communities. In the study, children of bipolar parents and children of unaffected parents are being regularly evaluated using a prospective design. Based on ratings done blindly to the family history, the children of bipolar parents were found to exhibit greater mood lability, anxiety, excitability, and somatic complaints, as well as often described as being 'stubborn' or 'determined.' A 10-year follow-up of this same sample revealed additional prodromal markers: high energy, decreased sleep, problems with thinking and concentration, and excessive loud talking (Shaw et al., 2005). Despite the unusual features of the sample and the limited generalizability of these findings, this study indicates that some pathophysiological processes may be under way in some individuals almost a decade prior to the onset of the full clinical disorder. Importantly, they also suggest that prodromal symptoms often are episodic.

Discovery of the specific genetic variations associated with these traits will be a major step forward. If the 'common disease–rare alleles' hypothesis is correct, here is a perfect opportunity to exploit our expanding knowledge base (Feinberg & Irizarry, in press; McClellan, Susser, and King, 2007). What better way to resolve the current diagnostic controversies than to actually have valid pathophysiological markers? It is also likely that some of the neurodevelopmental substrates of PBD will be shared by a range of other disorders including major depressive disorder (MDD), anxiety disorders, ADHD, and schizophrenia.

In contrast to schizophrenia and major depressive disorder, the development and use of preventive interventions focused on PBD is largely underexplored and, as pointed out by Luby et al. (in press), significant caution is warranted concerning the use of pharmacologic agents in high-risk children until additional data are available (Correll et al., 2009). Alternatively, there is an increasing body of empirical evidence supporting the efficacy of psychotherapeutic strategies, particularly Family Focused Therapy (FFT). The use of an adapted version of FFT for preventive intervention has also shown promise in preliminary studies (Miklowitz & Chang, 2008).

The Kovacs and Lopez-Duran (in press) review usefully summarizes the vast, convergent literature concerning the power of subclinical symptoms of depression and anxiety to predict the subsequent onset of MDD (Shankman et al., 2009). They also propose a clear set of strategies to enhance the impact of both primary and secondary prevention programs (Gladstone & Beardslee, 2009; Stice, Shaw, Bohon, Marti, & Rohde, 2009). Key to their strategy is to increase the 'synchrony' between dimensions of vulnerability and the content of intervention programs. Specific elements for the next generation of early intervention programs for MDD should include a rigorous selection process. Kovacs and Lopez-Duran advocate that selection should be based on well-established vulnerabilities: a positive family history of affective disorders; manifest low positive affectivity and compromised mood repair; and dysfunction in three intertwined physiological systems that contribute to affectivity and mood repair (the hypothalamic–pituitary–adrenal axis [HPA] axis, cerebral hemispheric asymmetry, and cardiac vagal control [CVC]). The intervention itself would also focus on developmentally sensitive approaches to support mood repair (Kovacs et al., 2006) as well as neurophysiological techniques to enhance mood and modify the HPA and CVC (DeGood & Redgate, 1982; Hatch, Borcherding, & German, 1992; Karavidas et al., 2007). Unfortunately, implementation of such a preventative intervention is years away as the relevant work in children and adolescents affected by MDD is just getting under way. Nevertheless, if Kovacs and Lopez-Duran are correct and these techniques can be utilized in a developmentally appropriate fashion, this may set the stage for a major step forward for the field.

Childhood and adolescence is the key developmental period for the development of anxiety symptoms and syndromes, ranging from transient mild symptoms to full-blown anxiety disorders (Kessler et al., 2005). Degnan, Almas, and Fox (2010) in their review focus almost exclusively on the importance of temperamental reactivity (i.e., behavioral inhibition) evident early in life and the child's early environment (parenting styles, child care, and peer relationships) as they consider the etiology of childhood anxiety disorders. Specifically, what is needed to advance the field is longitudinal research programs focused on exploring the associations between the environmental factors, e.g., specific parenting factors such as being taught how to be afraid as well as the impact of peer rejection, exclusion, and victimization, and a child's temperamental reactivity to novelty and threat. They argue that elucidating these factors and mechanisms is essential for the development of empirically based prevention and intervention programs. While we concur with this conclusion, we would also argue that similar to the longitudinal studies of early-onset schizophrenia and ADHD, discussed above, longitudinal studies of children with pediatric anxiety disorders that incorporate imaging and genetic components will also be crucial to move this area of work forward. Complementary evolutionary and epigenetic perspectives also support the importance of work across species (Feinberg & Irizarry, in press; Kaffman & Meaney, 2007; Leckman & Mayes, 1998; Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009).

Stice, Ng, and Shaw (in press) provide compelling evidence that a variety of self-perceptions, body

dissatisfaction, and dietary restraint may constitute prodromal elements of eating disorders. Despite the prevalence and high morbidity and mortality associated with these disorders (Crow et al., 2009), secondary prevention trials have been few in number. Their preliminary results, however, indicate that interventions that reduce the idealization of thinness and the associated 'body dissatisfaction' and negative affect significantly reduce eating disorder symptoms in at-risk groups (Stice, Shaw, & Marti, 2007; Stice, Marti, Spoor, Presnell, & Shaw, 2008). More research is needed to document the genetic and conserved neurodevelopmental pathways associated with appetite and weight control (Kas, Kaye, Foulds Mathes, & Bulik, 2009; Lowe, van Steenburgh, Ochner, & Coletta, 2009). Perhaps the most surprising observation for this body of work is that for bulimia nervosa dietary restriction reduces, rather than increases, eating pathology (Burton & Stice, 2006).

The last contribution for this annual research review issue is the challenging article by Costello and Angold (in press) that persuasively challenges whether or not prodromes can be defined for substance use disorder, or for that matter any CAMD, until the underlying pathobiology is known. Although they make a modest case that substance abuse might be considered prodromal to substance dependence, they argue that until they have a 'clear definition of the end-state disease,' the task of defining a prodrome is simply logically impossible. We agree, but given the urgent need for our interdisciplinary field to develop efficacious interventions aimed at prevention or early treatment (National Research Council and Institute of Medicine., 2009), we are grateful to all of the scientists who have contributed to this field and especially to those who authored the articles contained in this issue. With regard to substance abuse, there is evidence of modest multiyear effects of preventive interventions on reducing substance abuse (National Research Council and Institute of Medicine., 2009). The most effective of these programs are delivered primarily by peer leaders (Gottfredson & Wilson, 2003) and focus on life and social skills (Faggiano et al., 2005). We also note, with some relief, that substantial progress is being made in understanding at a deeper level the neurobiology of substance use disorders (Haber & Knutson, 2010; Koob & Volkow, 2010; Sesack & Grace, 2010).

Finally, we are pleased to announce that the 2011 annual review research issue will focus on the importance of the advances within the developmental neurosciences and their impact on our understanding of developmental psychopathology. The reviews will cover everything from the patterning and plasticity of the cerebral cortex and the fetal origins of mental health, to critical periods and the role of epigenetic modifications on brain development, to a focus on the developmental shifts in the effects of genes and environment over the course of human brain development, to the promise of stem cell research to understand and treat CAMDs.

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