Early neurodevelopmental and temperamental characteristics in childhood onset depression

Ph.D. Thesis

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RELATED ARTICLES

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III. Vetró, Á., & Kapornai, K., (2008). A pszichopathológia fejlődése in Vetró, Á. (Ed.) *Gyermek és Ifjúságpszichiátria Medicina*, Budapest

IV. Vetró, Á., Baji, I., Benák, I., Besnyő, M., Csorba, J., Daróczy, G., Dombovári, E., Kiss, E., Gádoros, J., Kaczvinszky, E., Kapornai, K., Mayer, L., Rimay, T., Skultéty, D., Szabó, K., Tamás, Zs., Székely, J., Kovács, M.. (2009) „Risk factors in childhood onset depression" research design, implementation, proceeding: history of 13 years: experience in grant preparation, writing organization in relation to an American NIMH Grant. *Psychiatria Hungarica*, 24(1), 6-14.

V. Kiss, E., Kapornai, K., Tamás, Zs., Baji, I., Rimay, T., Mayer, L., Gádoros, J., Barr, C., Kovacs, M., Vetró, Á. And the International Consortium for Childhood-Onset Depression: Characteristics and risk factors of childhood-onset depression in Hungarian child and adolescent population. *European Psychiatric Review*, in press.

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Summary

Introduction: Identification of early risks for childhood onset major depression (COD) can play a significant role in the intervention and prevention to reduce the severity, duration and long-term consequences of major depressive disorder (MDD). Although some investigators have studied the role of perinatal problems and developmental delay in the development of different psychiatric disorders in children and in depressed adults, the number of available studies investigating the effects of these early risk factors in relation to early onset internalizing psychopathology (COD and anxiety disorders) is limited. From other atypical childhood characteristics, early difficult temperament has been well documented as risk for psychopathology later in life. **Hypothesis:** 1.a) Perinatal problems, developmental delay, and difficult temperament are more frequent in children with COD than in community control kids and 1.b) in their unaffected siblings. 2.a) Early atypical childhood characteristics would render children vulnerable to earlier onset and more severe first episode of major depressive disorder in children. 2.b) A stable, intact, two-parent family early on will act as a protective factor and attenuate the negative impact of atypical childhood characteristics on the onset of COD. 3) Early atypical childhood characteristics would render children vulnerable to earlier onset of first internalizing disorder (i.e., the age at which the first episode of MDD or comorbid dysthymia or anxiety disorder began). **Method:** Participants were children (ages 7–14) with MDD, their unaffected (up to 18 years of age) siblings and community control kids from elementary schools. Diagnoses (via DSM-IV criteria) and onset dates of disorders were finalized "best estimate" psychiatrists, and based on multiple information sources. Mothers provided developmental data in a face-to face structured interview (COD kids and unaffected siblings) and via self-rated version of the same interview about controls. Depressive symptoms were measured by CDI (community controls). **Results:** Early neurodevelopmental characteristics (perinatal problems, delayed motor development, difficult temperament) elevated the risk for COD. Difficult temperament predicted earlier onset of MDD and first internalizing disorder, but its effect was ameliorated if the family was intact during early childhood. Further, the importance of difficult temperament decreased as a function of time. Perinatal problems and developmental delay did not impact onset ages of disorders, and none of the early childhood characteristics associated with MDD episode severity.

Conclusions: Children with MDD may have added disadvantage of earlier onset if they had a difficult temperament in infancy. Early caregiver stability may attenuate some adverse effects of difficult infant temperament. Thus improving the support for mothers dealing with infants after perinatal/neurodevelopmental problems and/or with difficult early temperament could have positive effect in the prevention of emotional disorders later in childhood.

1. Introduction

A growing body of literature confirms that major depressive disorder (MDD) is common and persistent illnesses in young people (Ryan, 2005; Birmaher et al., 1996; Nobil et al., 2003) is associated with significant impairment in school achievement, interpersonal functioning and increased risk of suicidal behavior and substance use. Based on epidemiologic studies, depression affects about 0.3%-1.4% of preschoolers (Egger and Angold, 2006; Stalets and Luby 2006), 1-2% of prepubertal children and about 3-8% of adolescents, with equal prevalence prior to adolescence in girls and boys (Birmaher et al., 1996, Costello et al., 2003; Lewinsohn et al., 1993; Zalsman et al, 2006). Thus, identification of specific risks for childhood onset major depression (COD) can play a significant role in the early intervention and prevention to reduce the severity, duration, and long-term consequences of this serious disorder.

1.1 Vulnerability factors in childhood onset depression

Numerous individual and familial vulnerability factors have been documented as risks for elevated depressive symptoms and disorder (Kapornai & Vetró, 2008). Among individual vulnerability factors, differences in temperamental and cognitive characteristics, in emotion regulation and in neurobiological regulation, as well as non-affective psychopathology (anxiety) have been extensively identified as possible risk for depression in children (Birmaher et al., 1996; Garber, 2006; Zalsman et al, 2006). Familial risks involve both genetic factors (e.g., familial or parental history of mood disorder, specific gene polymorphisms) and psychosocial factors (e.g., quality of attachment, marital discord, poor family support, dysfunctional parenting practices) which may contribute to the development of depression in the child. Also, there are several other environmental factors (parental loss, divorce, physical/sexual abuse, illness or death of family member) which have been found to have depressiogenic effect (Mayer et al., 2008; Paykel 2003), including early adverse events (e.g., perinatal problems, maltreatment). It is most likely that the accumulation and/or interaction among multiple risks from different domains of vulnerability factors (individual/familiar; biological/environmental) play role in the development of depression (Kapornai & Vetró, 2008).

Thus, in my work I was particularly interested in early neurodevelopmental characteristics (perinatal complications, neurodevelopment problems, and atypical early temperament) that may mirror individual physiological vulnerability to onset and severity of

major depression, and in other biological and environmental factors (age, stable family background) that could have moderating effect in the development of COD.

1.2. Early neurodevelopmental characteristics and internalizing psychopathology

1.2.1. Internalizing psychopathology

Problem behavior in children and adolescents can be distinguished into internalizing disorders, which reflects the child's internal distress (e.g., anxiety and depression), and externalizing disorders, which brings the child into conflict with others (e.g., rule-breaking, aggressive behavior and ADHD) (Oldehinkel et al.,2004). These two broad dimensions of psychopathology originally generated from multivariate statistical analyses of different child behavior checklists (Kovacs & Devlin, 1998). In this empirically derived classification, dimensions of „internalizing versus externalizing" behaviors accounted for most signs and symptoms of psychopathology in juveniles (see Achenbach and Edelbrock, 1978). Disorders usually classified as internalizing are listed in the DSM-IV (American Psychiatric Assocoation., 1994) under the anxiety and depressive disorders. There are three types of depressive disorders (major depressive disorder, dysthymic disorder, atypical depressive disorder) and more than 10 anxious diagnostic entities in the DSM classification system (e.g., separation anxiety, generalized anxiety, specific phobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder).

Current research indicates that there is a strong relationship between early onset depression and anxiety disorders (Axelson and Birmaher., 2001). About 25-50% of depressed youth have comorbid anxiety disorders and about 10-15% anxious youth have depression. Regarding the comorbidity between depressive and anxiety disorders, retrospective and prospective longitudinal researches also indicate that there is a temporal relationship between the two, with anxiety predating depression (Cole et al., 1998; Kovacs et al.,1989).

1.2.2. Perinatal and neurodevelopmental problems and internalizing psychopathology

Based on previous researches obstetric-perinatal problems have been defined as preterm birth, delayed labor, atypical birth weight, caesarian section, and special care after birth (e.g., Allen et al., 1998), and neurodevelopmental difficulties as delayed standing, walking, speaking (e.g., van Os et al., 1997). Although some investigators have studied the role of obstetric-perinatal problems and developmental delay in the development of schizophrenia, obsessive compulsive disorder, bipolar disorder or attention deficit hyperactive disorder in children (e.g., Cannon et al., 2002; Geller et al., 2008; Kinney et al., 1998;

Matsumoto et al., 1999; Milberger et al., 1997, Verdoux et al., 1997), and in depressed adults (e.g., Guth et al., 1993; Preti et al., 2000), the number of available studies investigating the effects of these early risk factors in relation to early onset internalizing psychopathology is limited.

According to Preti et al., (2000), adult patients with histories of mood disorder had significantly lower birth weight (for their gestational ages) than did matched normal controls. Furthermore, Guth et al. (1993) found that obstetric complications were more common among cases with early-onset mood disorder than among those with late-onset. Vocisano et al., (1996) reported that inpatients with prolonged, severe, and functionally impairing MDD had higher frequencies of birth related problems and physical disorder in infancy than did less severely depressed outpatients. Additionally, in a birth cohort study, Gale and Martyn (2004) found that low birth weight (LBW) was associated with self-reported depressive symptoms in women during adulthood. Also, adults with childhood-onset affective disorders have been found to attain motor milestones later, and score higher on perinatal insults and lower on gross motor skills (Jaffee et al., 2002; van Os et al., 1997).

The effect of low birth weight and developmental milestones was also investigated in childhood psychopathology. For example, in a population sample of 3344 children and adolescents Liu et al. (2001) concluded that LBW and delayed early childhood development may predict the occurrence of behavioral and emotional problems (measured by Child Behavior Checklist) in later childhood and adolescence. The lower birth weight recently was investigated in relation to genetic susceptibility on depressive symptoms in children using a sample of 2046 twins (aged 8-17 years) (Rice et al., 2006). As Rice et al (2006) found, the effect of lower birth weight for gestational age on depressive symptoms is greater in children with genetic risk, although they emphasized that the association between birth weight and depression does not imply causality. Indeed, there are conflicting results about the link between LBW and early onset depression. A recently reported finding suggested that LBW predicts depression only in adolescent girls (Costello et al., 2007) and there are reports of negative findings in the literature (e.g., Allen et al., 1998; Buka et al., 1993; Najman et al., 2005). For example, findings of associations between perinatal problems and anxiety but not mood disorders (e.g., Allen et al., 1998; Cohen et al., 1989), and findings of positive relationships but lack of diagnostic specificity (e.g., Hirshfeld-Becker et al., 2004).

Inconsistencies in the literature is not surprising, given not only sampling differences, but the various ways in which studies have defined depression (i.e., clinical diagnoses, operational criteria, self-rated scales), ascertained early developmental problems (e.g., retrospective reports of adults, pediatric records, contemporaneous ratings), and quantified key variables

(e.g., event counts, severity scales). Therefore, investigating perinatal problems and other early developmental problems in larger, carefully diagnosed samples using different design in method could serve additional information to improve our knowledge about role of these factors in the development of depression (Kapornai et al., 2007; Kiss et al., 2009).

1.2.3. Temperament and internalizing psychopathology.

Although theorists differ in their definitions of temperament and in determination of its dimensions, there is a shared assumption that temperament consists of biologically rooted individual differences in behavioral tendencies that are present early in life and are relatively stable across situations and time (Doussard-Roosevelt et al., 1997; Vetró and Kapornai, 2008). For example, temperament is believed to reflect neurophysiological regulatory capacities (e.g., Rothbart and Bates, 1998), while Buss and Plomin (1984) define temperament as a set of inherited personality traits that are genetic in origin and that appear in infancy (Buss and Plomin, 1984). Twin and adoption studies also suggest that individual differences in infant and child temperament are genetically influenced. However, there is also common understanding among developmental scientists that environmental factors (perinatal events, nutrition, illness, parenting style), including impact of the child's behavior on the environment, may influence the development of the child and thus contribute to his or her expressed temperament. Based on behavioral genetic studies which are intended to estimate the extent to which genetic and environmental factors contribute to temperamental variability, genes account for approximately 20-60% of the variability in most temperament dimensions, while nonshared environments (environmental influences that are unique to each individual) account for the remaining 40-80% of the variance (see, Saudino, 2005). There is little evidence about the influence of shared environmental factors (environmental influences that are shared by family members) on some dimensions of temperament (rhythmicity, soothability, shyness, activity).

Research in infant temperament originally was stimulated by work of Thomas and Chess in the New York Longitudinal Study (NYLS) (Thomas and Chess, 1977). Based on their data of 138 infants from 85 families they posited 9 temperamental dimensions (activity, rhythmicity, approach or withdrawal to unfamiliarity, adaptability, happy or irritable mood, intensity, responsiveness, distractibility, attention-span persistence). Each dimension ranges from high to low, and an individual infant could be placed anywhere on each of the nine dimensions. Infants who were placed high on given dimensions could place high on others as well. From these clustering, Thomas and Chess collapsed the findings across dimensions and posited 3 categories of temperament: easy, slow to warm up and difficult (Vetró and

Kapornai, 2008). Temperamentally difficult infants are typically irregular in their biorhythm, they are prone to intense reactions and adapt slowly to change, and show withdrawal to novelty. Similarly, Rothbart (1989) proposed that infant temperament was comprised of differences in the degree to which infants reacted and regulated their reactivity. Whereas reactivity itself was the response to external stimuli, regulation was the manner in which the infant returned to homeostasis. Regulation could be best measured by the time it took the infant to soothe after the initial reaction. Although Fox (1998) emphasized that infants may be born with individual differences in reactivity, their regulatory capacities are far from complete at birth, infants with difficult temperament (low rhythmicity, intense reactivity, difficulty in soothing) were most likely to develop emotional and behavioral problems in later childhood. Indeed, the link between difficult temperament in infancy and in early childhood and later behavioral problems has been well documented in the literature (Goldsmith and Lemery, 2000; Keenan et al., 1998; Maziade et al., 1989; Mehregany, 1991, Rubin et al., 2003;). For example, in relation to internalizing psychopathology, early difficult temperament as biological regulatory problems including persistent crying and atypical sleeping and/or feeding patterns has been associated with subsequent internalizing symptoms and disorders in childhood (e.g., Keenan et al., 1998; Maziade et al., 1989) and adults with childhood-onset affective disorders have been found to be rated as more difficult babies compared to individuals with adult-onset depression (Jaffee et al., 2002). Specifically, Jaffee et al. (2002) investigated a representative birth cohort (Dunedin Multidisciplinary Health and Development Study) from childhood to adulthood, using DSM-IV diagnoses of MDD. The infant temperament was categorized as “easy” or “difficult” based on mothers’ report on a 3-point scale (0, “easy all of the time” to 2, “very difficult to manage”) whether their child had been difficult to manage as a baby. Furthermore, early low rhythmicity (sleep and eating irregularity) were also reported as predictive factor in childhood and adolescent internalizing psychopathology (Ong et al., 2006). In this study, maternally reported irregular sleep rhythmicity predicted adolescent onset MDD and anxiety disorders in an at risk population of offsprings of depressed parent. To evaluate the early temperament rhythmicity of the child up to 6 years of age, the authors used items regarding the eating and sleeping habits from the Dimensions of Temperament Survey (Lerner at al., 1982) with modified time framing to enhance the accuracy of retrospective recall of the parent. However, there was positive association between the depression and sleep irregularity in adolescent, they didn’t find such association regarding childhood onset MDD and the low eating rhythmicity was predictive for childhood onset anxiety only.

Notwithstanding the well documented link between early temperament and emotional problems later in childhood, the association between early difficult temperament and childhood onset depression is far from clear and could be moderated by other factors (parental attitude) as well (Rothbart, 1981; Wasserman et al., 1990). Similarly, it was postulated by Fox (1998) that although temperament seems to be biologically based, learning to regulate emotional expressions (which is key element in the development of internalizing psychopathology) depends on caregiver input and socialization. Additionally, the cognitive social learning theory acknowledge the importance of biological (genetic, neurophysiologic) factors in emotional development, the role of learning process of emotion regulation (highly depend on family factors such as parental behavior, parent- child relationships, caregiver changes) in the development is also emphasized (Vetró and Kapornai, 2008).

1.3. Factors which may have influence on the link between early neurodevelopmental characteristics and depression

In line with theories detailed above and with suggestions that early risk factors should be studied in models that examine multiple and interactive effects (e.g., Goodman, 2002), in my work several factors are considered which could moderate the association between early childhood characteristics and COD. For example, the child's sex emerged as possible moderator factor, given that neonatal health or motor skill problems have been found to relate to depression or anxiety for boys but not for girls (Reinherz et al., 1999; Sigurdsson et al., 2002). Also, there are some indications that marital partner changes early during a child's life may be one factor in child depression (Kasen et al., 1996; Najman et al., 2005; Phillips et al., 2005). For example, in relation to family status, Kasen et al., (1996) have found elevated risk for depression in boys from families with single mother, while in families with step-parent the girls had higher risk for depression. These results also highlighted the importance of multiple interactive effects of different vulnerability factors. Furthermore, mother's age at birth of the child suggested as influencing factor as well, because relatively younger (Jaffee et al., 2001) and older maternal ages are associated with increased rates of complications for offspring (Gray et al., 2004; van Katwijk & Peeters, 1998). Finally, parents' educational level, and household size are those variables which are usually used as proxy measures for socioeconomic status, which also may affect the development of depressive symptoms and disorder in children (Vetró and Kapornai, 2008).

1.4. Aims and hypotheses

Based on the findings from the literature detailed above, I intended to explore the role of early neurodevelopmental and temperamental problems in the development of childhood onset depression using different study design (case-control studies using different control samples, cross sectional study of children with COD) in a large, representative national sample of Hungarian children. The aims of my work were: 1) to test whether depressed children differed from community controls and/or unaffected siblings in terms of early neurodevelopmental and temperamental characteristics; 2) to examine how early atypical neurodevelopment and difficult temperament affect the features of major depression (age of onset, severity) in COD children; and 3) given that MDD often presents with comorbid dysthymic and anxiety disorders (generally emerge earlier than does MDD), to examine whether early neurodevelopmental and temperamental problems have affect on these diagnoses as well. More specifically, I hypothesized:

1.a) Perinatal problems, developmental delay, and difficult temperament are more frequent in children with COD than in community control kids.

1.b) Perinatal problems, developmental delay, and difficult temperament are more frequent in children with COD than in their unaffected siblings.

2.a) Perinatal problems, developmental delay, and difficult infant temperament would render children vulnerable to earlier onset and more severe episodes of major depressive disorder.

2.b) a stable, intact, two-parent family early on will act as a protective factor and attenuate the negative impact of atypical childhood characteristics on the onset of COD.

3.) Given that the effects of early neurodevelopmental problems may not be specific to MDD I hypothesized that perinatal problems, developmental delay, and difficult infant temperament would render children vulnerable to earlier onset of first internalizing disorder (i.e., the age at which the first episode of MDD or comorbid dysthymia or anxiety disorder began).

2. Methods

Participants

In the present work I report on three different studies using different samples (MDD probands, their unaffected siblings, community controls from school based sample) from a large Hungarian study (Vetró et al., 2009; Kiss et al., in press) (a part of a Program Project in

Pittsburgh, NIMH grant #MH056193, ended in June, 2007) of genetic and psychosocial risk factors in childhood-onset depression (COD study) (Figure 1.). The recruitment procedures and the descriptions of the different samples I used in my different exploratory studies are detailed below.

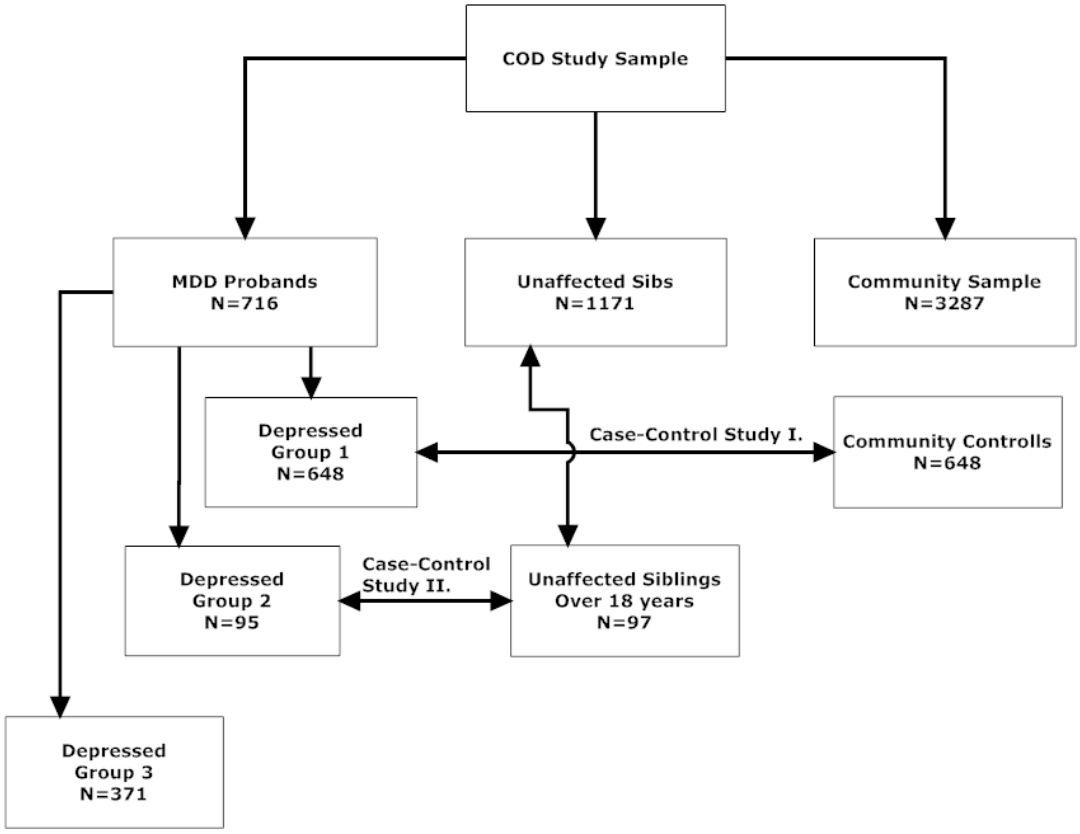


Figure 1. Study Samples

2.1 Enrollment and assessment procedures in COD study

2.1.1 MDD probands

Children were recruited through 23 child psychiatric facilities (7 of which had both inpatient and outpatient units) across Hungary, serving both urban and rural areas (Vetró et al., 2009). They provided services to at least 85% of the newly registered child psychiatry cases, giving us access to a significant portion of the referred population nationwide. Children presenting at each site were scheduled for a research assessment if they met the following criteria: 7.0 years to 14.9 years old, not mentally retarded, no evidence of major systemic medical disorder, had available at least one biologic parent and a 7 –17.9 year-old sibling (required by the study's genetic component), and attained a predetermined cut-off score on one of various depressive symptom screens (e.g., the short version of the Children's Depressive Inventory; Kovacs and MHS Staff, 2003; selected items from the Child Behavior

Checklist (Achenbach, 1991). Seeking to maximize sensitivity and specificity, these initial screens were based on a previous pilot study with a different clinical sample in Hungary. A clinician-rated symptom scale was used with those patients who had been under care for a while. Further, over the course of recruitment, we adjusted the screen cut-offs, and also screening measures used, so that we could minimize false positives. Children meeting these initial criteria were scheduled for a 2-part evaluation, conducted on 2 separate occasions, about 6 weeks apart, by different clinicians. We obtained written consent for participation signed by both parents and the child, in accordance with the legal requirements in Hungary and the University of Pittsburgh, Pittsburgh, USA. All study procedures and consent forms were approved by the University of Pittsburgh's Institutional Review Board and the Board of Ethics of Human Research of the Hungarian Council for Scientific Research in order to comply with both countries' ethical rules.

The first part of the evaluation entailed administration of the "Mood Disorder Module" of a diagnostic interview (see measurement section), as well as the Intake General Information Sheet (IGIS), a comprehensive demographic and anamnestic data form. Participants also completed self-rated scales (not included in the present report). To set the proper framework and facilitate recall, evaluations started with a semistructured interview, designed to construct a "time line" for the patient from birth to the date of the assessment. The time-line anchors included major "public" events with the corresponding dates (e.g., Christmas, start of a school year) and personally relevant events (e.g., birth of a sibling, both positive and negative familial events, variables reflecting on adjustment). The time-line ("chronograph") served to identify the times when the child's symptoms became problematic and to date disorder onsets and offsets.

The second part of the evaluation involved the full diagnostic interview and the completion of additional self-rated scales, but was administered only if the child proband had met DSM criteria for mood disorder at the first evaluation. (If DSM criteria were not met, the child was assigned an "at-risk" status and entered a follow-up arm of the study). For our diagnostic interview, we used the Interview Schedule for Children and Adolescents–Diagnostic Version (ISCA-D), which is an extension of the Interview Schedule for Children and Adolescents (ISCA) (Sherrill and Kovacs, 2000). The interview, which covers the relevant Axis-I DSM-IV as well as some DSM-III disorders, was conducted by the same interviewer separately with the parent about the child, and the child about him/herself, yielding symptom ratings and diagnoses for "current" as well as "lifetime" disorders. Results of both the first and second parts of the assessments and associated documentation (e.g., psychiatric records) were subjected to a consensus diagnostic procedure (Maziade et al.,

1992). Pairs of senior child psychiatrists, trained as Best Estimate Diagnosticians (BEDs), separately reviewed all material, and then together derived consensus diagnoses. Proband status as well as onset dates of disorders, was based on best-estimate consensus. As described in connection with previous work ([Kovacs et al., 1984a] and [Kovacs et al., 1984b]), operational rules were used to define disorder onset and recovery, and "midpoint" rules were used to date onsets and offsets, if more exact dating was not possible.

The interviews were administered by child psychiatrists and psychologists who completed 3 months of didactic and practical training in the semi-structured interview technique. They were required to reach an average of 85% symptom-agreement on 5 consecutive videotaped interviews against "gold standard" interview ratings provided by the trainers. Routine monitoring and follow-up training sessions served to minimize rater drift. All interviews were audiotaped. Interrater reliability on ISCA-D symptoms was satisfactory (using audiotapes of interviews for *n*=46 pairs of raters). For MDD symptoms, kappas ranged from .64 to .88, with 80% of the coefficients at or above 0.70. For DD symptoms (using DSM-IV criteria), kappas ranged from 0.38 to 0.93, with 80% at or above 0.70. For Generalized Anxiety Disorder symptoms (the most common DSM-IV anxiety diagnosis), kappas ranged from 0.53 to 1.00, with 62.5% at or above 0.70. Similar inter-rater reliability coefficients were obtained for other ISCA-D disorders as well (e.g., Kiss et al., 2007).

The available MDD probands (n= 716) in the COD study, aged 11.8 years (SD= 2.1) on average at study entry, included 390 (54.5%) boys, and 62.2% lived in intact families (both biological parents present); the average household had 4.6 people (SD= 1.2). Reflecting the ethnic composition of Hungary, 94.4% of the sample was Caucasian and the rest were minorities, including Roma (gypsy) and Africans. Mothers had, on average, 11.3 years of education (SD=2.7); fathers had 11.2 years (SD=2.7) of schooling. Anxiety (32%) was the most common co-morbid diagnosis; altogether 50% had major Axis I. psychiatric comorbidity.

2.1.2 Unaffected siblings

If a child met the diagnostic criteria of major depressive disorder and become MDD proband in the COD study, the available siblings of him/her in the appropriate age range were scheduled for the same research screening procedure and in case of positive screening, for the same comprehensive diagnostic assessment procedure, described above. As the probands in the study, siblings were followed up to at least 18 years of age by sending yearly a mail-follow-up test packet (MFU). The packet (which was mailed back by the families) includes: a) parental report of interim medical and psychosocial events (short version of our SR-GIS) and

a 26-item DSM depressive symptom checklist (DSC) and b) each child's self-rated depression scale (short CDI). In case of positive screening based on this packet, the sibling was scheduled for the diagnostic assessment procedure. Unaffected siblings are the participants who have never been turned out as depressed up to their age of 18 years during the COD study. Additionally, to increase the available number of unaffected siblings we invited for assessment all the siblings over 18 years of age (not assessed earlier because of negative screenings during the study) to evaluate the existence of current as well as lifetime episode of MDD.

From the COD study, the number of available unaffected siblings over 18 years of age was 97 youngsters (for sample description see **Description of different samples** section).

2.1.3 Community controls

Children were recruited from 2 regions of Hungary (north-west and south-east). 1st – 8th grade elementary students were approached from 9 elementary schools in Szeged (2 schools), Győr (4 schools) and the vicinity (Kapuvár, Csorna and Szőreg, 1 school each). Children participated after receiving written consents from the parents. Testing was organized through the schools. Every child received a parental test package including all the forms and parental consent. Parents wishing to participate completed the forms at home and returned all questionnaires and the signed consent to school. Only those children were tested whose parents sent back the completed package. Children filled the questionnaires in school during class under supervision. The questions were read out loud in 1st through 3rd grades; children completed the forms by themselves in higher grades. Members of the research team or psychology/medical students were present during testing in some schools, in others teachers were instructed before distributing the questionnaires. Testing was done anonymously, child-parent pairs were identified by identical 6-digit code numbers. 5224 families were contacted initially, 62.9% of the families agreed to participate (N=3287).

2.2 Measurements

2.2.1 Intake General Information Sheet for Children and Adolescents (IGIS) and Self-Rated General Information Sheet (SR-GIS).

The IGIS and SR-GIS are event-focused structured interviews containing fully structured, pre-coded item response choices. In IGIS the parent is interviewed about the child's socio-demographic/family background, developmental, educational, and health history, and major life events. An entire section of the IGIS is dedicated to enumerating parental caregivers for each year of the child's life. The SR-GIS is a self-rated version of the

IGIS for the parent and both versions are used for lifetime information. The IGIS was used as a structured interview in the MDD sample, and SR-GIS was used in the community controls.

Using IGIS and SR-GIS items that pertain to the child's early development history from his/her birth to toddler age, we created four indices of atypical development: *Neurodevelopmental problems* (9 items), *Perinatal Problems* (4 items), *Developmental Delay* (2 items), and *Difficult Temperament* (3 items). The construct of temperament includes multiple dimensions tapping emotional, biological, and behavioral reactivity and regulation (). Our temperament scale included a global question on how difficult it was to comfort the infant (similar to the single-item question included as part of the investigation of Jaffee et al. (2002), and because we were particularly interested in physiological vulnerability, two items measuring biological irregularity (similar to Thomas and Chess's (1977) temperament category of rhythmicity). Each scale reflects the number of "yes" responses to the corresponding items.

In SR-GIS to make easier the rating for the parents, education categories (0=no qualification, 1=elementary school, 2=vocational school, 3=high school, 4=3 years college, 5=university) were used and coded on a scale of 0-5 points to evaluate the level of education of parents. Years of educations of the parents in the group of depressed kids had been recoded to correspond to the education categories of the community controls as follows: 0=0-7 years; 1=7,1-10 years; 2=11years; 3=12-14 years; 4=15 years; 5=16 years or more.

2.2.2 Interview Schedule for Children and Adolescents - Diagnostic Version (ISCA-D)

ISCA-D is a semi-structured interview to assess lifetime psychiatric disorders and current psychiatric status in youths up to ~age 19 to 20. It extends our earlier, symptom-based interview, which has been widely used and it has good inter-rater reliability (Sherrill & Kovacs, 2000). The ISCA-D organizes symptoms into disorders, includes most DSM-IV Axis-I diagnoses and allows assessment of "current" and "lifetime" disorders. Hungarian interviewers have achieved satisfactory inter-rater reliability (Kiss et al, 2006). The ISCA-D is completed by interviewing separately the parent (or other adult informant) about the youth, and then the youth about him/herself. For each symptom, the clinician thus has a rating derived from the adult informant interview and one from the child interview: the clinician's final rating of each symptom serves as the basis for diagnoses.

Using ISCA-D information we created an index to evaluate the MDD episode severity. This index was computed for the first episode of MDD based on 15 symptoms, each rated on a 3-point severity scale: 0 = not present; 1 = subthreshold; and 2 = threshold/clinical. If only one item was missing, that item was pro-rated. Because all children in the sample had MDD,

and the minimum of 5 symptoms rated at the "clinical" level was required for the diagnosis, the possible range for the severity score was 10 to 30.

2.2.3 Children depression Inventory-short version (CDI-Short Form)

The 10-item CDI Short Form was developed from the CDI that is a 27-item self-rated symptom oriented scale suitable for school-aged children and adolescents. The Short Form provides an easily measured, empirical assessment of the extent to which the child exhibits depressive symptoms. Based on data from normative sample (N=1266) CDI Short Form correlates r=0,89 with the full inventory (Kovacs M. & MHS Stuff; 1993). Its alpha reliability coefficient is equal to 0.80, indicating that is approximates the overall content of the full CDI at an acceptable level. Each item consists of three choices, keyed 0 (absence of a symptom), 1 (mild symptom), 2 (definite symptom), with higher scores indicating increasing severity. The total score can range from 0-20. The cut-off value for clinical depression is 7 points (Mayer et al., 2006).

2.3 Description of different samples investigated in different studies

2.3.1 Depressed group 1. and community control group in case-control study I.

To compare children with depression to community control group on early neurodevelopmental characteristics (article in preparation), I included 648 MDD probands (**depressed group 1.**) from the COD study who were 15 years of age or younger at the time of the interview on behalf of matching on age to **community controls** (from elementary schools). In the depressed group 1. there were 296 (45.68%) girls and the mean age of the children at interview was 11.69 years (SD: 2.03). The girls were older (12.02, SD:2.02) than boys (11.28, SD: 1.95). Mothers' age at the interview on average was 36.57 years (SD:5.16) and mean number of members in the household was 4.63 (SD:1.15). The mean value on the 0-5 likert scale of education was 2.36 (SD:1.21) for the mothers and 2.25 (SD:1.19) for the fathers.

The **community control group** consisted of 648 kids (45.68% girls) from the available community sample (Figure 1). Based on the SR-GIS we included those who had no psychiatric hospitalization, never had taken psychiatric medication or experienced psychiatric or behavioral problems, and did not have short-CDI scores above 7 points. The community control group further was matched to depressed group 1. on age and sex. The mean age in the community controls' group was 11.69 (SD:2.03). Mothers' age at the interview on average was 38.29 years (SD:5.05) and mean number of members in the household was 4.28

(SD:0.87). The mean education level for the mothers was 3.31 (SD: 1.24) and 3.21 (SD:1.32) for the fathers.

2.3.2 Depressed group 2. and unaffected siblings in case-control study II.

To compare children with depression to unaffected siblings on early neurodevelopmental characteristics (article in preparation), I included 95 MDD probands (**depressed group 2.**), given their available **unaffected siblings** (N=97) over 18 years of age.

In the **depressed group 2.** children (49.5% girls) were aged on average 11.35 years (SD:1.8) and their mothers at the first interview of the child were 37.81 (SD:4.10) on average. The mean number of persons were living together in the household was 4.95 (SD:1.5) in the depressed group 2. In this sample mothers were educated on average for 11.43 (SD:2.6) years of age, while this value for fathers was 10.67 (SD: 3.6) years.

According to inclusion criteria in the comparison group of **unaffected siblings** (52.6% girls) the mean age was higher (18.3 years, SD:1.30) than in depressed group, and again, by design the mothers were also older (40.87 years on average; SD: 4.30). The mean number of members in the household was 4.79 (SD:1.5). Mothers average education level was 11.31years (SD:2.5) and fathers were educated on average for 11.13 years (SD: 2.5).

2.3.3 Depressed group 3. in the study of early developmental characteristics and features of MDD

During the recruitment of MDD sample in COD study, to explore the effect of early neurodevelopmental characteristics on the features (e.g., first episode onset, severity) of MDD I investigated 371 MDD probands (**depressed group 3.**) who were enrolled by December 31, 2003 (Kapornai et al., 2007). They were aged 11.7 years on average (SD = 2.0 years, range: 7.3 - 14.9 years). At study entry, mothers' ages ranged from 26 to 57 years, with a mean of 36.5 years (SD = 5.1). Mothers' years of education ranged from 6 to 21 years (M = 11.6 years, SD = 2.8). A subset of children had comorbid disorders in addition to MDD (e.g., 34.5% had an anxiety disorder, 3.5% conduct disorder; 6.2% had oppositional defiant disorder; and 15.5% attention deficit/hyperactive disorder).

2.4 Statistical analyses

2.4.1 Case-control studies

To compare MDD probands (depressed group 1., 2.) to both community controls and unaffected siblings on neurodevelopmental variables and scales Chi2 test and Fischer exact test were used for categorical variables, and independent sample t-test for continuous variables. During the comparison the correlations between psycho-social variables and early

characteristics variables were tested by using correlation matrix with Pearson correlation coefficients method. To compare the group differences in early neurodevelopmental scales (perinatal, developmental, temperamental and total neurodevelopmental) we did analysis of covariance (ANCOVA) with controlling for psychosocial variables (sex, level of parents education, mothers' age at birth, household size). We also did separate analysis by sex to test whether the sex has influence on the associations between the early characteristics and MDD.

2.4.2 Early developmental characteristics and features of MDD study

We used survival analysis to examine the effects of variables on onset age of MDD or internalizing disorder. Survival analysis is useful with outcomes or events that depend on elapsed time, and can estimate how predictors may be associated with time to the event. Kaplan-Meier survival curves were generated for subgroups; log-rank tests were used to test statistical significance.

To test for relations between the predictors and the age at which children's first episodes occurred, we first conducted univariate Cox regression analyses with each risk scale and covariate. We report hazard ratios and 95% confidence intervals to indicate the risk of the outcome in any given unit of time, with one unit increase of the predictor. We also checked the proportional hazards assumption about time-dependence for each predictor variables. Second, in an initial multiple regression model, we included the three risk scales, as well as covariates with $p \leq 0.05$ in the univariate Cox models. All hypothesis-driven interaction terms were also included. We then used a backward elimination method, removing each (starting with the one with the largest p-value), and retaining covariates or interaction terms in the final model with $p \leq .05$. Thus, the final multivariate Cox regression models reflect the impact of independent variables and significant interaction terms, while adjusting for demographic factors (where $p \leq 0.05$).

To model the effects of early risk factors on the severity of the children's first depressive episode, we used GLM procedure. We examined the associations between the perinatal, developmental, and temperament problems, as well as how the interaction terms and covariates related to the severity of the MDD symptomatology.

3. Results

3.1 Case-control study I.

3.1.1. Prevalence rates of neurodevelopmental variables and scores of neurodevelopmental scales in depressed group 1. and community controls

Although we did matching on age and sex between depressed group 1. and community controls, other psychosocial variables still differed between them. Specifically, based on t-test in the depressed group 1. parents were less educated on average ($p<0.0001$), mothers were younger ($p<0.0001$), and household size was larger ($p<0.0001$). On average the number of persons living in household was 4.63 (SD=1.16) in MDD sample and 4.28 (SD=0.87) in community controls. The prevalence rates of specific early developmental variables (except the variable of premature/late delivery time) and all the scores on the developmental scales were significantly higher in depressed group 1. (Table 1.). Overall, the most frequent item in the depressed group 1. was the early sleep problems (about 29% of the cases) followed by the item of usually hard to comfort (28.6%), while these items were significantly ($p<0.0001$) less common in community controls (11.11% and 5.25 % of the controls respectively). Regarding the subscales, the greatest difference between the depressed and controls emerged on the difficult temperamental scale. The psychosocial variables are not correlated significantly any of the subscales (r values ranged: from 0.0005 to 0.06 in the depressed and from 0,001 to 0,06 in the control group $p>0,13$). Whereas, in both the depressed and the control group perinatal scale is slightly correlated with early difficult temperament ($r=0.13$; $p=0.008$ and $r=0.11$; $P=0.004$ respectively) and delayed development scale ($r=0.08$; $p=0.036$ and $r=0.14$; $p=0.0003$ respectively).

Table 1. Early neurodevelopmental characteristics of depressed group 1. and community controls

	Depressed group 1. (N=648)			Community controls (N=648)		
	Item endorsement		Score Mean (SD)	Item endorsement		Score Mean (SD)
Variables	**N**	**%**		**N**	**%**	
Perinatal problem scale			0.76 (0.99)*			0.57 (0.88)
Premature/late delivery	90	13.89		81	12.50	
Complications during delivery[a]	151	23.30*		104	16.05	
Very large/small at birth	135	20.83*		115	17.75	
Special care after birth[b]	117	18.06*		75	11.57	
Difficult temperament scale			0.78 (0.92)*			0.29 (0.60)
Recurrent feeding problems	139	21.52*		83	12.81	
Recurrent/chronic sleeping problems	187	28.90*		72	11.11	
Usually/often hard to comfort/soothe	185	28.59*		34	5.25	
Developmental delay scale			0.23 (0.51)*			0.10 (0.34)
Late for age when began to walk	58	8.95*		22	3.40	
Late to start to speak in sentences	97	14.97*		46	7.10	
Neurodevelopmental scale (0-9)			1.78 (1.58)*			0.99 (1.21)

[a]E.g.. excessive bleeding. "cord" around the neck. Rh incompatibility
[b]E.g.. placed in incubator. under special observation
* $p \leq 0.001$

3.1.2. Association between neurodevelopmental scales and depression

Results of the ANCOVA analyses indicated that while controlling for all psychosocial variables (sex, parents' education, age of the mothers, household size) depression significantly associated with the perinatal (F=10.73; p=0.0011), the developmental (F=21.73; p<0.0001), the temperamental (F=90.38 p<0.0001) scales and with the total score (F=80.09; p<0.0001) as well. Further, sex of the child's also associated significantly with the developmental subscale and with the total score. Regarding the developmental subscale there was significant depression-by-sex interaction as well (F=6.09; p=0.01) even after adjusting for psychosocial factors (F=6.09; p=0.01), indicating that depressed boys scored significantly higher on developmental scale (delayed in standing, walking and talking) than depressed and control girls.

3.1.3. Repeated analysis by sex

The girls (12.02. SD:2.02) in the depressed group 1. were older than boys (11.28. SD: 1.95) and scored lower on developmental (0.13; SD:0.39), temperamental subscales (0.78; SD:0.92) and on the total scale (1.56; SD:1.46) than boys did (0.33; SD:0.58. 0.79; SD:0.93 and 1.95; SD:1.65 respectively). By design, in the community control group girls were also older (mean age for girls: 12.20; SD:2.02; mean age for boys: 11.28; SD:1.95). Girls had lower ratings on developmental (0.07; SD:0.28) and on total scales (0.85; SD:1.08) than boys (0.13; SD:0.39; 1.08; SD:1.30 respectively) in this group as well. The effect of sex, indicated by the depressionXsex interaction in the developmental subscale mentioned above can be seen in the results from these data as well (Table 2.)

Table 2. Developmental delay scale in the depressed group1. and the community controls by sex

	Depressed group 1.	**Community controls**
Developmental delay scale in females (mean±SD)	0.1318±0.3856 * (N=296)	0.0709±0.2823 (N=296)
Developmental delay scale in males (mean±SD)	0.3295±0.5842** (N=352)	0.1335±0.3876 (N=352)

* $p \leq 0.05$. ** $p \leq 0.01$.

To investigating the group (depressed vs. community controls) differences by sex, chi2 test and t-test procedures were made separately for girls and boys. Results showed that in females there were no significant differences between the depressed and controls regarding the variables of late for walk (p=0.055) and late for speak (p=0.057) and the variable of premature/late delivery was significantly more frequent in control girls (p=0.0112), however at p<0.05 level, all the other early variables and subscales were significantly differentiated between the two groups favoring the depressed sample. In males the differences between depressed and controls were not significant in relation to premature/late delivery (p=0.1267), birth size (p=0.116) and early eating problems (p=0.0921). Yet, the differences between the depressed and controls boys were significant on all neurodevelopmental subscales (at p<0.05), and further the difference on the developmental scale was greater than the difference between the depressed and control females. The depression is also associated significantly to each subscales and total scores in girls and boys as well, while controlling for psychosocial variables was conducted using ANCOVA model.

3.2. Case-control study II.

3.2.1. Prevalence rates of neurodevelopmental variables and scores of neurodevelopmental scales in depressed group 2. and unaffected siblings

According to the inclusion criteria (>18 years of age) unaffected siblings were older than kids in the depressed group 2. Other psychosocial characteristics (sex rates, parents' education level, number of living in the household, mothers' age) were similar in the two groups. The psychosocial variables further are not correlated significantly any of the early neurodevelopmental subscales.

The prevalence rates of specific early developmental variables and specific scores on the different neurodevelopmental indices in the depressed group 2. and in the group of unaffected siblings are shown in Table 3. Overall, the highest prevalence rates were observed regarding the hard to comfort (27.4%) and the sleeping problems (18.9%) in the depressed group, while these items were far less common in unaffected siblings (13.4% and 9.3% respectively). Based on Chi^2 procedures, the differences on these items were statistically significant between the two groups ($p=0.01$ and $p=0,05$ respectively). The probands in the depressed group scored significantly ($p=0,021$) higher (0.62 ± 0.81) on difficult temperament scale than youths in the group of unaffected siblings (0.37 ± 0.88). Other early variables or indices didn't differentiate significantly between the two groups. Further the perinatal problem scale was slightly higher in unaffected siblings, however the difference was not statistically significant ($P=0.279$).

In both the depressed and unaffected siblings' group perinatal scale is correlated with the total developmental scale ($r=0.651$; $p<0.0001$ and $r=0.645$; $p<0.001$ respectively). Further, in the group of unaffected siblings the early difficult temperament scale significantly correlated with the developmental subscale ($r=0.262$; $p=0.010$) and with the total score ($r=0.642$, $p<0.0001$), while in the depressed group 2. the difficult temperament scale showed significant correlation with the total score only ($r=0.751$; $p<0.001$).

Table 3. Early neurodevelopmental characteristics of the depressed group 2. and unaffected siblings

	Depressed group 2. (N=95)			Unaffected Siblings>18yr (N=97)		
	Item endorsement		Score Mean (SD)	Item endorsement		Score Mean (SD)
Variables	**N**	**%**		**N**	**%**	
Perinatal problem scale			0.54 (0.79)			0.67 (0.83)
Premature/late delivery	9	9.50		9	9.30	
Complications during delivery[a]	19	20.2		17	17.5	
Very large/small at birth	11	11.6		20	20.6	
Special care after birth[b]	15	15.8		19	19.8	
Difficult temperament scale			0.62 (0.81)*			0.37 (0.88)
Recurrent feeding problems	15	15.8		14	14.4	
Recurrent/chronic sleeping problems	18	18.9*		9	9.3	
Usually/often hard to comfort/soothe	26	27.4**		13	13.4	
Developmental delay scale			0.23 (0.47)			0.18 (0.46)
Late for age when began to walk	8	8.4		5	5.2	
Late to start to speak in sentences	14	14.7		12	12.4	
Neurodevelopmental scale (0-9)			1.39 (1.28)			1.22 (1.18)

[a]E.g.. excessive bleeding, "cord" around the neck, Rh incompatibility
[b]E.g.. placed in incubator, under special observation
* $p \leq 0.05$, ** $p \leq 0.01$.

3.2.2. Association between neurodevelopmental scales and depression

Based on ANCOVA procedure, only the difficult temperament scale differentiated significantly (F=5.556; p=0.019) between the depressed group 2. and the group of unaffected siblings. Further, significant depression status-by-sex interaction was found (F=2.908; p=0.036) in the difficult temperament scale. There were no significant associations between the group status and any of the early neurodevelopmental indices in the model.

3.3. Integrated results from Case-control study I. and II. regarding the difficult temperament

The proportions of kids in the different samples with different early temperamental problems can be seen on Figure 2. All the variables referring the difficulty of early temperament were more frequent in the depressed groups than in the community controls. Although, the group of unaffected siblings was not compared to community controls, the data from case-control studies showed that early eating problems and soothability problems emerged with higher frequency in unaffected siblings, while sleeping problems were more common in community controls (11.11%) than in unaffected siblings (9.3%). The difference was the most robust regarding the item of hard to comfort/soothability, which was six times frequent in the depressed group (28.59%) comparing to community controls (5.25%) and about twice as frequent than in unaffected siblings (13.4%). Similarly, sleeping problem was far more common in the group (1.) of depressed youngsters (about 29%) than in community controls (11,11%). Investigating the difficult temperament scale, the results showed significantly higher scores in the depressed group 1. (0.78) and in the unaffected group as well (0.37) compared to the community sample (0.29), however the magnitude of the difference regarding unaffected siblings was smaller.

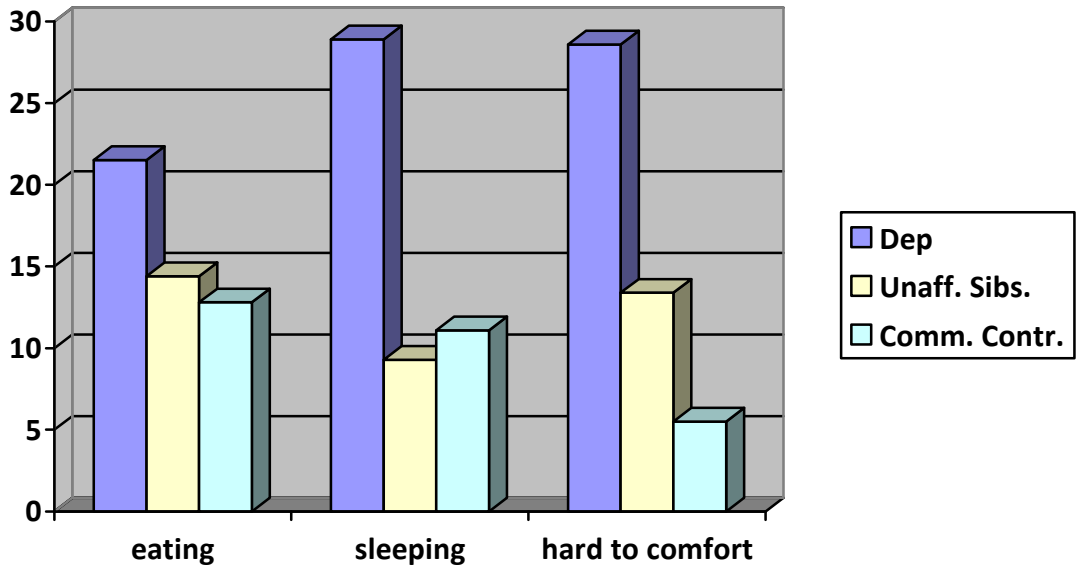


Figure 2. Rates of variables refer to difficult temperament in the different samples

3.4 Early developmental characteristics and features of MDD study

3.4.1. Prevalence rates of neurodevelopmental variables and scores of neurodevelopmental scales in the depressed group 3.

The specific variables, which comprised the 3 indices of early neurodevelopmental characteristics, had various rates in our sample (Table 4.); in general, developmental delays were least common (from about 8% to 12%) while features of difficult temperament were reported for about 24% to 32% of the cases. The 3 indices were unrelated to each other (r-values ranged from 0.02 to 0.06, $p > 0.24$), and were unrelated to mothers' age at child's birth, mothers' education level, and whether the child was reared in an intact vs. non-intact family early in life. However, boys scored higher on developmental delays ($M = 0.25$, $SD = 0.52$) than did girls ($M = 0.15$, $SD = 0.38$), $t(369) = -2.11$, $p < 0.05$.

Table 4. Early neurodevelopmental characteristics of depressed group 3. (N=371)

	Item endorsement		Score
Variables	**N**	**% of sample**	**Mean (SD)**
Perinatal problem scale (0-4)			0.72 (.98)
Premature/late delivery	47	12.7%	
Complications during delivery[a]	79	21.3%	
Very large/small at birth	70	18.9%	
Special care after birth[b]	73	19.7%	
Difficult temperament scale (0-3)			0.87 (.97)
Recurrent feeding problems	88	23.9%	
Recurrent/chronic sleeping problems	118	31.9%	
Usually/often hard to comfort/soothe	119	32.2%	
Developmental delay scale (0-2)			0.20 (.48)
Late for age when began to walk without help	30	8.1%	
Late to start to speak in sentences	46	12.4%	

[a]E.g., excessive bleeding, "cord" around the neck, Rh incompatibility
[b]E.g., placed in incubator, under special observation

3.4.2. Onset age of MDD

A series of univariate Cox Regression models yielded significant effects for child's sex, early intact family status, and maternal age at child's birth. (See Table 2 for Hazard ratios.) At the onset of their MDD, boys (M = 10.08; SD = 2.12 years) were 1 year younger than girls (M = 11.03; SD = 2.37 years). Children exposed to changes in caregivers before age four were younger at the onset of their MDD (M = 9.68; SD = 1.96 years) than those from intact families (M = 10.60; SD = 2.30 years), and children whose mothers were 35 years and older when they gave birth had earlier onset of MDD (M = 9.14; SD = 1.89) than children with mothers in the normative age group (M = 10.57; SD = 2.30).

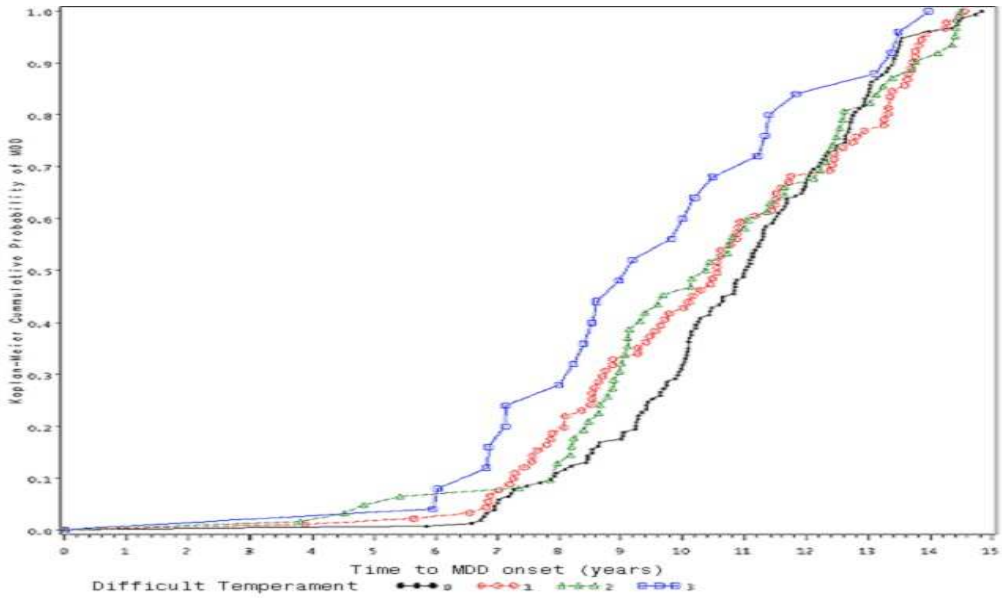
However, in the final multivariate model, mother's age at child's birth became nonsignificant, and only one interaction term was retained. The results indicate that having a difficult temperament and being a boy were associated with earlier onset of MDD (Table 5.). Furthermore, the main effect of temperament was qualified by its interaction with intact family status, and is illustrated by Kaplan-Meier survival curves (separately for intact vs. not-intact families).

Table 5. Modeling Age of Onset of first MDD Episode (N=371)

	Univariate Models	**Final Multivariate Model**
Variables	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
Perinatal problems	0.98 (0.88, 1.08)	0.96 (.86, 1.06)
Developmental delay	0.96 (0.77, 1.19)	0.87 (.69, 1.10)
Difficult temperament	1.11 (0.99, 1.23)$^{+}$	5.88 (2.05, 16.83)**
Sex (male = 1)	1.68 (1.36, 2.08)***	1.75 (1.41, 2.17)***
Intact family until age 4	0.64 (0.45, 0.91)*	0.93 (0.58, 1.47)
Mother's education (years)	0.98 (0.94, 1.01)	--
Maternal age at birth (years)		
16-18 vs. 19-34	0.94 (0.60, 1.46)	--
35-46 vs. 19-34	1.73 (1.10, 2.72)*	--
Temperament X Intact Family	--	0.65 (.45, .92)*
Temperament X Time	--	0.58 (.37, .92)*

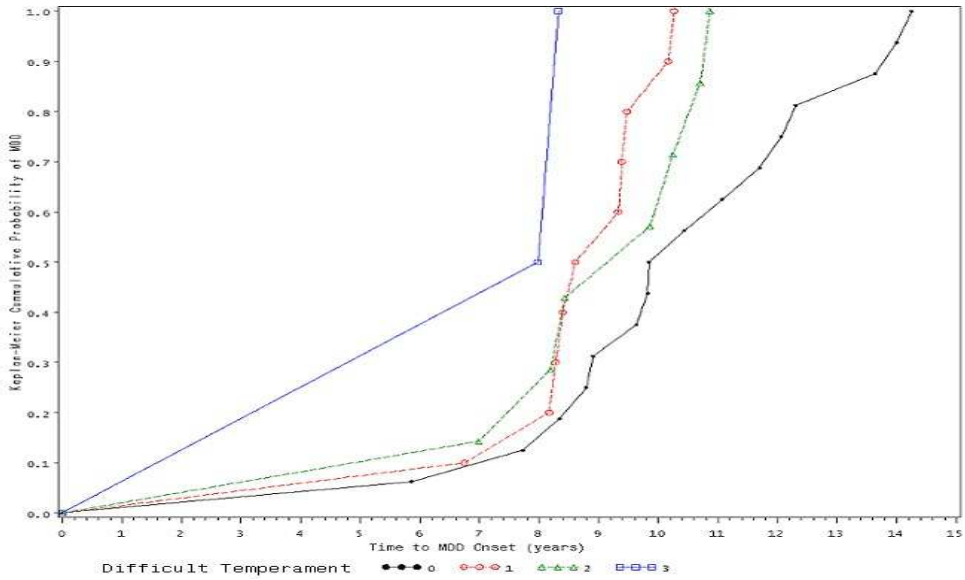
Note. MDD = major depressive disorder; CI = confidence interval; Cox regression analyses were used.
$^{+}p < .07$. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

For children in intact families (see Figure 1), temperament was unrelated to age at MDD onset (χ^2 (3) = 3.95, p = 0.27). However, for non-intact families (see Figure 2), children with a more difficult temperament had an earlier MDD onset age than did children with fewer difficulties (χ^2 (3) = 13.57, p < 0.01). Temperament also interacted with elapsed time, suggesting that its effect is not constant. Specifically, as indicated by the parameter estimate of the interaction term (-.540), the effect is attenuated across time. For example, comparing children at age 14 to children at age 7, the hazard ratio for temperament problems is decreased by exp{-.540*[log(14) – log (7)]} = 0.69.



0: no temperament difficulty; 1: minimal temperament difficulty; 2: moderate temperament difficulty
3: severe temperament difficulty

Figure 3. Effect of Early Temperament on MDD-onset among children from Intact Families



0: no temperament difficulty; 1: minimal temperament difficulty; 2: moderate temperament difficulty
3: severe temperament difficulty

Figure 4. Effect of Early Temperament on MDD-onset among children from Non-Intact Families

3.4.3. Severity of first episode of MDD

In a series of univariate general linear models, we found no significant associations between perinatal problems, developmental delay, difficult temperament and the severity of the first MDD episode. Only an association to child's sex was found, F (1, 369) = 4.32, p < 0.05, with girls showing more severe symptoms (M = 20.15) than boys (M = 19.36). In multivariate GLM analyses, the interactions of the three developmental indices with sex and with family status were not statistically significant and were dropped from the final model. The final model, including just the three indices and child sex, was not significant, F (4, 362) = 1.60, p = 0.17.

3.4.4. Onset age of first internalizing disorder (MDD/Dysthymia/Anxiety)

We first examined if children, who had developed dysthymic and/or anxiety disorder (Anx) in addition to MDD (n = 158), differed from children with MDD only (n = 213) in early risk factors. The groups did not differ in perinatal problems or developmental delays (p= .95, p= .065, respectively). However, children with comorbid DD or Anx were rated as having had a more difficult early temperament (M = .99, SD = 1.02) than were those without DD or Anx (M = .78, SD = .91), t (365) = -2.10, p < .05.

Univariate Cox regression models revealed two significant effects: boys (M = 9.50, SD = 2.51) had an earlier onset of MDD/DD/Anx than did girls (M = 9.98, SD = 2.69), and more difficult temperament was associated with earlier disorder onset. In the final model (see Table 6), child's temperament and sex remained significant, and a significant interaction between

Temperament and Intact Family was found, in the same direction as with MDD Onset-Age. Also, Temperament interacted with elapsed time, with the parameter estimate once again indicating that temperament better predicted onset-age among younger than older children.

Table 6. Modeling Age of Onset of First Internalizing Disorder Episode (MDD/DD/Anx)

Variables	**Univariate Models**	**Final Multivariate Model**
	Hazard Ratio (95% CI)	**Hazard Ratio (95% CI)**
Perinatal problems	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)
Developmental delay	1.11 (0.89, 1.38)	1.06 (0.84, 1.33)
Difficult temperament	1.22 (1.09, 1.36)***	4.07 (1.80, 9.20)***
Sex (male = 1)	1.30 (1.06, 1.60)*	1.36 (1.10, 1.68)**
Intact family until age 4	0.77 (0.54, 1.09)	1.01 (.63, 1.60)
Mother's education (years)	0.99 (.96, 1.02)	--
Maternal age at birth (years)		
16-18 vs. 19-34	0.92 (0.59, 1.43)	--
35-46 vs. 19-34	1.58 (1.00, 2.52) $^{+}$	--
Temperament X Intact Family	--	0.65 (.45, .93)*
Temperament X Time	--	0.70 (.49, 1.00)*

Note. MDD = major depressive disorder; CI = confidence interval; Cox regression analyses were used.
$^{+}$p < .10. *p < .05. **p < .01. ***p < .001.

Discussion

My work is the first to investigate the possible impact of early neurodevelopmental difficulties on the development and features of major depressive and related internalizing disorders in a very large clinical sample of youngsters with COD. I was particularly interested in developmental characteristics that may mirror physiological vulnerability because such factors could be helpful in the early identification of cases at risk. Overall, the results complement a growing body of literature, which suggests that various atypical early childhood characteristics may affect both the risk and timing of internalizing psychopathology.

In the case-control study of depressed and community control children, as I predicted, childhood-onset depression significantly associated with greater scores on all early developmental scales, suggesting that having a history of early atypical development (perinatal problems, developmental delay, and difficult temperament) may pose elevated risk for early onset MDD. Thus, findings of my work similar to findings from research with depressed adults, which suggest that perinatal-obstetric problems may have role in the development of MDD (Gale and Martin, 2004; Preti et al., 2000). My results also concordant with results of Jaffe et al. (2002) and van Os et al. (1997) regarding the effect of perinatal problems and delayed motor development toward higher vulnerability to early onset depression. Although, I investigated the direct relationship between perinatal complications and COD, there are several other pathways thorough which early developmental characteristics may act, and it is likely that interacting effect of different domains of vulnerability factors which play role in the development of depression (Kapornai & Vetró, 2008). Although, there are clearly several other factors which are proven to have role in the development of emotional problems were not investigated in my research, on the Figure 4. I depicted some vulnerability factors from risk domains (individual, familial, environmental) of internalizing disorders including those were investigated in the present research. I also figured some possible pathways which may suggested based on findings from former and my studies.

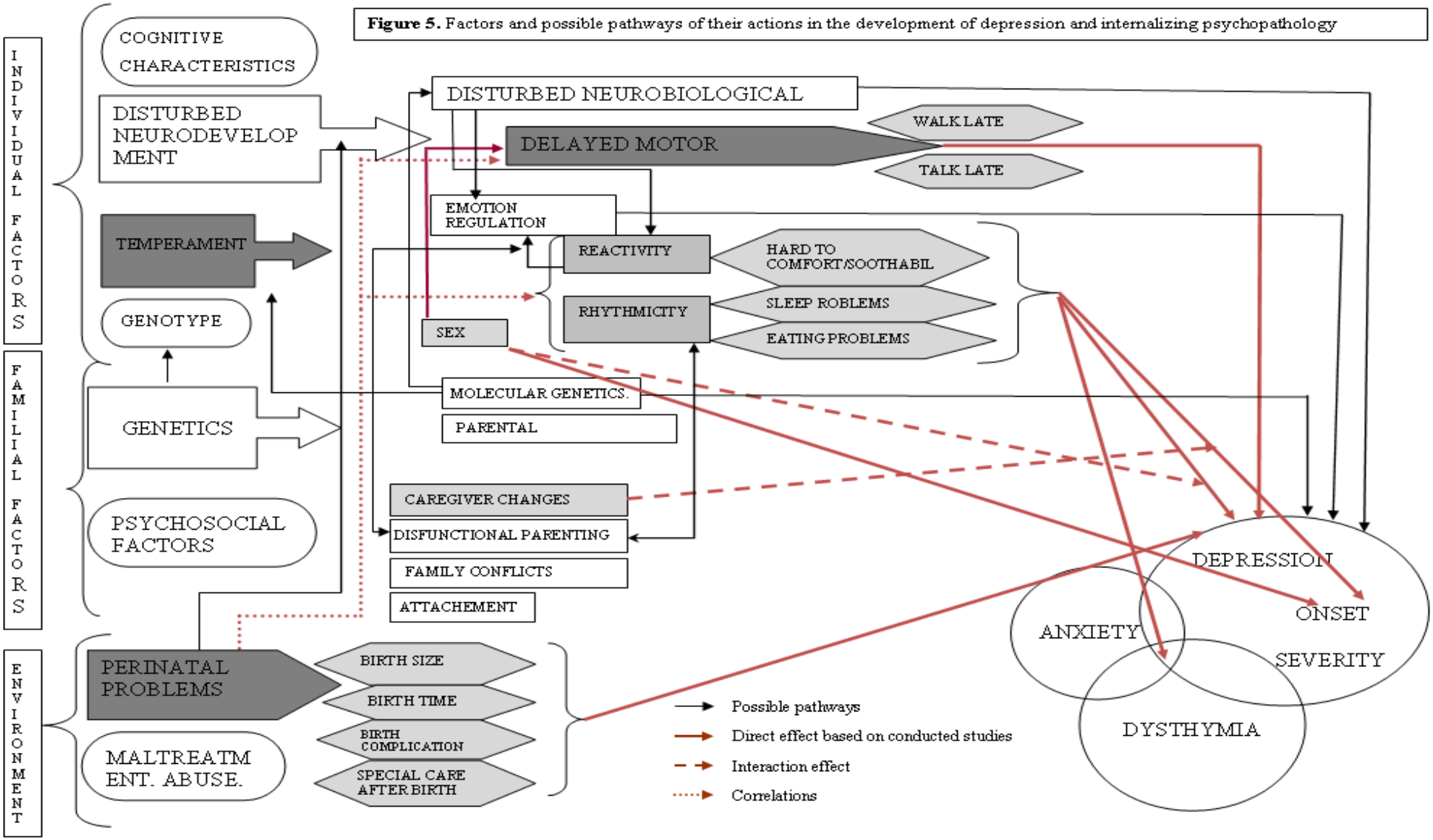


Figure 5. Factors and possible pathways of their actions in the development of depression and internalizing psychopathology

One possible mechanism through which perinatal problems might increase risk for depressive disorders is by altering the neurobiological regulatory systems (such as hypothalamic-pituitary-adrenal [HPA] axis function) (not investigated in the study) that govern emotion regulation and reactivity. As the correlation between perinatal scale and delayed development scale in my study indicates, perinatal problems by altering neurodevelopment, also could lead to disturbed motor development, which may than elevate the risk for COD. It is important to note, that consistent with a large body of literature on the greater vulnerability of male infants to a variety of problems (e.g., Halpern, 1997); boys in all of my samples had higher scores on developmental delay than did girls. Perinatal problem scale also correlated with difficult temperament scale suggesting other relevant pathways should be examined in the future. Namely, perinatal problems may act thorough increase the probability of difficult temperament by disturbing some neurobiological correlates of rhythmicity reactivity/emotion regulation domains of temperament. In general, other factors (illness, parenting style, social interactions) including the impact of the child behavior on the environment, may influence the psychophysiology of the child and thus contribute to the expressed temperament. Furthermore, it is also could be the case, that the perinatal problems influence on parenting early in life leads to mutual effect of temperament and dysfunctional parenting on each other, which then render children vulnerable to internalizing symptoms. Additionally, evidence has increasingly been found for interactions between temperament and parenting in psychopathology outcomes (Rothbart & Posner, 2006) The authors proposed this mechanism in the coercion model which suggests that child characteristics can influence parental reactions leading to increased risk for psychopathology. Although we had no data about the possible depressive psychopathology in the mother, in the case of infant temperament-by-parent characteristics interaction, it would be reasonable to consider the maternal depression as well. Namely, beside the genetic pathway, infant with difficult temperament and lower emotional regulatory capacity may have difficulty organizing their emotional and behavioral responses in the context of interactions with a depressed mother, leading to increasing their own risk for early manifestations of depression. Based on case-control study II. depressed probands were not differed from unaffected siblings on variables or scales of perinatal problems and delayed development, thus, in part, I failed to confirm my hypothesis 2)a. However, the lower sample sizes in case-control study II. could be a limitation to detect the possible associations between the aforementioned variables. I also failed to confirm the hypotheses regarding the effects of perinatal problems and motor skills delay on age of onset of depressive and related disorders. Although clinical or population based studies

have found that such characteristics distinguish childhood onset from adult onset affective disorders (Guth et al., 1993; Jaffee et al., 2002; van Os et al., 1997), differences in methodologies and samples may partly account for the inconsistent results. In our depressed group 3., early childhood characteristics also were unrelated to the severity of first MDD episode, despite Vocisano et al. (1996) finding a link between obstetric complications and severity of affective illness in adulthood.

I examined three types of early developmental characteristics. From these only the difficult early temperament was related to the development of depression and to the earlier onset of depression as well. More specifically, depressed kids with difficult early temperament, indexed by mother-reported problems with feeding, sleeping, or soothability, more frequently were difficult baby in their infancy than community children or then unaffected siblings and had earlier onset of MDD than had children with milder or no temperamental difficulties. Furthermore, the variables that refer to difficult temperament are emerged with significantly higher frequency in unaffected siblings than in community controls as well. This result suggests a possible endophenotype variation (genetic influence) in COD and/or could be explained by the influence of shared familiar factors as it was proposed in some behavioral genetic studies in relation to rhythmicity and soothability dimensions of temperament (Saudino, 2005). Notably, Jaffee et al. (2002) have reported that infant temperament (having been a "difficult baby") distinguished young adults with childhood-onset and those with adult-onset depression. However, having had a difficult temperament also was associated with earlier DD, or anxiety disorder, as well as MDD (whichever emerged first), indicating a lack of specificity to MDD. Thus, atypical infant temperament may presage vulnerability to a range of internalizing psychiatric problems later on, underscoring that risk factors should be examined in relation to a range of disorders rather than a single condition (Kessler et al., 1997). Additionally, children who had comorbid dysthymic or anxiety disorder reportedly had more difficult temperaments than children without DD or anxiety.

If a difficult temperament prognosticates earlier onset of emotional disorder, what could be the mechanisms? As I noted earlier, toddlers with difficult temperaments may be compromised on some psychoneurophysiologic parameter related to emotionality or emotion regulation (e.g., Fox, 1994), which may interfere with the development of effective coping responses, and render them susceptible to earlier onset of disorders. Findings that depressed children, or those at risk for depression, differ from comparison peers in their neuroendocrine or physiological responses to negative experimental mood induction, do suggest the existence

of physiological or neurobiological dimensions of vulnerability to depression (e.g., Forbes, et al., 2006; Luby et al., 2003) (Figure 4.)

Genes may contribute to individual differences in both temperament and psychopathology. For example, some emerging research suggests that genetic variations associated with the phenotype of a difficult temperament may be the same that predispose an individual to develop a psychiatric disorder (e.g., Pezawas et al., 2005). Furthermore, several researches propose evidences that depression and anxiety disorders may share a genetically determined neurobiological component that could involve neural circuits that include or are modulated by serotonergic regulation. This component could contribute to the negative affectivity dimension of temperament which appears to be common in childhood onset internalizing disorders.

Notably, however, in depressed group 3. it was found that early caregiver stability may mitigate some of the ramification of an infant having difficulties in rhythmicity or in being soothed, which is consistent with the buffering effects of a positive environment (e.g., Rothbart & Bates, 1998). Intact families may have available more of the emotional or material resources needed to take care of a "difficult" child. But because parenting and parent-infant relationships are influenced by the infant's temperament as well (e.g., Kochanska et al., 2004), future research should examine whether parents from non-intact families experience more deleterious effects of having a difficult baby, and how this may impact offspring's psychopathology.

Interestingly, the effect of temperament on disorder onset was attenuated across time in the sample. This finding may reflect that our anamnestic assessment focused on the period of infancy and toddlerhood. But, it is also possible that, across development, disorder parameters, such as age of onset, are subject to a variety and varying influences of risk variables (environmental stress, puberty, genetic effect, gene-by-environment interactions) other than early characteristics. Indeed, in risk research of mental disorders, there is a growing interest in the investigation of moderating effect of genes on individuals' sensitivity to environmental risk factors (not shown in Figure 4.), known as gene–environment interactions (GXE), gene–environment correlation (rGE) (Jaffe and Price, 2007; Moffit et al, 2005), and other varieties in gene–environment interplay (Rutter et al, 2006). In the past few years, GXE studies with young people reported associations between 5-HTTLPR variation and risk for depression following adverse life experiences (Kaufman et al 2006; Eley et al 2004; Caspi et al 2003; Kendler et al 2005), and association of variation in brain-derived neurotrophic factor (BDNF) genetics with childhood-onset depression (Strauss et al 2004a, 2004b). Based on

these findings Kaufman et al. (2006) recently examined the role of 5-HTTLPR-BDNF interaction in the development of depression in maltreated children and the potential modifying effect of social support available for the child. Children with the met allele of the BDNF gene and two short alleles of 5-HTTLPR had the highest depression scores, but the vulnerability associated with these two genotypes was only evident in maltreated children. Social support was further found to be a moderator factor in this study.

Other possible interacting mechanism suggested by the results of my work was also proposed by other researchers (MacPhee & Andrews, 2006; Oldehinkel et al., 2006). In these studies dysfunctional parenting (along with the strong effect of child's self-esteem) also emerged as an important predictor for depression, but for example, the association was dependent on the temperament characteristics and the gender of the children in the population sample of preadolescents examined by Oldehinkel et al. (2006).

Several other findings are of note. First, consistent with a large body of literature on the greater vulnerability of male infants to a variety of problems (e.g., Halpern, 1997), boys in all samples had higher scores on developmental delay than did girls, and their first episode of MDD, DD, or anxiety disorder occurred at a younger age than did girls'. But once an episode of MDD had onset, girls displayed more severe symptoms than boys, consistent with findings reported for adolescents (Reinhertz et al., 1999). Thus, in my work, sex emerged as a main effect and not as a moderator variable on age of onset of MDD as I had predicted. Additionally, diagnostic comorbidity in our patients was associated with reports of more difficult infantile temperaments. Notably, I reconfirmed prior reports (e.g., Kovacs, 1989) that, if depressed juveniles have comorbid anxiety disorders, the anxiety disorders will tend to onset earlier than the depressive disorder.

The finding in depressed group 3., that older maternal age at the child's birth (compared to maternal age between 19 and 34 years at childbirth) conferred earlier onset of MDD to their offspring, partly confirm those of Reinhertz et al. (1993). Reinhertz et al. (1993) found that older parental age at childbirth was associated with an increased risk of depression in female adolescent offspring. Maternal age at childbirth, however, was unrelated in our analyses to any of the early risk factors and failed to enter the final predictive models. This finding suggests that older maternal age affects offspring's psychopathology through other variables not examined in this study.

Limitations

Beside the unique strengths in sampling (very large clinical sample, which is representative to Hungary) and design (parallel investigations using case-control and cross-sectional design), my study has several limitations. The depressed and school-based community controls were not well matched geographically because the former group was recruited across Hungary thorough multiple sites, whereas the latter group was recruited from schools in some midsize cities. The control sample in the case-control study I. consisted of families who agreed to participate in the study in response to written invitation. This raises the possibility of un-known self-selection bias (Mayer et al., 2009). However, the depressed sample likewise included self-selected families willing to participate. Data ascertainment format (face-to-face interview versus mailed questionnaires) also may carry some sources of bias in responses (Mayer et al, 2009). Further, the lack of psychiatric control group limited the information to be draw regarding the specificity of the early neurodevelopmental characteristics in depression.

Additionally, because the anamnestic data on our patients were obtained retrospectively from their mothers, inaccuracies and biases in recall are of concern. In spite of its drawbacks, however, the retrospective reporting of perinatal and early developmental events has been an important component of various clinically oriented investigations (e.g., Buka et al., 2004; Foley et al., 2001; Lewis & Murray, 1987; Sanderson et al., 1998). Research has shown that the reproducibility and validity of maternal recall of perinatal events can vary from very good to poor (e.g., Foley et al., 2001; Launer et al., 1992; Tomeo et al., 1999) and is affected by the type of the data being sought and the method of acquisition (Buka et al., 2004). Data gathering procedures in my research had been designed with several features in mind, which have been recently recognized as facilitating (although not guaranteeing) the accuracy of retrospective recall (Buka et al., 2004), including face-face-interviews by clinically trained assessors, use of “common” rather than medical terms and phrases, and focusing on fairly frequently occurring events and readily observable and reportable signs (eating and sleeping habits). The finding of an interaction effect between child temperament and family status also argues against an overall bias in maternal recall because the association was evident only for a subgroup of participants.

Further limitation is that mothers reported on both their children’s early development and psychiatric history, introducing shared method (within-reporter) variance. However, this source of bias was reduced by the fact that a child’s final psychiatric diagnosis was: a) based

both on parental and child report, b) determined on two occasions by different clinical interviewers, and c) subjected to two "best estimate" child psychiatrists independently, who also had access to psychiatric and mental health records. While questions could also be raised about the accuracy of dating the onsets of disorders, two features of the design support my findings. First, the method of obtaining clinical history and onset dates (including the use of "time-lines" with culturally standard and personally meaningful marker events, visual aids, verbal summaries, and cross-links of information) has been shown to be the preferred approach for collecting various types of retrospective data (e.g., Caspi et al., 1996). And, second, my clinically referred sample did not have protracted illness, which is likely to reduce errors in dating; the average time elapsed between the age of onset of MDD and the date of the psychiatric evaluation was 1.14 years (SD = 1.34 years), and for about 67% of the sample, it was within one year.

It could be argued that the portion of youths in my sample of depressed group 3. who were not raised by both biological parents between birth and 4 years of age (9.4%) constitutes a very small segment of the sample. Although high rates of intact families have also been found in other pediatric samples, including those of Najman et al., 2005 (82% intact) and Hirshfeld-Becker et al., (2004) (86% intact), it would be informative to replicate my study with a sample that includes more single-parent or blended families. Another extension of my study could include other environmental factors in the analyses, such as parenting behavior given the information from earlier research on temperament-environment interactions in adaptive and maladaptive emotional development (e.g., Bates et al., 1998; Kochanska, 2004) and in depression as well (MacPhee & Andrews, 2006; Oldehinkel et al., 2006).

Respective findings and clinical implications

My results are concordant with results in research of adult depression, while extend evidences regarding the possible link between neurodevelopmental and temperamental adversities and the development of major depression in childhood, by suggesting the effect of difficult infant temperament on the age of onset of first depressive episode. Also, my research is the first to investigate the possible impact of early neurodevelopmental difficulties on the development and features of major depressive and related internalizing disorders in a very large, nationally representative clinical sample of youngsters with MDD. My findings highlight that, even in a vulnerable sample, the putative negative effects of early infant characteristics are not immutable, but can be ameliorated by family resources. Thus

improving the support provided by health professionals for mothers dealing with infants after perinatal complications and/or with difficult temperament could have positive effect in the prevention of emotional disorders later in life. Further, the impact of some early child characteristics on features of juvenile psychopathology seems to be attenuated by the passage of time.

Additionally, in clinical practice, psychiatrists typically have access only to parents' reports of early child characteristics and are unlikely to have documents of early development. Based on our findings, careful interviewing of parents can yield data that may illuminate some aspects of children's clinical history.

References

1. Achenbach, T.M. (1991) Manual for the Child Behavior Checklist 4–18 and 1991 Profile, *University of Vermont, Department of Psychiatry*, Burlington.

2. Achenbach, T. M., & Edelbrock, C. S. (1978). The classification of child psychopathology: A review and analysis of empirical efforts. *Psychological Bulletin, 85*(6), 1275-1301.

3. Allen, N. B., Lewinsohn, P. M., & Seeley, J. R. (1998). Prenatal and perinatal influences on risk for psychopathology in childhood and adolescence. *Development and Psychopathology, 10*(3), 513-529.

4. American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association

5. Axelson, D. A., & Birmaher, B. (2001). Relation between anxiety and depressive disorders in childhood and adolescence. *Depression and Anxiety, 14*(2), 67-78.

6. Bates, J. E., Pettit, G. S., Dodge, K. A., & Ridge, B. (1998). Interaction of temperamental resistance to control and restrictive parenting in the development of externalizing behavior. *Developmental Psychology, 34*(5), 982-995.

7. Birmaher, B., Ryan, N. D., Williamson, D. E., Brent, D. A., Kaufman, J., Dahl, R. E., et al. (1996). Childhood and adolescent depression: A review of the past 10 years. part I. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*(11), 1427-1439.

8. Buka, S. L., Goldstein, J. M., Spartos, E., & Tsuang, M. T. (2004). The retrospective measurement of prenatal and perinatal events: Accuracy of maternal recall. *Schizophrenia Research, 71*(2-3), 417-426.

9. Buka, S. L., Tsuang, M. T., & Lipsitt, L. P. (1993). Pregnancy/delivery complications and psychiatric diagnosis. A prospective study. *Archives of General Psychiatry, 50*(2), 151-156.

10. Buss, A. H., & Plomin, R. (1984). Temperament: Early developing personality traits. Hillsdale, NJ: *Lawrence Erlbaum.*

11. Cannon, M., Jones, P. B., & Murray, R. M. (2002). Obstetric complications and schizophrenia: Historical and meta-analytic review. *The American Journal of Psychiatry, 159*(7), 1080-1092.

12. Caspi, A., Moffitt, T.E., Thornton, A., Freedman, D., Amell, J.W., Harrington, H., Smeijers, J., Silva, P.A. (1996). The life history calendar: A research and clinical assessment method for collecting retrospective event-history data. *Int. J. Methods in Psychiatr. Res. 6*, 101-114.

13. Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science (New York, N.Y.), 301*(5631), 386-389.

14. Cole, D. A., Peeke, L. G., Martin, J. M., Truglio, R., Seroczynski, A.D. (1998). A longitudinal look at the relation between depression and anxiety in children and adolescents. *Journal of Consultant Clinical Psychology,* 66(3), 451-460.

15. Cohen, P., Velez, C. N., Brook, J., & Smith, J. (1989). Mechanisms of the relation between perinatal problems, early childhood illness, and psychopathology in late childhood and adolescence. *Child Development, 60*(3), 701-709.

16. Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry, 60*(8), 837-844.

17. Costello, E. J., Worthman, C., Erkanli, A., & Angold, A. (2007). Prediction from low birth weight to female adolescent depression: A test of competing hypotheses. *Archives of General Psychiatry, 64*(3), 338-344.

18. Doussard-Roosevelt, J. A., Porges, S. W., Scanlon, J. W., Alemi, B., & Scanlon, K. B. (1997). Vagal regulation of heart rate in the prediction of developmental outcome for very low birth weight preterm infants. *Child Development, 68*(2), 173-186.

19. Egger, H. L., & Angold, A. (2006). Common emotional and behavioral disorders in preschool children: Presentation, nosology, and epidemiology. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 47*(3-4), 313-337.

20. Eley, T. C., Sugden, K., Corsico, A., Gregory, A. M., Sham, P., McGuffin, P., et al. (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry, 9*(10), 908-915.

21. Foley, D. L., Thacker, L. R.,2nd, Aggen, S. H., Neale, M. C., & Kendler, K. S. (2001). Pregnancy and perinatal complications associated with risks for common psychiatric disorders in a population-based sample of female twins. *American Journal of Medical Genetics, 105*(5), 426-431.

22. Forbes, E. E., Fox, N. A., Cohn, J. F., Galles, S. F., & Kovacs, M. (2006). Children's affect regulation during a disappointment: Psychophysiological responses and relation to parent history of depression. *Biological Psychology, 71*(3), 264-277.

23. Fox, N.A. (Ed.) (1994). The development of emotion regulation: Biological and behavioral considerations. *Monographs of the Society for Research in Child Development, 59*, 2-3, Serial No 240.

24. Fox, N. A. (1998). Temperament and regulation of emotion in the first years of life. *Pediatrics, 102*(5 Suppl E), 1230-1235.

25. Gale, C. R., & Martyn, C. N. (2004). Birth weight and later risk of depression in a national birth cohort. *The British Journal of Psychiatry : The Journal of Mental Science, 184*, 28-33.

26. Garber, J. (2006). Depression in children and adolescents: Linking risk research and prevention. *American Journal of Preventive Medicine, 31*(6 Suppl 1), S104-25.

27. Geller, D.A., Wieland, N., Carey, K., Vivas, F., Petty, C.R., Johson, J., Reichert, E., Pauls, D., Biederman, J. (2008). Perinatal factors affecting expression of obsessive compulsive disorder in children and adolescents. *Journal of Child and Adolescent Psychopharmacology,* 18(4), 373-379.

28. Goldsmith, H. H., & Lemery, K. S. (2000). Linking temperamental fearfulness and anxiety symptoms: A behavior-genetic perspective. *Biological Psychiatry, 48*(12), 1199-1209.

29. Goodman, S.H. (2002) Depression and early adverse experiences. In: Gotlieb, I., Hammen, C. (Eds.) *Handbook of Depression,* Guilford Press, NY, 245–267.

30. Gray, R. F., Indurkhya, A., & McCormick, M. C. (2004). Prevalence, stability, and predictors of clinically significant behavior problems in low birth weight children at 3, 5, and 8 years of age. *Pediatrics, 114*(3), 736-743.

31. Guth, C., Jones, P., & Murray, R. (1993). Familial psychiatric illness and obstetric complications in early-onset affective disorder. A case-control study. *The British Journal of Psychiatry : The Journal of Mental Science, 163,* 492-498.

32. Halpern, D. F. (1997). Sex differences in intelligence. implications for education. *The American Psychologist, 52*(10), 1091-1102.

33. Hirshfeld-Becker, D. R., Biederman, J., Faraone, S. V., Robin, J. A., Friedman, D., Rosenthal, J. M., et al. (2004). Pregnancy complications associated with childhood anxiety disorders. *Depression and Anxiety, 19*(3), 152-162.

34. Jaffee, S., Caspi, A., Moffitt, T. E., Belsky, J., & Silva, P. (2001). Why are children born to teen mothers at risk for adverse outcomes in young adulthood? results from a 20-year longitudinal study. *Development and Psychopathology, 13*(2), 377-397.

35. Jaffee, S. R., Moffitt, T. E., Caspi, A., Fombonne, E., Poulton, R., & Martin, J. (2002). Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Archives of General Psychiatry, 59*(3), 215-222.

36. Jaffee, S. R., & Price, T. S. (2007). Gene-environment correlations: A review of the evidence and implications for prevention of mental illness. *Molecular Psychiatry, 12*(5), 432-442.

37. Kapornai, K., Gentzler, A. L., Tepper, P., Kiss, E., Mayer, L., Tamas, Z., et al. (2007). Early developmental characteristics and features of major depressive disorder

among child psychiatric patients in hungary. *Journal of Affective Disorders, 100*(1-3), 91-101.

38. Kapornai, K., & Vetro, A. (2008). Depression in children. *Current Opinion in Psychiatry, 21*(1), 1-7.

39. Kasen, S., Cohen, P., Brook, J. S., & Hartmark, C. (1996). A multiple-risk interaction model: Effects of temperament and divorce on psychiatric disorders in children. *Journal of Abnormal Child Psychology, 24*(2), 121-150.

40. Kaufman, J., Yang, B. Z., Douglas-Palumberi, H., Grasso, D., Lipschitz, D., Houshyar, S., et al. (2006). Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biological Psychiatry, 59*(8), 673-680.

41. Keenan, K., Shaw, D., Delliquadri, E., Giovannelli, J., & Walsh, B. (1998). Evidence for the continuity of early problem behaviors: Application of a developmental model. *Journal of Abnormal Child Psychology, 26*(6), 441-452.

42. Kendler, K. S., Kuhn, J. W., Vittum, J., Prescott, C. A., & Riley, B. (2005). The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: A replication. *Archives of General Psychiatry, 62*(5), 529-535.

43. Kessler, R. C., Davis, C. G., & Kendler, K. S. (1997). Childhood adversity and adult psychiatric disorder in the US national comorbidity survey. *Psychological Medicine, 27*(5), 1101-1119.

44. Kinney, D. K., Yurgelun-Todd, D. A., Tohen, M., & Tramer, S. (1998). Pre- and perinatal complications and risk for bipolar disorder: A retrospective study. *Journal of Affective Disorders, 50*(2-3), 117-124.

45. Kiss, E., Gentzler, A. M., George, C., Kapornai, K., Tamas, Z., Kovacs, M., et al. (2007). Factors influencing mother-child reports of depressive symptoms and agreement among clinically referred depressed youngsters in hungary. *Journal of Affective Disorders, 100*(1-3), 143-151.

46. Kiss, E., Kapornai, K., Tamás, Zs., Baji, I., Rimay, T., Mayer, L., Gádoros, J., Barr, C., Kovacs, M., Vetró, Á. And the International Consortium for Childhood-Onset Depression: Characteristics and risk factors of childhood-onset depression in Hungarian child and adolescent population. *Eur Psychiatric Review,* in press.

47. Kochanska, G., Friesenborg, A. E., Lange, L. A., Martel, M. M., & Kochanska, G. (2004). Parents' personality and infants' temperament as contributors to their emerging relationship. *Journal of Personality and Social Psychology, 86*(5), 744-759.

48. Kovacs, M. (1989). Affective disorders in children and adolescents. *The American Psychologist, 44*(2), 209-215.

49. Kovacs, & MHS Staff, (2003) Children's Depression Inventory (CDI): Technical Manual Update, *Multi-Health Systems, Inc.,* North Tonawanda, NY.

50. Kovacs, M., & Devlin, B. (1998). Internalizing disorders in childhood. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 39*(1), 47-63.

51. Kovacs, M., Feinberg, T. L., Crouse-Novak, M. A., Paulauskas, S. L., & Finkelstein, R. (1984a). Depressive disorders in childhood. I. A longitudinal prospective study of characteristics and recovery. *Archives of General Psychiatry, 41*(3), 229-237.

52. Kovacs, M., Feinberg, T. L., Crouse-Novak, M., Paulauskas, S. L., Pollock, M., & Finkelstein, R. (1984b). Depressive disorders in childhood. II. A longitudinal study of the risk for a subsequent major depression. *Archives of General Psychiatry, 41*(7), 643-649.

53. Launer, L. J., Forman, M. R., Hundt, G. L., Sarov, B., Chang, D., Berendes, H. W., et al. (1992). Maternal recall of infant feeding events is accurate. *Journal of Epidemiology and Community Health, 46*(3), 203-206.

54. Lerner, R.M., Palermo, M., Spiro, A., Nessleroade, J. (1982). Assessing the dimensions of temperament individuality across the life-span: the Dimensions of Temperament Survey (DOTS). *Child Development, 53,* 149–159.

55. Lewinsohn, P. M., Hops, H., Roberts, R. E., Seeley, J. R., & Andrews, J. A. (1993). Adolescent psychopathology: I. prevalence and incidence of depression and other DSM-III-R disorders in high school students. *Journal of Abnormal Psychology, 102*(1), 133-144.

56. Liu, X., Sun, Z., Neiderhiser, J. M., Uchiyama, M., & Okawa, M. (2001). Low birth weight, developmental milestones, and behavioral problems in chinese children and adolescents. *Psychiatry Research, 101*(2), 115-129.

57. Luby, J. L., Heffelfinger, A. K., Mrakotsky, C., Brown, K. M., Hessler, M. J., Wallis, J. M., et al. (2003). The clinical picture of depression in preschool children. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(3), 340-348.

58. MacPhee, A. R., & Andrews, J. J. (2006). Risk factors for depression in early adolescence. *Adolescence, 41*(163), 435-466.

59. Matsumoto, H., Takei, N., Saito, H., Kachi, K., & Mori, N. (1999). Childhood-onset schizophrenia and obstetric complications: A case--control study. *Schizophrenia Research, 38*(2-3), 93-99.

60. Mayer, L., Kiss, E., Baji, I., Skultéti, D., Vetró, A., (2006). Quality analysis of life events and their relationship to depressive symptoms in a school age population. *Psychiatria Hungarica,* 21(5), 360-370.

61. Mayer, L., Lopez-Duran, N. L., Kovacs, M., George, C. J., Baji, I., Kapornai, K., et al. (2009). Stressful life events in a clinical sample of depressed children in hungary. *Journal of Affective Disorders, 115*(1-2), 207-214.

62. Maziade, M., Cote, R., Bernier, H., Boutin, P., & Thivierge, J. (1989). Significance of extreme temperament in infancy for clinical status in pre-school years. I: Value of extreme temperament at 4-8 months for predicting diagnosis at 4.7 years. *The British Journal of Psychiatry : The Journal of Mental Science, 154*, 535-543.

63. Maziade, M., Roy, M. A., Fournier, J. P., Cliche, D., Merette, C., Caron, C., et al. (1992). Reliability of best-estimate diagnosis in genetic linkage studies of major psychoses: Results from the quebec pedigree studies. *The American Journal of Psychiatry, 149*(12), 1674-1686.

64. Mehregany, D. V. (1991). The relation of temperament and behavior disorders in a preschool clinical sample. *Child Psychiatry and Human Development, 22*(2), 129-136.

65. Milberger, S., Biederman, J., Faraone, S. V., Guite, J., & Tsuang, M. T. (1997). Pregnancy, delivery and infancy complications and attention deficit hyperactivity disorder: Issues of gene-environment interaction. *Biological Psychiatry, 41*(1), 65-75.

66. Moffitt, T.E., Caspi, A., Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry; 62*:473–481.

67. Najman, J. M., Hallam, D., Bor, W. B., O'Callaghan, M., Williams, G. M., & Shuttlewood, G. (2005). Predictors of depression in very young children--a prospective study. *Social Psychiatry and Psychiatric Epidemiology, 40*(5), 367-374.

68. Nobile, M., Cataldo, G. M., Marino, C., & Molteni, M. (2003). Diagnosis and treatment of dysthymia in children and adolescents. *CNS Drugs, 17*(13), 927-946.

69. Oldehinkel, A. J., Hartman, C. A., De Winter, A. F., Veenstra, R., & Ormel, J. (2004). Temperament profiles associated with internalizing and externalizing problems in preadolescence. *Development and Psychopathology, 16*(2), 421-440.

70. Oldehinkel, A. J., Veenstra, R., Ormel, J., de Winter, A. F., & Verhulst, F. C. (2006). Temperament, parenting, and depressive symptoms in a population sample of preadolescents. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 47*(7), 684-695.

71. Ong, S. H., Wickramaratne, P., Tang, M., & Weissman, M. M. (2006). Early childhood sleep and eating problems as predictors of adolescent and adult mood and anxiety disorders. *Journal of Affective Disorders, 96*(1-2), 1-8.

72. Paykel, E. S. (2003). Life events and affective disorders. *Acta Psychiatrica Scandinavica Supplementum, (418)*(418), 61-66.

73. Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience, 8*(6), 828-834.

74. Phillips, N. K., Hammen, C. L., Brennan, P. A., Najman, J. M., & Bor, W. (2005). Early adversity and the prospective prediction of depressive and anxiety disorders in adolescents. *Journal of Abnormal Child Psychology, 33*(1), 13-24.

75. Preti, A., Cardascia, L., Zen, T., Pellizzari, P., Marchetti, M., Favaretto, G., et al. (2000). Obstetric complications in patients with depression--a population-based case-control study. *Journal of Affective Disorders, 61*(1-2), 101-106.

76. Reinherz, H. Z., Giaconia, R. M., Hauf, A. M., Wasserman, M. S., & Silverman, A. B. (1999). Major depression in the transition to adulthood: Risks and impairments. *Journal of Abnormal Psychology*, *108*(3), 500-510.

77. Reinherz, H.Z., Giaconia, R.M., Pakiz, B., Silverman, A.B., Frost, A.K., Lefkowitz, E.S. (1993). Psychosocial risks for major depression in late adolescence: A longitudinal community study. *Journal of the American Academy of Child and Adolescent Psychiatry 32*, 1155-1163.

78. Rice, F., Harold, G. T., & Thapar, A. (2006). The effect of birth-weight with genetic susceptibility on depressive symptoms in childhood and adolescence. *European Child & Adolescent Psychiatry*, *15*(7), 383-391.

79. Rothbart, M.K. (1981). Measurement of temperament in infancy, *Child development,* 52, 569-578.

80. Rothbart, M.K. (1989) Temperament and development. In: Kohnstamm, G.A., Bates, J.E., &Rothbart, M.K. (Eds) *Temperament in childhood,* Wiley, New York, 187-248.

81. Rothbart, M.K., & Bates, J.E. (1998) Temperament. In: Damon, W., & Eisenberg, N. (Eds), Handbook of Child Psychology: Social, Emotional, and Personality Development (5th ed.), *Wiley*, New York, 105–176.

82. Rothbart, M. K., & Posner, M. I. (2006). Temperament, attention, and developmental psychopathology. In D. Cicchetti (Ed.), *Developmental Psychopathology. Volume 2, Developmental Neuroscience, 2 nd Edition.*

83. Rubin, K. H., Burgess, K. B., Dwyer, K. M., & Hastings, P. D. (2003). Predicting preschoolers' externalizing behaviors from toddler temperament, conflict, and maternal negativity. *Developmental Psychology, 39*(1), 164-176.

84. Rutter, M., Moffitt, T.E., Caspi, A. (2006) Gene–environment interplay and psychopathology: multiple varieties but real effects. *Journal of Child Psychology and Psychiatry; 47*:226–261.

85. Ryan, N. D. (2005). Treatment of depression in children and adolescents. *Lancet, 366*(9489), 933-940.

86. Saudino, K. J. (2005). Behavioral genetics and child temperament. *Journal of Developmental and Behavioral Pediatrics : JDBP, 26*(3), 214-223.

87. Sherrill, J. T., & Kovacs, M. (2000). Interview schedule for children and adolescents (ISCA). *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(1), 67-75.

88. Sigurdsson, E., Van Os, J., & Fombonne, E. (2002). Are impaired childhood motor skills a risk factor for adolescent anxiety? results from the 1958 U.K. birth cohort and the national child development study. *The American Journal of Psychiatry, 159*(6), 1044-1046.

89. Stalets, M. M., & Luby, J. L. (2006). Preschool depression. *Child and Adolescent Psychiatric Clinics of North America, 15*(4), 899-917, viii-ix.

90. Strauss, J., Barr, C. L., George, C. J., King, N., Shaikh, S., Devlin, B., et al. (2004a). Association study of brain-derived neurotrophic factor in adults with a history of childhood onset mood disorder. *American Journal of Medical Genetics.Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics, 131B*(1), 16-19.

91. Strauss, J., Barr, C. L., George, C. J., Ryan, C. M., King, N., Shaikh, S., et al. (2004b). BDNF and COMT polymorphisms: Relation to memory phenotypes in young adults with childhood-onset mood disorder. *Neuromolecular Medicine, 5*(3), 181-192.

92. Thomas, A., & Chess, S. (1977) Temperament and Development, *Brunner/Mazel*, New York.

93. Tomeo, C. A., Rich-Edwards, J. W., Michels, K. B., Berkey, C. S., Hunter, D. J., Frazier, A. L., et al. (1999). Reproducibility and validity of maternal recall of pregnancy-related events. *Epidemiology (Cambridge, Mass.), 10*(6), 774-777.

94. van Katwijk, C., & Peeters, L. L. (1998). Clinical aspects of pregnancy after the age of 35 years: A review of the literature. *Human Reproduction Update, 4*(2), 185-194.

95. van Os, J., Jones, P., Lewis, G., Wadsworth, M., & Murray, R. (1997). Developmental precursors of affective illness in a general population birth cohort. *Archives of General Psychiatry, 54*(7), 625-631.

96. Verdoux, H., Geddes, J. R., Takei, N., Lawrie, S. M., Bovet, P., Eagles, J. M., et al. (1997). Obstetric complications and age at onset in schizophrenia: An international collaborative meta-analysis of individual patient data. *The American Journal of Psychiatry, 154*(9), 1220-1227.

97. Vetró, Á., and Kapornai, K., (2008). A pszichopathológia fejlődése in Vetró, Á. (Ed.) *Gyermek és Ifjúságpszichiátria Medicina*, Budapest

98. Vetró, Á., Baji, I., Benák, I., Besnyő, M., Csorba, J., Daróczy, G., Dombovári, E., Kiss, E., Gádoros, J., Kaczvinszky, E., Kapornai, K., Mayer, L., Rimay, T., Skultéty, D., Szabó, K., Tamás, Zs., Székely, J., Kovács, M.. (2009) „A gyermekkori depresszió rizikó tényezői" kutatás megtervezése, implementációja, lefolyása: 13 év története : Pályázat előkészítés, írás és kutatásszervezés tapasztalatai egy amerikai NIMH kutatási pályázat kapcsán. *Psychiatria Hungarica*, 24(1), 6-14.

99. Vocisano, C., Klein, D. N., Keefe, R. S., Dienst, E. R., & Kincaid, M. M. (1996). Demographics, family history, premorbid functioning, developmental characteristics, and course of patients with deteriorated affective disorder. *The American Journal of Psychiatry, 153*(2), 248-255.

100. Wasserman, G. A., Rauh, V. A., Brunelli, S. A., Garcia-Castro, M., & Necos, B. (1990). Psychosocial attributes and life experiences of disadvantaged minority mothers: Age and ethnic variations. *Child Development, 61*(2), 566-580.

101. Zalsman, G., Brent, D. A., & Weersing, V. R. (2006). Depressive disorders in childhood and adolescence: An overview: Epidemiology, clinical manifestation and risk factors. *Child and Adolescent Psychiatric Clinics of North America, 15*(4), 827-41

Appendix

Depression in children

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Purpose of review

This summary of literature published during the past year focuses on research into factors that may contribute to development of childhood-onset depression and on appropriate assessment and treatment.

Recent findings

The recent literature suggests that investigating risk factors and gene–environment interactions could be fruitful in elucidating the aetiology of childhood-onset depression and could have implications for developing preventive (selective or targeted programmes) and therapeutic strategies. These strategies clearly should involve interventions to improve parent–child relationships and parenting style, especially in children at high risk early in their lives. Cognitive–behavioural therapy, interpersonal therapy and (in the case of severe depression) selective serotonin reuptake inhibitor medications (fluoxetine as the first-line option, with close monitoring for adverse effects during treatment) appear to be effective in the management of depression in children. However, recent reports on psychotherapies yield a less clear picture about their effectiveness in childhood depression than was previously indicated.

Summary

Controlled trial data and evidence-based guidelines for management of depressed children are limited with respect to pharmacological and psychotherapeutic options, especially in prepubertal and preschool children. Further research in this area is therefore warranted.

Keywords

children, depression, management, vulnerability

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Introduction

Depression in children [major depressive disorder (MDD) and dysthymia] imposes significant burdens on individuals and public health systems, and therefore it is of great importance to develop appropriate management algorithms for depressed children. A growing body of literature has confirmed that MDD and dysthymia are common and persistent illnesses in adolescents as well as children (< 14 years old) [1–3], and both are associated with significant impairment in school achievement, interpersonal functioning, and increased risks for suicidal behaviour and substance use. Therefore, it is extremely important to recognize, treat, or prevent early-onset depression, although evidence-based treatment guidelines are limited.

Epidemiology

Based on epidemiological studies, depression affects about 0.3–1.4% of preschool children [4••,5••], 1–2% of prepubertal children and about 3–8% of adolescents, with equal prevalence prior to adolescence in girls and boys [2,6,7,8•]. Dysthymia occurs in 0.6% of preschool children [5••], 0.6–4.6% of prepubertal children and 1.6–8% of adolescents [3]. Recently, reports on the increase in prevalence of child and adolescent depression have appeared not only in academic journals but also in the popular media [9,10••]. To determine whether there is currently an 'epidemic' of early-onset depression, Costello *et al.* [10••] conducted a meta-analysis of 26 epidemiologic studies. As for data available from studies using concurrent assessment (structured psychiatric interview) to identify cases of depression, they concluded that there is no evidence for an increase in prevalence over the past 30 years. They suggested that the perception of increased prevalence could be accounted for by heightened awareness of the disorders.

Vulnerability and risk factors

Numerous familial and individual vulnerability factors have been identified as conferring risks for elevated depressive symptoms and depressive disorders. Familial risks involve both genetic factors (e.g. familial history of mood disorder) and psychosocial factors (e.g. quality of attachment, marital discord, poor family support and

dysfunctional parenting) that may contribute to development of depression in the child. Among individual vulnerability factors, certain temperamental and cognitive characteristics (easily upset, poor self-esteem and negative cognitions) and differences in emotion regulation and in neurobiological and physiological regulation, as well as nonaffective psychopathology (anxiety) and subclinical depressive syndrome, have all been extensively identified as possibly conferring risk for depression [2,8•,11••]. Also, several environmental factors (parental loss, divorce, physical/sexual abuse and illness or death of family member) have been found to have depressive effects [12], including those early adverse events that may influence brain development (perinatal problems and maltreatment). Overall, it is likely that accumulation of or interaction between multiple risk factors contributes to development of depression.

In risk research into mental disorders, there is also growing interest in investigating the moderating effects of genes on the sensitivity of individuals to environmental risk factors, for instance gene–environment interactions, gene–environment correlation [13,14] and other aspects of the gene–environment interplay [15]. During the past few years, gene–environment studies conducted in young people identified associations between variation in the 5-hydroxytryptamine (serotonin) transporter gene-linked polymorphic region (5-HTTLPR) and risk for depression following adverse life experiences [16–19], and associations of variations in brain-derived neurotrophic factor (BDNF) genetics with childhood-onset depression [20,21]. Based on these findings, Kaufman *et al.* [22••] recently examined the role played by interactions between 5-HTTLPR and BDNF in the development of depression in maltreated children, and the potential modifying effect of social support available for the child. Children with the *met* allele of the *BDNF* gene (val66met polymorphism) and two short alleles of 5-HTTLPR exhibited the highest depression scores, but the vulnerability associated with these two genotypes was evident only in maltreated children. Social support was further found to be a moderating factor in this study. Furthermore, stressful life events had a mediating effect on the relationship between family history of mood disorder and the severity of depression in preschool children [23•], which highlights the importance of early intervention or prevention strategies focusing on psychosocial factors in this age group.

Parental behaviour (along with the strong effect of child self-esteem) also emerged as an important predictor for depression [24,25•], but the association was dependent on the temperament characteristics and sex in the population sample of pre-adolescent children examined by Oldehinkel *et al.* [25•]. Furthermore, based on other population-based and clinical studies, early difficult temperament and care giver instability also portended earlier onset of the first episode of MDD [26,27]. Additionally, perinatal problems [e.g. low birth weight (LBW)] were also proposed to be specific early childhood risk factors for depression [26,28,29], and recently were investigated by Rice *et al.* [30•] in relation to genetic susceptibility to depressive symptoms in a sample of 2046 twins (aged 8–17 years). Those investigators reported that the effect of lower birth weight for gestational age on depressive symptoms was greater in children with genetic risk factors, although the identified association between birth weight and depression does not imply causality. Indeed, there are conflicting results about the link between LBW and depression. A recent report [31•] suggested that LBW predicts depression only in adolescent girls.

There is no doubt, however, about the interacting roles played by various domains of biological and environmental factors in the development of depression. It is important to note that there is evidence that variation in the relative influences of these factors on development of depression is a function of the child's age and sex [32,33].

In summary, further information is needed about possible risk factors, causal risk mechanisms, and the timing of their actions and their interactions in the development of depression, because all these have substantial implications for effective early preventive and therapeutic interventions. Indeed, regarding prevention, Garber [11••] and Feinberg *et al.* [34] also emphasized the highly important bi-directional communication between risk research and prevention.

Prevention

Based on the findings of the meta-analysis of 30 prevention trials recently reported by Horowitz and Garber [35••], selective (for individuals at elevated risk for depression) and indicated (for individuals with subthreshold depression) prevention programmes were superior to universal (to all members in the target population) programmes, with small to moderate degrees of effect in children and adolescents. As is highlighted in the report, however, effective programmes can actually be viewed as treatment if a more accurate definition of prevention is used. In addition, the universal programme was not found to be an effective approach in the study reported by Spence and Shortt [36•].

Assessment and diagnosis

Diagnosis of a depressive disorder requires a thorough medical and psychiatric evaluation [37,38•]. During psychiatric assessment a developmental perspective is essential, and the diagnosis of depression must rely on multiple information sources (interviews with parents,

and interviews directly with the child and with the child's teachers or other members of the family). Given indications that the frequently existing psychopathology in the families of depressed children is known to influence agreement about the child's symptoms between child and parents, clinicians must also consider the depressive state of the informant family member [39]. Diagnostic criteria for depression in children are essentially the same as in adults, and screening and diagnostic instruments have been developed for preschool children, older children and adolescents, as have instruments to improve the accuracy of the assessment [40–42]. Defining depressive symptoms could be a challenge in preschool children, however, despite the growing body of evidence that a clinically significant depressive syndrome can occur in this age group [5••,41]. Further information is needed to determine whether the modified diagnostic criteria identify a depressive prodrome, a subsyndrome, or clinically significant depression that requires intervention [38•]. In addition to diagnostic interviews, evaluation of parent–child interactions, play observation and age-appropriate puppet interview should also be a part of the assessment in preschool and older children [5••].

Treatment

The general aims of treatment in childhood-onset depression are to achieve full remission of symptoms and functional improvement, and to prevent symptom relapse (with continuation of treatment) and new episodes or recurrences (with maintenance of treatment). In spite of existing clinical guidelines [37,43,44•], debate continues about the optimal developmentally appropriate methods (settings, modality and combined approaches) for management of depression in youngsters (age < 18 years). Moreover, randomized clinical trials with preschool or older children involving either psychosocial or pharmacological interventions are few or have not even been conducted. Thus, availability of evidence-based treatment options for individuals under the age of 14 years (who are usually considered children in the literature) is limited, and data from adolescent and mixed studies with patients aged between 6 and 18 years are often considered in guidelines. Nevertheless, the treatment strategy should be planed individually, taking into consideration the child's age, developmental stage and risk/protective characteristics (e.g. psychopathology in the family, individual temperament, cognitive and emotional regulatory factors, existing co-morbidity and experience of stressful life events), and the medication or psychotherapy preferences of the patient and the care giver. Usually, a multimodal approach is required, including psychoeducation, individual psychotherapy, family intervention and medication. In primary care practice, however, treatment options are frequently limited by lack of availability of trained psychotherapists.

Psycho-education

Psycho-education should always be provided to both child and care givers, regardless of whether psychological treatment or medication is used. The aims of psychoeducational interventions are to inform the child, the family and the school about symptoms, their consequences, prognosis, treatment duration and adverse effects of medication. It is important to help the child to cope with depressed mood and to foster better compliance with treatment [3].

Psychosocial interventions

Among the psychotherapeutic approaches proposed in the management of depression (psychodynamic, cognitive–behaviour, interpersonal and family-based attachment therapies, and supportive treatment) [2,45], cognitive–behaviour therapy (CBT) and interpersonal therapy (IPT) appear to be the most effective and are considered first-line therapies for mild to moderate depression in children and adolescents. Various meta-analyses [46–48] have consistently reported excellent effect sizes for the effectiveness of these psychotherapies; however, some less convincing findings regarding effect size have also been reported in the meta-analyses conducted by Weisz *et al.* [49••]. Also, it is important to note that most controlled trials have focused on CBT in adolescents with MDD, whereas far fewer controlled studies have been conducted in pre-adolescents using CBT or other psychotherapies [49••,50]. The same interventions are usually recommended for the treatment of paediatric dysthymia [37] but, given its chronicity, longer treatment may be required [3].

CBT is time limited (8–12 manual-based sessions) and is delivered either individually or in group sessions. It uses various techniques (self-monitoring, reinforcement, social skills training, cognitive reframing, relaxation and impulse control) to help patients identify and change distorted cognitions, and improve their problem-solving ability, as well as manage affects in cases of environmental stress. There is evidence that CBT may be appropriate for patients with mild to moderate depression as a single therapy, but severe depression usually requires combination with psychopharmacological treatment [45]. The effect of CBT may not be as strong if youths also exhibit externalizing behaviour problems or if their parents are depressed [51•]. Also, CBT may not be developmentally appropriate for younger children with less developed abstract reasoning and limited control over their personal environments.

IPT focuses on improving the individual's interpersonal functioning and on identifying the problems associated with the onset of the depressive episode. Treatment is time limited and manual based, focusing on one or more

problem areas. [52]. ITP has been adapted for adolescents [53], and there are versions for indicated preventive intervention in adolescents with subthreshold depression; in their recent study, Young *et al.* [54•] found it to be effective. Interventions in children with dysthymia are of particular importance, given its deleterious effect on development, social competence and school achievement, and the possibility of vulnerability to depressive disorders in later life [55•]. Contextual emotion–regulation therapy, which was developed specifically for school-aged children and which was tested for its efficacy in treating chronic depression by Kovacs *et al.* [55•], represents a new and promising goal-directed and problem-focused intervention.

Family-based interventions

Family-based interventions (infant–parent therapy, family therapy, parent–child interaction training) are particularly important in preschool children with depressive symptoms [5••,38•]. Medication is not appropriate in this age group because of the lack of clinical trial data to inform evidence-based recommendations.

Psychopharmacological treatment

Based on recent reviews summarizing data on efficacy and safety of antidepressants in youths [56,57•,58,59•], fluoxetine appears to be effective in the treatment of depressed children and adolescents, demonstrating effectiveness over placebo in three randomized controlled trials (RCTs) [60–62]. Fluoxetine was also found to be superior to nonblinded CBT alone in the Treatment of Adolescent Depression Study (TADS) [62]. Importantly, in that study the combination of fluoxetine plus CBT emerged as more effective than either treatment alone. Regarding other selective serotonin reuptake inhibitors (SSRIs), citalopram was also found to be more effective than placebo in one trial [63], and sertraline was found to be effective in youngsters aged 6–17 years but only when data were pooled from two separate RCTs [64]. Other trials aimed to investigate CBT and medication (sertralin) and their combination in adolescent depression [65•]. CBT was found superior to low-dose sertralin, and combined treatment was not superior to either treatment alone. Studies of other SSRIs and newer antidepressants (venlafaxine, nefazodone and mirtazapine) yielded less evidence (usually based on evaluation of secondary outcomes) of efficacy, and therefore they are not recommended as first-line treatments for depression in youths. Tricyclic antidepressants are generally ineffective and may have serious adverse effects; hence, their use is usually not recommended.

The degree of efficacy of SSRIs in childhood-onset depression reported by different RCTs (even of the same drug) varied between studies. This highlights the importance of considering those individual factors that are assumed to cause such variations in findings (neurobiological and developmental correlates, differences in pharmacokinetics and pharmacodynamics, high rates of placebo response and several methodological issues) when designing further clinical trials [59•].

Reanalyses of published and unpublished studies by the US Food and Drug Administration raised alerts regarding higher suicidal behaviour rates with SSRIs in youths [1,58,66], which resulted in different regulatory actions regarding the use of antidepressants in children and adolescents worldwide [66]. According to the pooled analyses conducted by the US Food and Drug Administration, the risk for suicidal ideation or suicidal behaviour (actual suicide attempt or preparatory actions for imminent suicidal behaviour) was 4% in patients treated with the active drug, whereas it was 2% in those receiving placebo [57•]. Notably, no completed suicide was reported by any RCT in children and adolescents. In addition, based on reports published during the past few years, overall suicide rates are decreasing in adolescents, and there appears to be a correlation between the use of SSRIs and a decrease in the number of completed suicides over the past decade [67,68]. Furthermore, toxicological studies have not supported the association between SSRIs and suicidality [69]. On the other hand, the results of a case–control study recently conducted by Olfson *et al.* [70•] indicated that antidepressant treatment appeared to be related to suicide attempts and death in severely depressed children and adolescents but not in adults. Nonetheless, during treatment with antidepressants (which is recommended in cases of severe depression or nonresponse to adequate psychotherapeutic interventions) close monitoring is required to identify adverse events, including suicidal behaviour and agitation. In addition, the clinicians should be guided by the recommendations and warnings issued by their national drug regulatory authorities [71]. Regarding suicidality, it is noteworthy that in the TADS [62] suicidal events were twice as common in patients treated with fluoxetine alone than in those who were treated with combined treatment or with CBT alone. This finding suggests a protective effect of CBT against suicidal events, but CBT alone did not differ from placebo on any measured outcome [72•].

Conclusion

Accurate assessment of depressive and other symptoms of frequently co-morbid disorders, and evaluation of functional impairment, suicide risk and patient risk, and protective characteristics are all essential in the clinicians' decision regarding the optimal management approach for the individual patient. Psychotherapeutic (CBT and IPT), and in cases of severe depression psychopharmacological intervention combined with CBT,

appear to be effective. In children, however, we have limited data on the effectiveness and safety of various approaches that are corroborated by adolescent and adult research. In preschool children, family-based approaches are recommended. Given the serious impact of paediatric depression on individuals, families and the community, early selective and indicated preventive interventions should also be an important component of management of this serious disorder.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 94–95).

1 Ryan ND. Treatment of depression in children and adolescents. Lancet 2005; 366:933–940.

2 Birmaher B, Ryan ND, Williamson DE, *et al.* Childhood and adolescent depression: a review of the past 10 years: part I. J Am Acad Child Adolesc Psychiatry 1996; 35:1427–1439.

3 Nobile M, Cataldo GM, Marino C, *et al.* Diagnosis and treatment of dysthymia in children and adolescents. CNS Drugs 2003; 17:927–946.

4 •• Egger HL, Angold A. Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. J Child Psychol Psychiatry 2006; 47:313–337.
Given the limited information available in the literature, this review article provides important data about nosology and epidemiology of preschool psychiatric disorders, including depression.

5 •• Stalets MM, Luby JL. Preschool depression. Child Adolesc Psychiatric Clin N Am 2006; 15:899–917.
This is an impressive summary of findings regarding validation, epidemiology, assessment and diagnosis of preschool depression. The authors emphasize the lack of evidence-based data on the treatment of depressive symptoms in this age group.

6 Costello EJ, Mustillo S, Erkanli A, *et al.* Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry 2003; 60:837–844.

7 Lewinsohn PM, Hops H, Roberts RE, *et al.* Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. J Abnorm Child Psychol 1993; 102:133–144.

8 • Zalsman G, Brent DA, Weersing VR. Depressive disorders in childhood and adolescence: an overview epidemiology, clinical manifestation and risk factors. Child Adolesc Psychiatric Clin N Am 2006; 15:827–841.
Focusing on presentation and risk factors, this article reviews research in early-onset depression. It also provides important recommendations for clinicians regarding evidence-based treatment options.

9 Ryan ND, Williamson DE, Iyengar S, *et al.* A secular increase in child and adolescent onset affective disorder. J Am Acad Child Adolesc Psychiatry 1992; 31:600–605.

10 •• Costello EJ, Erkanli A, Angold A. Is there an epidemic of child or adolescent depression? J Child Psychol Psychiatry 2006; 47:1263–1271.
This meta-analytic review of 26 epidemiologic studies explores whether there is a real increase in the prevalence rate of early-onset depression. Controlling the estimate for several influencing factors, year of birth was not found to have effect on prevalence of depression.

11 •• Garber J. Depression in children and adolescents linking risk research and prevention. Am J Prev Med 2006; 31 (6 Suppl 1):S104–S125.
This article reviews risk factors for depression in children and adolescents from the perspective of prevention, to emphasize the essential role played by the link between the risk and prevention research in the development of appropriate interventions.

12 Paykel ES. Life events and affective disorder. Acta Psychiatr Scand 2003; 108:61–66.

13 Jaffee SR, Price TS. Gene–environment correlations: a review of the evidence and implications for prevention of mental illness. Mol Psychiatry 2007; 12:432–442.

14 Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. Arch Gen Psychiatry 2005; 62:473–481.

15 Rutter M, Moffitt TE, Caspi A. Gene–environment interplay and psychopathology: multiple varieties but real effects. J Child Psychol Psychiatry 2006; 47:226–261.

16 Kaufman J, Yang B-Z, Douglas-Palumberi H, *et al.* Social supports and serotonin transporter gene moderate depression in maltreated children. Proc Natl Acad Sci USA 2004; 101:17316–17321.

17 Eley TC, Sugden K, Corsico A, *et al.* Gene–environment interaction analysis of serotonin system markers with adolescent depression. Mol Psychiatry 2004; 9:908–915.

18 Caspi A, Sugden K, Moffitt TE, *et al.* Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003; 31:386–389.

19 Kendler KS, Kuhn JW, Vittum J, *et al.* The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch Gen Psychiatry 2005; 62:529–535.

20 Strauss J, Barr CL, George CJ, *et al.* Association study of brain-derived neurotrophic factor in adults with a history of childhood onset mood disorder. Am J Med Genet B Neuropsychiatr Genet 2004; 131:16–19.

21 Strauss J, Barr CL, George CJ, *et al.* Brain-derived neurotrophic factor variants are associated with childhood-onset mood disorder: confirmation in a Hungarian sample. Mol Psychiatry 2005; 10:861–867.

22 •• Kaufman J, Yang B-Z, Douglas-Palumberi H, *et al.* Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Biol Psychiatry 2006; 59:673–680.
This study first examined the role of gene–gene interactions along with other multiple interactions in the development of early-onset depression. Their results showed significant three-way interactions between BDNF genotype, 5-HTTLPR and maltreatment, and a further four-way interaction with social support. This finding emphasizes the protective role of social support for children at elevated risk for depression.

23 • Luby JL, Belden AC, Spitznagel E. Risk factors for preschool depression: the mediating role of early stressful life events. J Child Psychol Psychiatry 2006; 47:1292–1298.
This article highlights the importance of identification of early risk factors, which could be the targets of early prevention measures in depressed preschool children with familial risks for mood disorders.

24 MacPhee AR, Andrews JJ. Risk factors for depression in early adolescence. Adolescence 2006; 41:435–466.

25 • Oldehinkel AJ, Veenstra R, Ormel J, *et al.* Temperament, parenting, and depressive symptoms in a population sample of preadolescents. J Child Psychol Psychiatry 2006; 47:684–695.
The results of this study on pre-adolescent children underline the importance of the examination of possible factors that may have influence on the well known relation between parenting and depressive symptoms.

26 Jaffee SR, Moffitt TE, Caspi A, *et al.* Differences in early childhood risk factors for juvenile-onset and adult-onset depression. Arch Gen Psychiatry 2002; 59:215–222.

27 Kapornai K, Gentzler AL, Tepper P. Early developmental characteristics and features of major depressive disorder among child psychiatric patients in Hungary. J Affect Disord 2007; 100:91–101.

28 Gale CR, Martyn CN. Birth weight and later risk of depression in a national birth cohort. Br J Psychiatry 2004; 18:428–433.

29 Saigal S, Pinelli J, Hoult L, *et al.* Psychopathology and social competencies of adolescents who were extremely low birth weight. Pediatrics 2003; 111:969–975.

30 • Rice F, Harold GT, Thapar A. The effect of birth-weight with genetic susceptibility on depressive symptoms in childhood and adolescence. Eur Child Adolesc Psychiatry 2006; 15:383–391.
This is the first study to examine the relation between birth weight and childhood depression, along with the moderating effect of familial risk for depression, in a sample of twins.

31 • Costello EJ, Worthman C, Erkanli A, *et al.* Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. Arch Gen Psychiatry 2007; 64:338–344.
This study explored the predictive role of LBW in depression, about which there are conflicting findings in the literature. The authors also tested the potential risk mechanisms that may explain the possible association between LBW and depression.

32 Lau JYF, Eley TC. Changes in genetic and environmental influences on depressive symptoms across adolescence and young adulthood. Br J Psychiatry 2006; 189:422–427.

33 Scourfield J, Rice F, Thapar A, *et al.* Depressive symptoms in children and adolescents: changing etiological influences with development. J Child Psychol Psychiatry 2003; 44:968–976.

34 Feinberg ME, Button TMM, Neiderhiser JM, *et al.* Parenting and adolescent antisocial behavior and depression. Arch Gen Psychiatry 2007; 64:457–465.

35 •• Horowitz JL, Garber J. The prevention of depressive symptoms in children and adolescents: A meta-analytic review. J Consult Clin Psychol 2006; 74:401–415.
Given the deleterious effect of depression on communities, this is a very important meta-analytic review of research into prevention of early-onset depressive symptoms. The results suggest the superiority of selective and indicated programmes over universal interventions in preventing childhood depression.

36 • Spence SH, Shortt AL. Research review: can we justify the widespread dissemination of universal, school-based interventions for the prevention of depression among children and adolescents? J Child Psychol Psychiatry 2007; 48:526–542.
Based on findings reviewed by this article, the authors suggested that the available evidence does not support the effectiveness of universal preventive programmes.

37 American Academy Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry 1998; 37(Suppl. 10):63S–83S.

38 • Sheik RM, Weller EB, Weller RA. Prepubertal depression: diagnostic and therapeutic dilemmas. Curr Psychiatry Rep 2006; 8:121–126.
Emphasizing the developmental perspective, this article provides a brief summary of current questions and options regarding the diagnosis and appropriate therapy in pre-adolescent and preschool depression.

39 Kiss E, Gantzler AM, George C, *et al.* Factors influencing mother-child reports of depressive symptoms and agreement among clinically referred depressed youngsters in Hungary. J Affect Disord 2007; 100:143–151.

40 Angold A, Costello AJ. Structured interviewing. In: Lewis M, editor. Child and adolescent psychiatry: a comprehensive textbook. Baltimore, Maryland: Williams & Wilkins; 1995. pp. 545–555.

41 Carter AS, Briggs-Gowan MJ, Davis NO. Assessment of young children's social-emotional development and psychopathology: recent advances and recommendations for practice. J Child Psychol Psychiatry 2004; 45:109–134.

42 Task Force on Research Diagnostic Criteria. Infancy preschool: research diagnostic criteria for infants and preschool children: the process and empirical support. J Am Acad Child Adolesc Psyciatry 2003; 42:1504–1512.

43 Park RJ, Goodyear IM. Clinical guidelines for depressive disorders in childhood and adolescence. Eur Child Adolesc Psychiatry 2000; 9: 147–161.

44 • Hughes CW, Emslie GJ, Crimson LM, *et al.* Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. J Am Acad Child Adolesc Psychiatry 2007; 46:667–686.
Based on scientific evidence and expert clinical consensus, this is the updated guideline for medication treatment of childhood depression.

45 Harrington R, Whittaker J, Shoebridge P. Psychological treatment of depression in children and adolescents: a review of treatment research. Br J Psychiatry 1998; 173:291–298.

46 Reinecke MA, Ryan NE, Dubois DL. Cognitive-behavioral therapy of depression and depressive symptoms during adolescence: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry 1998; 37:26–34.

47 Lewinsohn PM, Clarke GN. Psychosocial treatments for adolescent depression. Clin Psychol Rev 1999; 19:329–342.

48 Harrington R, Campbell F, Shoebridge P, *et al.* Meta-analysis of CBT for depression in adolescents. J Am Acad Child Adolesc Psychiatry 1998; 37:1005–1007.

49 •• Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. Psychol Bull 2006; 132:132–149.
This meta-analytic review, with a large study sample, examined the effectiveness, duration of action and specificity of the effects of different psychotherapies using strict analytic methods. The estimated mean effect size was 0.34, which is significantly lower than effect sizes reported by earlier analyses. CBT was not found to be superior to noncognitive approaches.

50 Compton SN, March JS, Brent DA, *et al.* Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Adolesc Psychiatry 2004; 43:930–959.

51 • Weersing VR, Brent DA. Cognitive behavioral therapy for depression in youth. Child Adolesc Psychiatric Clin N Am 2006; 15:939–957.
This is an extensive review of the concept of CBT and of empirical findings from published CBT trials in childhood depression. The authors also provide a detailed discussion of the possible explanations for the conflicting results of CBT trials that emerged during the past few years.

52 Curry JF. Specific psychotherapies for childhood and adolescent depression. Biol Psychiatry 2001; 49:1091–1100.

53 Moreau D, Mufson L, Weissman MM, *et al.* Interpersonal psychotherapy for adolescent depression: description of modification and preliminary application. J Am Acad Child Adolesc Psychiatry 1991; 30:642–651.

54 • Young JF, Mufson L, Davis M. Efficacy of Interpersonal Psychotherapy-Adolescent Skills Training: an indicated preventive intervention for depression. J Child Psychol Psychiatry 2006; 47:1254–1262.
This article reports positive preliminary data of the efficacy trial on the IPT-Adolescent Skills Training preventive intervention, which was developed for adolescents with depressive symptoms.

55 • Kovacs M, Sherrill J, George CJ. Contextual emotion-regulation therapy for childhood depression: Description and pilot testing of a new intervention. J Am Acad Child Adolesc Psychiatry 2006; 45:892–903.
This article presents a new intervention for school-aged children suffering from chronic depression and reports positive findings (regarding efficacy and acceptability) during the pilot testing of this therapy. These findings are particularly important in clinical practice with dysthymic younger children, given the limited availability of treatment options in this age group.

56 Vasa RA, Carlino AR, Pine DS. Pharmacotherapy of depressed children and adolescents: current issues and potential directions. Biol Psychiatry 2006; 59:1021–1028.

57 • Mann JJ, Emslie G, Baldessarini LJ, *et al.* ACNP Task Force report on SSRIs and suicidal behavior in youth. Neuropsychopharmacology 2006; 31:473–492.
This article provides an extensive review of efficacy and safety data from all published and unpublished paediatric antidepressants studies.

58 Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006; 63:332–339.

59 • Moreno C, Roche AM, Greenhill LL. Pharmacotherapy of child and adolescent depression. Child Adolesc Psychiatr Clin N Am 2006; 15:977–998.
Reviewing the data on the effects of antidepressants in children and adolescents, this article provides a comprehensive discussion of differences between efficacy findings across studies.

60 Emslie GJ, Rush AJ, Weinberg WA. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997; 54:1031–1037.

61 Emslie GJ, Heiligenstein JH, Wagner KD, *et al.* Fluoxetine for acute treatment of depression in children and adolescents: a placebo controlled randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2002; 41: 1205–1215.

62 March J, Silva S, Petrycki S, *et al.* Fluoxetine, cognitive-behavioural therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 2004; 292:807–820.

63 Wagner KD, Robb AS, Findling RL, *et al.* A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. Am J Psychiatry 2004; 161:1079–1083.

64 Wagner KD, Ambrosini PJ, Rynn M, *et al.* Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder. JAMA 2004; 290:1033–1041.

65 • Melvin GA, Tonge BJ, King NJ, *et al.* A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. J Am Acad Child Adolesc Psychiatry 2006; 45:1151–1161.
In this randomized trial without placebo arm, combined treatment with CBT and sertraline medication did not exhibit benefit over either treatment alone. Furthermore, CBT was superior to antidepressant therapy.

66 Varley CK. Treating depression in children and adolescents: what options now? CNS Drugs 2006; 20:1–13.

67 Gibbons RD, Hur K, Bhaumik DK, *et al.* The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 2005; 62:165–172.

68 Olfson M, Shaffer D, Marcus SC. Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 2003; 60:978–982.

69 Isacsson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. Acta Psychiatr Scand 2005; 111:286–290.

70 Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in • severely depressed children and adults. Arch Gen Psychiatry 2006; 63:865–872.
The study sought to estimate the relative risk for suicide attempt and suicide death in children and adults with severe depression using a case–control design. The results show that the risk for suicide attempt and death might relate to antidepressant treatment in children and adolescents. This finding strongly suggests the importance of close monitoring during the medication treatment of depressed children.

71 Hazell P. Depression in children and adolescents. Clin Evid 2006; 15:398–414.

72 March J, Silva S, Vitiello B, *et al.* The Treatment for Adolescents with • Depression Study (TADS): methods and message at 12 weeks. J Am Acad Child Adolesc Psychiatry 2006; 45:1393–1403.
This article summarizes all of the currently available data about intent-to-treat outcomes across multiple end-points at 12 weeks of the TADS trial, the most comprehensive randomized clinical trial in adolescent depression treatment.

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Research report

Early developmental characteristics and features of major depressive disorder among child psychiatric patients in Hungary☆

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Abstract

Objective: We investigate the relations of early atypical characteristics (perinatal problems, developmental delay, and difficult temperament) and onset-age (as well as severity of) first major depressive disorder (MDD) and first internalizing disorder in a clinical sample of depressed children in Hungary.
Method: Participants were 371 children (ages 7–14) with MDD, and their biological mothers, recruited through multiple clinical sites. Diagnoses (via DSM-IV criteria) and onset dates of disorders were finalized "best estimate" psychiatrists, and based on multiple information sources. Mothers provided developmental data in a structured interview.
Results: Difficult temperament predicted earlier onset of MDD and first internalizing disorder, but its effect was ameliorated if the family was intact during early childhood. Further, the importance of difficult temperament decreased as a function of time. Perinatal problems and developmental delay did not impact onset ages of disorders, and none of the early childhood characteristics associated with MDD episode severity.
Conclusions: Children with MDD may have added disadvantage of earlier onset if they had a difficult temperament in infancy. Because early temperament mirrors physiological reactivity and regulatory capacity, it can affect various areas of functioning related to psychopathology. Early caregiver stability may attenuate some adverse effects of difficult infant temperament.

Keywords: Childhood characteristics; Depression; Age of onset; Temperament; Intact family

A substantial body of research has documented that various developmental characteristics early in childhood increase the risk of subsequent depression (e.g., Kessler et al., 1997; Reinherz et al., 1993, 1999). Perinatal complications, neurodevelopment problems, and atypical temperament represent one broad category of risk variables that may mirror physiological vulnerabilities

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to later psychological disorders. Perinatal problems have been defined as including preterm birth, delayed labor, atypical birth weight, caesarian section, and special care after birth (e.g., Allen et al., 1998). Neurodevelopmental difficulties have been operationalized as delayed standing, walking, speaking (e.g., Van Os et al., 1997), and early difficult temperament as regulatory problems including persistent crying and atypical sleeping and/or feeding patterns (e.g., Keenan et al., 1998).

Focusing mostly on perinatal variables, studies of depressed adults have reported that mood disordered patients have higher rates of one or more obstetric complications than do various comparison groups (e.g., Guth et al., 1993; Preti et al., 2000). For example, according to Preti et al. (2000), adult patients with histories of mood disorder had significantly lower birth weight (for their gestational ages) than did matched normal controls. Guth et al. (1993) found that obstetric complications were more common among cases with early-onset mood disorder than among those with late-onset. And Vocisano et al. (1996) reported that inpatients with prolonged, severe, and functionally impairing MDD had higher frequencies of birth related problems and physical disorder in infancy than did less severely depressed outpatients.

Several studies with broader (e.g., community-based, birth cohort) sampling bases also have found relations between atypical early developmental features and affective psychopathology. For example, in a birth cohort study, Gale and Martyn (2004) found that low birth weight was associated with self-reported depressive symptoms in women during adulthood. Adults with childhood-onset affective disorders have been found to attain motor milestones later, score higher on perinatal insults and lower on gross motor skills, and be rated as more difficult babies compared to individuals with adult-onset depression (Jaffee et al., 2002; Van Os et al., 1997). Early difficult temperament also has been associated with subsequent internalizing symptoms and disorders in childhood (e.g., Keenan et al., 1998; Maziade et al., 1989).

However, the literature on the relations of atypical development and mood disorder is far from consistent, given also reports of negative findings (e.g., Allen et al., 1998; Buka et al., 1993; Najman et al., 2005), findings of associations between perinatal problems and anxiety but not mood disorders (e.g., Allen et al., 1998; Cohen et al., 1989), and findings of positive relationships but lack of diagnostic specificity (e.g., Hirshfeld-Becker et al., 2004). Inconsistencies in the literature is not surprising, given not only sampling differences, but the various ways in which studies have defined depression (i.e., clinical diagnoses, operational criteria, self-rated scales), ascertained early developmental problems (e.g., retrospective reports of adults, pediatric records, contemporaneous ratings), and quantified key variables (e.g., event counts, severity scales).

Whereas the bulk of evidence appears to indicate some association between features of atypical early development and psychopathology, the clinician seeking to translate such findings into practical terms is faced with two questions: a) do atypical developmental features "matter" if the patient *already developed mood disorder*, and if so then how? and b) are the effects, if any, specific to depressive disorder? In the present study of a large sample of clinically depressed children, we sought to address these two questions. Given that age of onset and illness severity convey important clinical information and also can influence treatment decisions, we defined them as our dependent variables and examined their relations to indices of atypical neurodevelopment (during the first several years of life) as reported by mothers. Additionally, given that MDD often presents with comorbid dysthymic and anxiety disorders, and that the latter comorbidities generally emerge earlier than does MDD (e.g., Axelson and Birmaher, 2001; Kovacs et al., 1989), we examined whether our independent variables were related to these diagnoses as well. We used multiple informants and sources of information (including medical and related records) to date onset of disorders.

More specifically, we hypothesized that perinatal problems, developmental delay, and difficult infant temperament would render children vulnerable to earlier onset and more severe episodes of major depressive disorder. We also posited that the effects of risk factors may not be specific to MDD-onset, but would also relate to onset age of the first internalizing disorder (i.e., the age at which the first episode of MDD or comorbid dysthymia or anxiety disorder began). In line with suggestions that early risk factors should be studied in models that examine multiple and interactive effects (e.g., Goodman, 2002), we also investigated factors that could moderate associations between early childhood characteristics and our dependent variables. Because neonatal health or motor skill problems have been found to relate to depression or anxiety for boys but not for girls (Reinherz et al., 1999; Sigurdsson et al., 2002), we tested whether child's sex serves as a moderator. Given some indications that marital partner changes early during a child's life may be one factor in child depression (Najman et al., 2005), we predicted that having a stable, intact, two-parent family early on may act as a protective factor and attenuate the negative impact of

atypical childhood characteristics. Finally, we considered as covariates: a) mother's age at birth of the child, given indications that relatively younger (Jaffee et al., 2001) and older maternal ages are associated with increased rates of complications for offspring (Van Katwijk and Peeters, 1998), and b) mother's educational level, as a proxy for socioeconomic status.

1. Method

1.1. Participants

In the present article we report on 371 children (168 girls), aged 11.7 years on average (SD=2.0 years, range: 7.3–14.9 years), who were enrolled by December 31, 2003 in a study of genetic and psychosocial risk factors in childhood-onset depression, had biological mothers as parental informants, and met diagnostic criteria for MDD (detailed below). Racial composition was 95.1% Caucasian, 0.3% African, 1.9% multiracial, and 2.7% Roma or other minorities, representative of the population of Hungary. The subjects in this article partially overlap with those in other papers that address different facets of children's depressive illness (e.g., Liu et al., 2006). A subset of children had comorbid disorders in addition to MDD (e.g., 34.5% had an anxiety disorder, 3.5% with conduct disorder; 6.2% with oppositional defiant disorder; and 15.6% with Attention Deficit/Hyperactivity Disorder).

At study entry, mothers' ages ranged from 26 to 57 years, with a mean of 36.5 years (SD=5.1). Mothers' ages at their children's birth ranged from 16 to 46 years (M=25.3, SD=5.1). The majority (88.7%) were 19 to 34 years old at child's birth (the lowest 5.7% between 16–18 years, and the highest 5.7% between 35–46 years of age). Mothers' years of education ranged from 6 to 21 years (M=11.6 years, SD= 2.8). Most children (90.6%) lived in intact families of origin from birth to 4 years of age.

1.2. Enrollment and assessment procedures

Children were recruited through 23 child psychiatric facilities (7 of which had both inpatient and outpatient units) across Hungary, serving both urban and rural areas. Based on information available for most of our sites for the year 2004, we estimate that they provided services to at least 80% of the newly registered child psychiatry cases, giving us access to a significant portion of the referred population nationwide. Children presenting at each site were scheduled for a research assessment if they met the following criteria: 7.0 years to 14.9 years old, not mentally retarded, no evidence of major systemic medical disorder, had available at least one biologic parent and a 7 –17.9 year-old sibling (required by the study's genetic component), and attained a predetermined cut-off score on one of various depressive symptom screens (e.g., the short version of the Children's Depressive Inventory; Kovacs and MHS Staff, 2003; selected items from the Child Behavior Checklist, Achenbach, 1991). (Siblings are not included in this article.) Children meeting these initial criteria were scheduled for a 2-part evaluation, conducted on 2 separate occasions, about 6 weeks apart, by different clinicians. We obtained written consent for participation signed by both parents and the child, in accordance with the legal requirements in Hungary and the University of Pittsburgh, Pittsburgh, USA.

The first part of the evaluation entailed administration of the "Mood Disorder Module" of a diagnostic interview (described below), as well as the Intake General Information Sheet (IGIS), a comprehensive demographic and anamnestic data form. Participants also completed self-rated scales (not included in the present report). The IGIS is an event-focused structured interview with pre-coded item response choices covering, among others, demographic and family variables, as well as developmental, physical health, and psychosocial history, with the parent serving as informant. To set the proper framework and facilitate recall, evaluations started with a semistructured interview, designed to construct a "time line" for the patient from birth to the date of the assessment. The time-line anchors included major "public" events with the corresponding dates (e.g., Christmas, start of a school year) and personally relevant events (e.g., birth of a sibling, both positive and negative familial events, variables reflecting on adjustment). The time-line ("chronograph") served to identify the times when the child's symptoms became problematic and to date disorder onsets and offsets.

The second part of the evaluation involved the full diagnostic interview and the completion of additional self-rated scales, but was administered only if the child proband had met DSM criteria for mood disorder at the first evaluation. (If DSM criteria were not met, the child was assigned an "at-risk" status and entered a follow-up arm of the study). For our diagnostic interview, we used the Interview Schedule for Children and Adolescents–Diagnostic Version (ISCA-D), which is an extension of the Interview Schedule for Children and Adolescents (ISCA) (Sherrill and Kovacs, 2000). The interview, which covers the relevant Axis-I DSM-IV as well as some DSM-III disorders, was conducted by the same

interviewer separately with the parent about the child, and the child about him/herself, yielding symptom ratings and diagnoses for "current" as well as "lifetime" disorders. Results of both the first and second parts of the assessments and associated documentation (e.g., psychiatric records) were subjected to a consensus diagnostic procedure (Maziade et al., 1992). Pairs of senior child psychiatrists, trained as Best Estimate Diagnosticians (BEDs), separately reviewed all material, and then together derived consensus diagnoses. "Caseness," as well as onset dates of disorders, was based on best-estimate consensus. As described in connection with previous work (Kovacs et al., 1984a, b), operational rules were used to define disorder onset and recovery, and "midpoint" rules were used to date onsets and offsets, if more exact dating was not possible.

The interviews were administered by child psychiatrists and psychologists who completed 3 months of didactic and practical training in the semi-structured interview technique. They were required to reach an average of 85% symptom-agreement on 5 consecutive videotaped interviews against "gold standard" interview ratings provided by the trainers. Routine monitoring and follow-up training sessions served to minimize rater drift. All interviews were audiotaped. Interrater reliability on ISCA-D symptoms was satisfactory (using audiotapes of interviews for $n=46$ pairs of raters). For MDD symptoms, kappas ranged from .64 to .88, with 80% of the coefficients at or above .70. For DD symptoms (using DSM-IV criteria), kappas ranged from .38 to .93, with 80% at or above .70. For Generalized Anxiety Disorder symptoms (the most common DSM-IV anxiety diagnosis), kappas ranged from .53 to 1.00, with 62.5% at or above .70. Similar inter-rater reliability coefficients were obtained for other ISCA-D disorders as well.

1.3. Independent and dependent variables

1.3.1. Early atypical neurodevelopmental characteristics

Using IGIS items that pertain to the child proband's early development history from his/her birth to toddler age, we created three indices of atypical development: *Perinatal Problems* (4 items), *Developmental Delay* (2 items), and *Difficult Temperament* (3 items). The construct of temperament includes multiple dimensions tapping emotional, biological, and behavioral reactivity and regulation (Rothbart and Bates, 1998). Our temperament index included a global question on how difficult it was to comfort the infant (similar to the single-item question included as part of the investigation of Jaffee et al. (2002)), and because we were particularly interested in physiological vulnerability, two items measuring biological irregularity (similar to Thomas and Chess's (1977) temperament category of rhythmicity). Each index or scale reflects the number of "yes" responses to the corresponding items. See Table 1 for the specific items and their endorsement rates in our sample.

1.3.2. Intact family status

An entire section of the IGIS is dedicated to enumerating parental caregivers for each year of the child's life. Using these items, we created a dichotomous summary variable to reflect whether or not a child was continuously taken care of by both biological parents from birth until 4 years of age (intact vs. non-intact family). Altogether 35 children (9.4% of the sample) experienced broken homes early on.

1.3.3. Onset age of MDD and first internalizing disorder (MDD, dysthymic, or anxiety disorder)

The mean MDD onset age for the sample was 10.51 (SD=2.28), with a range from 3.80 to 14.84. Of the 371 children, 51 (13.7%) also had dysthymic disorder (DD), and 128 (34.5%) had anxiety disorders (Overanxious Disorder and Generalized Anxiety Disorder were the most common, with all the other anxiety disorders being

Table 1
Early neurodevelopmental characteristics of clinically referred depressed children ($N=367$–371)

Variables	Item endorsement		Score descriptives	
	N	% of sample	Mean (SD)	Range
Perinatal problem index			0.72 (.98)	0–4
Premature/late delivery	47	12.7%		
Complications during delivery [a]	79	21.3%		
Very large/small at birth	70	18.9%		
Special care after birth [b]	73	19.7%		
Difficult temperament index			0.87 (.97)	0–3
Recurrent feeding problems	88	23.9%		
Recurrent/chronic sleeping problems	118	31.9%		
Usually/often hard to comfort/soothe	119	32.2%		
Developmental delay index			0.20 (.48)	0–2
Late for age when began to walk without help	30	8.1%		
Late to start to speak in sentences	46	12.4%		

[a] E.g., excessive bleeding, "cord" around the neck, Rh incompatibility.
[b] E.g., placed in incubator, under special observation.

represented.) For 90 of the cases with anxiety comorbidity, the anxiety disorder onset earlier than MDD or DD. For our sample, the mean onset age of the first internalizing disorder was 9.72 (SD=2.60, range: 2.58–14.74).

1.3.4. MDD episode severity

This index was computed for the first episode of MDD (as recorded in the ISCA-D), based on 15 symptoms, each rated on a 3-point severity scale: 0=not present; 1=subthreshold; and 2= threshold/clinical. If only one item was missing, that item was pro-rated. Because all children in the sample had MDD, and the minimum of 5 symptoms rated at the "clinical" level was required for the diagnosis, the possible range for the severity score was 10 to 30. The actual range was 10 to 29 (M=19.72, SD=3.68).

1.4. Statistical analyses

We used survival analysis to examine the effects of variables on onset age of MDD or internalizing disorder. Survival analysis is useful with outcomes or events that depend on elapsed time, and can estimate how predictors may be associated with time to the event. Kaplan–Meier survival curves were generated for subgroups; log-rank tests were used to test statistical significance.

To test for relations between the predictors and the age at which children's first episodes occurred, we first conducted univariate Cox regression analyses with each risk index and covariate. We report hazard ratios and 95% confidence intervals to indicate the risk of the outcome in any given unit of time, with one unit increase of the predictor. We also checked the proportional hazards assumption about time-dependence for each predictor variables. Second, in an initial multiple regression model, we included the three risk scales, as well as covariates with $p<.05$ in the univariate Cox models. All hypothesis-driven interaction terms were also included. We then used a backward elimination method, removing each (starting with the one with the largest p-value), and retaining covariates or interaction terms in the final model with $p<.05$. Thus, the final multivariate Cox regression models reflect the impact of independent variables and significant interaction terms, while adjusting for demographic factors (where $p<.05$).

To model the effects of early risk factors on the severity of the children's first depressive episode, we used GLM procedure. We examined the associations between the perinatal, developmental, and temperament problems, as well as how the interaction terms and covariates related to the severity of the MDD symptomatology.

2. Results

The specific variables, which comprised the 3 indices of early neurodevelopmental characteristics, had various rates in our sample (Table 1); in general, developmental delays were least common (from about 8% to 12%) while features of difficult temperament were reported for about 24% to 32% of the cases. The 3 indices were unrelated to each other (r-values ranged from .02 to .06, $p>.24$), and were unrelated to mothers' age at child's birth, mothers' education level, and whether the child was reared in an intact vs. non-intact family early in life. However, boys scored higher on developmental delays (M=.25, SD=.52) than did girls (M=.15, SD=.38), t (369)=−2.11, $p<.05$.

2.1. Modeling onset age of MDD

A series of univariate Cox regression models yielded significant effects for child's sex, early intact family status, and maternal age at child's birth. (See Table 2 for hazard ratios.) At the onset of their MDD, boys (M=10.08; SD=2.12 years) were 1 year younger than girls (M=11.03; SD=2.37 years). Children exposed to changes in caregivers before age four were younger at

Table 2
Modeling age of onset of first MDD episode (N=367)

Variables	Univariate models	Final multivariate model
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Perinatal problems	0.98 (0.88, 1.08)	0.96 (.86, 1.06)
Developmental delay	0.96 (0.77, 1.19)	0.87 (.69, 1.10)
Difficult temperament	1.11 (0.99, 1.23)$^{+}$	5.88 (2.05, 16.83)**
Sex (male=1)	1.68 (1.36, 2.08)***	1.75 (1.41, 2.17)***
Intact family until age 4	0.64 (0.45, 0.91)*	0.93 (0.58, 1.47)
Mother's education (years)	0.98 (0.94, 1.01)	–
Maternal age at birth (years)		
16–18 vs. 19–34	0.94 (0.60, 1.46)	–
35–46 vs. 19–34	1.73 (1.10, 2.72)*	–
Temperament× intact family	–	0.65 (.45, .92)*
Temperament×time	–	0.58 (.37, .92)*

Note. MDD=major depressive disorder; CI=confidence interval; Cox regression analyses were used.
$^{+}p<.07$. *$p<.05$. **$p<.01$. ***$p<.001$.

the onset of their MDD (M=9.68; SD=1.96 years) than those from intact families (M=10.60; SD=2.30 years), and children whose mothers were 35 years and older when they gave birth had earlier onset of MDD (M=9.14; SD=1.89) than children with mothers in the normative age group (M=10.57; SD=2.30).

However, in the final multivariate model, mother's age at child's birth became nonsignificant, and only one interaction term was retained. The results indicate that having a difficult temperament and being a boy were associated with earlier onset of MDD (Table 2). Furthermore, the main effect of temperament was qualified by its interaction with intact family status, and is illustrated by Kaplan–Meier survival curves (separately for intact vs. non-intact families).

For children in intact families (see Fig. 1), temperament was unrelated to age at MDD onset (χ^2 (3)=3.95, p=.27). However, for non-intact families (see Fig. 2), children with a more difficult temperament had an earlier MDD onset age than did children with fewer difficulties (χ^2 (3)=13.57, p<.01). Temperament also interacted with elapsed time, suggesting that its effect is not constant. Specifically, as indicated by the parameter estimate of the interaction term (−.540), the effect is attenuated across time. For example, comparing children at age 14 to children at age 7, the hazard ratio for temperament problems is decreased by exp{−.540*[log(14)−log(7)]}=0.69.

2.2. Modeling severity of first MDD episode

In a series of univariate general linear models, we found no significant associations between perinatal problems, developmental delay, difficult temperament

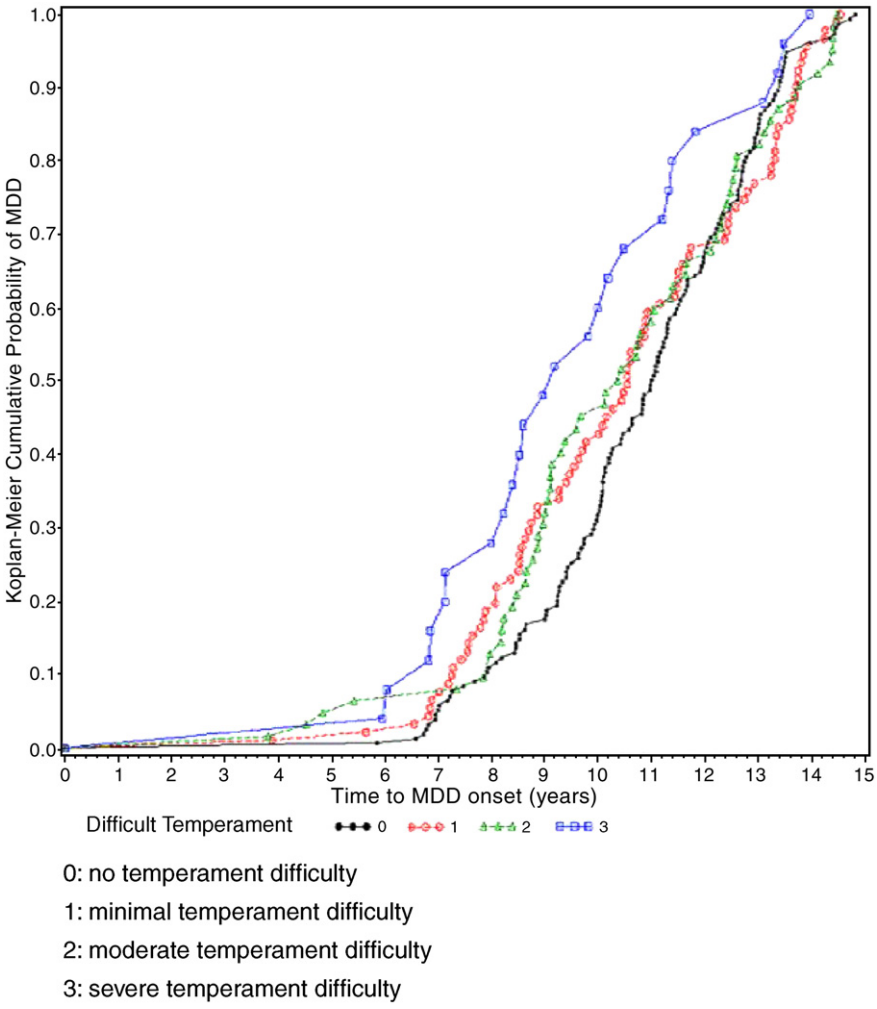

Fig. 1. Effect of early temperament on MDD-onset among children from intact families.

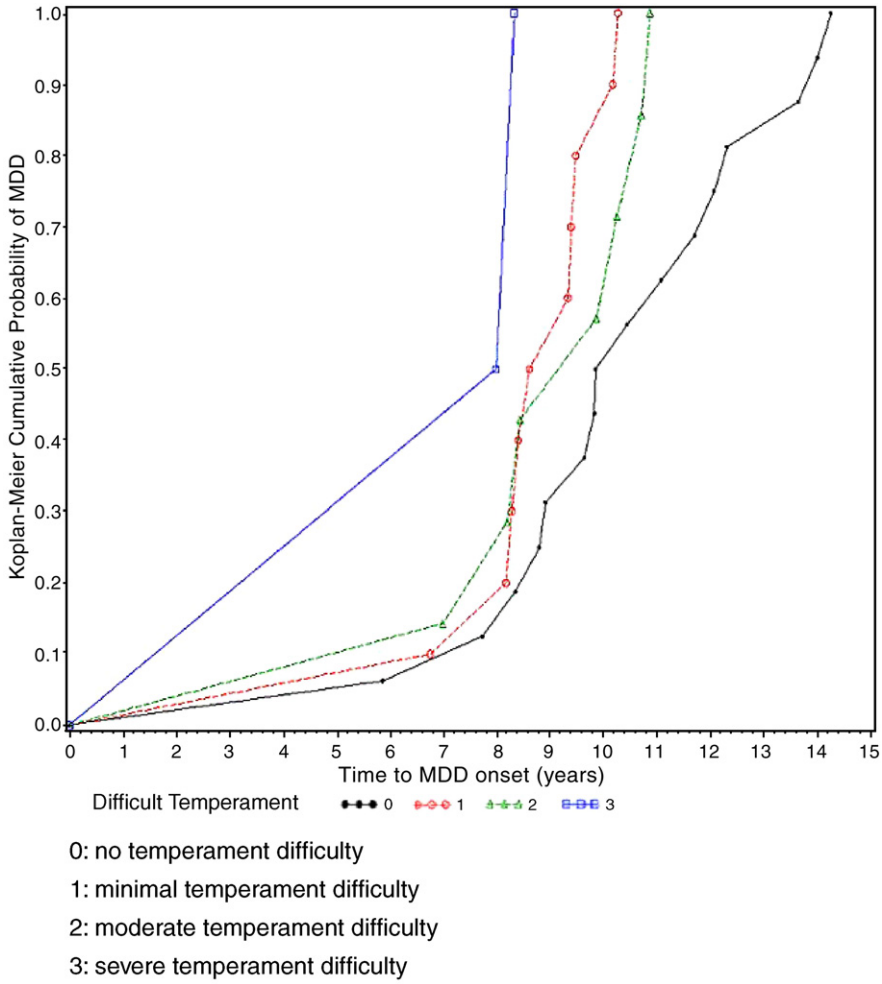

Fig. 2. Effect of early temperament on MDD-onset among children from non-intact families.

and the severity of the first MDD episode. Only an association to child's sex was found, F (1, 369)=4.32, $p<.05$, with girls showing more severe symptoms ($M=20.15$) than boys ($M=19.36$). In multivariate GLM analyses, the interactions of the three developmental indices with sex and with family status were not statistically significant and were dropped from the final model. The final model, including just the three indices and child sex, was not significant, F (4, 362)=1.60, $p=.17$.

2.3. Modeling onset age of MDD/dysthymic/anxiety disorders

We first examined if children, who had developed dysthymic and/or anxiety disorder (Anx) in addition to MDD ($n=158$), differed from children with MDD only ($n=213$) in early risk factors. The groups did not differ in perinatal problems or developmental delays ($p=.95$, $p=.065$, respectively). However, children with comorbid DD or Anx were rated as having had a more difficult early temperament ($M=.99$, SD=1.02) than were those without DD or Anx ($M=.78$, SD=.91), t (365)=−2.10, $p<.05$.

Univariate Cox regression models revealed two significant effects: boys ($M=9.50$, SD=2.51) had an earlier onset of MDD/DD/Anx than did girls ($M=9.98$, SD=2.69), and more difficult temperament was associated with earlier disorder onset. In the final model (see Table 3), child's temperament and sex remained significant, and a significant interaction between Temperament and Intact Family was found, in the same direction as with MDD onset-age. Also, Temperament interacted with elapsed time, with the

Table 3
Modeling Age of Onset of First Internalizing Disorder Episode (MDD/DD/Anx)

Variables	Univariate models	Final multivariate model
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Perinatal problems	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)
Developmental delay	1.11 (0.89, 1.38)	1.06 (0.84, 1.33)
Difficult temperament	1.22 (1.09, 1.36)***	4.07 (1.80, 9.20)***
Sex (male=1)	1.30 (1.06, 1.60)*	1.36 (1.10, 1.68)**
Intact family until age 4	0.77 (0.54, 1.09)	1.01 (.63, 1.60)
Mother's education (years)	0.99 (.96, 1.02)	–
Maternal age at birth (years)		
16–18 vs. 19–34	0.92 (0.59, 1.43)	–
35–46 vs. 19–34	1.58 (1.00, 2.52)$^{+}$	–
Temperament × intact family	–	0.65 (.45, .93)*
Temperament × time	–	0.70 (.49, 1.00)*

Note. MDD=major depressive disorder; DD=dysthymia; Anx=anxiety disorder; CI=confidence interval; Cox regression analyses were used.
$^{+}p<.10$. *$p<.05$. **$p<.01$. ***$p<.001$.

parameter estimate once again indicating that temperament better predicted onset-age among younger than older children.

3. Discussion

To our knowledge, the present study is the first to investigate, in a very large clinical sample of youngsters with MDD, the possible impact of early neurodevelopmental difficulties on features of major depressive and related disorders. We were particularly interested in developmental characteristics that may mirror physiological vulnerability because such factors could be helpful in the early identification of cases at risk. Overall, our results complement a growing body of literature, which suggests that various atypical early childhood characteristics may affect both the risk and timing of psychopathology.

Of the three types of early developmental characteristics we examined, only difficult temperament was related to the age of onset of depression. Children with difficult early temperaments, indexed by mother-reported problems with feeding, sleeping, or soothability, had earlier onset of their depression than did children with milder or no temperamental difficulties. Notably, Jaffee et al. (2002) have reported that infant temperament (having been a "difficult baby") distinguished young adults with childhood-onset and those with adult-onset depression. Our findings extend those results by suggesting that, even among clinically depressed young patients, problematic infant temperament does convey information about MDD onset age.

However, having had a difficult temperament also was associated with earlier DD, or anxiety disorder, as well as MDD (whichever emerged first), indicating a lack of specificity to MDD. Thus, atypical infant temperament may presage vulnerability to a range of mood-related psychiatric problems later on, underscoring that risk factors should be examined in relation to a range of disorders rather than a single condition (Kessler et al., 1997). Additionally, children who had comorbid dysthymic or anxiety disorder reportedly had more difficult temperaments than children without DD or anxiety.

If a difficult temperament prognosticates earlier onset of emotional disorder, what could be the mechanisms? Temperament, which is considered to be a relatively stable style of reactivity, is believed to reflect neurophysiological regulatory capacities (e.g., Rothbart and Bates, 1998). Toddlers with difficult temperaments may be compromised on some neurophysiologic parameter related to emotionality or emotion regulation (e.g., Fox, 1994), which may interfere with the development of effective coping responses, and render them susceptible to earlier onset of disorders. Findings that depressed children, or those at risk for depression, differ from comparison peers in their neuroendocrine or physiological responses to negative experimental mood induction, do suggest the existence of physiological or biological dimensions of vulnerability to depression (e.g., Forbes et al., 2006; Luby et al., 2003). Genes may contribute to individual differences in both temperament and psychopathology. For example, some emerging research suggests that genetic variations associated with the phenotype of a difficult temperament may be the same that predispose an individual to develop a psychiatric disorder (e.g., Pezawas et al., 2005).

Notably, however, we found that early caregiver stability may mitigate some of the ramification of an infant having difficulties in rhythmicity or in being soothed, which is consistent with the buffering effects of a positive environment (e.g., Rothbart and Bates, 1998). Intact families may have available more of the emotional or material resources needed to take care of a "difficult" child. But because parent–infant relationships are influenced by the infant's temperament as well (e.g., Kochanska et al., 2004), future research should examine whether parents from non-intact families experience more deleterious effects of having a difficult baby, and how this may impact offspring's psychopathology.

Interestingly, the effect of temperament on disorder onset was attenuated across time in the sample. This

finding may reflect that our anamnestic assessment focused on the period of infancy and toddlerhood. But, it is also possible that, across development, disorder parameters, such as age of onset, are subject to a variety and varying influences (other than individual characteristics).

We failed to confirm our hypotheses regarding the effects of perinatal problems and motor skill delay on age of onset of depressive and related disorders. Although clinical or population based studies have found that such characteristics distinguish childhood onset from adult onset affective disorders (Guth et al., 1993; Jaffee et al., 2002; Van Os et al., 1997), differences in methodologies and samples may partly account for the inconsistent results. In our sample, early childhood characteristics also were unrelated to the severity of first MDD episode, despite Vocisano et al. (1996) finding a link between obstetric complications and severity of affective illness in adulthood.

Several other findings are of note. First, consistent with a large body of literature on the greater vulnerability of male infants to a variety of problems (e.g., Halpern, 1997), boys in our sample had higher scores on developmental delay than did girls, and their first episode of MDD, DD, or anxiety disorder occurred at a younger age than did girls'. But once an episode of MDD had onset, girls displayed more severe symptoms than boys, consistent with findings reported for adolescents (Reinherz et al., 1999). Thus, in our sample, sex emerged as a main effect and not as a moderator variable as we had predicted. Additionally, diagnostic comorbidity in our patients was associated with reports of more difficult infantile temperaments. Notably, we reconfirmed prior reports (e.g., Kovacs et al., 1989) that, if depressed juveniles have comorbid anxiety disorders, the anxiety disorders will tend to onset earlier than the depressive disorder.

Our finding that older maternal age at the child's birth (compared to maternal age between 19 and 34 years at childbirth) conferred earlier onset of MDD to their offspring, partly confirm those of Reinherz et al. (1993). Reinherz et al. (1993) found that older parental age at childbirth was associated with an increased risk of depression in female adolescent offspring. Maternal age at childbirth, however, was unrelated in our analyses to any of the early risk factors and failed to enter the final predictive models. This finding suggests that older maternal age affects offspring's psychopathology through other variables not examined in this study.

3.1. Limitations

Our study has several limitations. Because the anamnestic data on our patients were obtained retrospectively from their mothers, inaccuracies and biases in recall are of concern. In spite of its drawbacks, however, the retrospective reporting of perinatal and early developmental events has been an important component of various clinically oriented investigations (e.g., Buka et al., 2004; Foley et al., 2001; Lewis and Murray, 1987; Sanderson et al., 1998). Research has shown that the reproducibility and validity of maternal recall of perinatal events can vary from very good to poor (e.g., Foley et al., 2001; Launer et al., 1992; Tomeo et al., 1999) and is affected by the type of data being sought and the method of acquisition (Buka et al., 2004). Our data gathering procedures had been designed with several features in mind, which have been recently recognized as facilitating (although not guaranteeing) the accuracy of retrospective recall (Buka et al., 2004), including face–to-face-interviews by clinically trained assessors, use of "common" rather than medical terms and phrases, and focusing on fairly frequently occurring events. Our finding of an interaction effect between child temperament and family status also argues against an overall bias in maternal recall because the association was evident only for a subgroup of participants. Nevertheless, given our temperament index was retrospective and based on just a subset of dimensions that contribute to early temperament, our findings should be replicated with a more comprehensive measure of temperament, or validated using other means (e.g., observational indices).

A second limitation is that mothers reported on both their children's early development and psychiatric history, introducing shared method (within-reporter) variance. However, this source of bias was reduced by the fact that a child's final psychiatric diagnosis was: a) based both on parental and child report, b) determined on two occasions by different clinical interviewers, and c) subjected to two "best estimate" child psychiatrists independently, who also had access to psychiatric and mental health records. While questions could also be raised about the accuracy of dating the onsets of disorders, two features of our design support our findings. First, our method of obtaining clinical history and onset dates (including the use of "time-lines" with culturally standard and personally meaningful marker events, visual aids, verbal summaries, and cross-links of information) has been shown to be the preferred approach for collecting various types of retrospective data (e.g., Caspi et al., 1996). And, second, our clinically referred sample did not have protracted illness, which is likely to reduce errors in dating; the average time elapsed between the age of onset of MDD and the date of the psychiatric evaluation was 1.14 years

(SD = 1.34 years), and for about 67% of the sample, it was within 1 year. It could be argued that the portion of our youths who were not raised by both biological parents between birth and 4 years of age (9.4%) constitutes a very small segment of the sample. Although high rates of intact families have also been found in other pediatric samples, including those of Najman et al., 2005 (82% intact) and Hirshfeld-Becker et al. (2004) (86% intact), it would be informative to replicate our study with a sample that includes more single-parent or blended families.

3.2. Clinical implications

Our findings highlight that, even in a vulnerable sample, the putative negative effects of early infant characteristics are not immutable, but can be ameliorated by family resources. Further, the impact of some early child characteristics on features of juvenile psychopathology seems to be attenuated by the passage of time. In clinical practice, psychiatrists typically have access only to parents' reports of early child characteristics and are unlikely to have documents of early development. Based on our findings, careful interviewing of parents can yield data that may illuminate some aspects of children's clinical history.

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References

Achenbach, T.M., 1991. Manual for the Child Behavior Checklist 4–18 and 1991 Profile. University of Vermont, Department of Psychiatry, Burlington.

Allen, N.B., Lewinsohn, P.M., Seeley, J.R., 1998. Prenatal and perinatal influences on risk for psychopathology in childhood and adolescence. Dev. Psychopathol. 10, 513–529.

Axelson, D.A., Birmaher, B., 2001. Relation between anxiety and depressive disorders in childhood and adolescence. Depress. Anxiety 14, 67–78.

Buka, S.L., Tsuang, M.T., Lipsitt, L.P., 1993. Pregnancy/delivery complications and psychiatric diagnosis: a prospective study. Arch. Gen. Psychiatry 50, 151–156.

Buka, S.L., Goldstein, J.M., Spartos, E., Tsuang, M.T., 2004. The retrospective measurement of prenatal and perinatal events: accuracy of maternal recall. Schizophr. Res. 71, 417–426.

Caspi, A., Moffitt, T.E., Thornton, A., Freedman, D., Amell, J.W., Harrington, H., Smeijers, J., Silva, P.A., 1996. The life history calendar: a research and clinical assessment method for collecting retrospective event-history data. Int. J. Methods Psychiatr. Res. 6, 101–114.

Cohen, P., Velez, C.N., Brook, J., Smith, J., 1989. Mechanisms of the relation between perinatal problems, early childhood illness, and psychopathology in late childhood and adolescence. Child Dev. 60, 701–709.

Foley, D.L., Thacker II., L.R., Aggen, S.H., Neale, M.C., Kendler, K.S., 2001. Pregnancy and perinatal complications associated with risks for common psychiatric disorders in a population-based sample of female twins. Am. J. Med. Genet., B Neuropsychiatr. Genet. 105, 426–431.

Forbes, E.E., Fox, N.A., Cohn, J.F., Galles, S.F., Kovacs, M., 2006. Children's affect regulation during a disappointment: psychophysiological responses and relation to parent history of depression. Biol. Psychol. 71, 264–277.

Fox, N.A. (Ed.), 1994. The Development of Emotion Regulation: Biological and Behavioral Considerations. Monographs of the Society for Research in Child Development, vol. 59, pp. 2–3. Serial No 240.

Gale, C.R., Martyn, C.N., 2004. Birth weight and later risk of depression in a national birth cohort. Br. J. Psychiatry 184, 28–33.

Goodman, S.H., 2002. Depression and early adverse experiences. In: Gotlieb, I., Hammen, C. (Eds.), Handbook of Depression. Guilford Press, NY, pp. 245–267.

Guth, C., Jones, P., Murray, R., 1993. Familial psychiatric illness and obstetric complications in early-onset affective disorder: a case-control study. Br. J. Psychiatry 163, 492–498.

Halpern, D.F., 1997. Sex differences in intelligence. Am. Psychol. 52, 1091–1102.

Hirshfeld-Becker, D.R., Biederman, J., Faraone, S.V., Robin, J.A., Friedman, D., Rosenthal, J.M., Rosenbaum, J.F., 2004. Pregnancy complications associated with childhood anxiety disorders. Depress. Anxiety 19, 152–162.

Jaffee, S., Caspi, A., Moffitt, T.E., Belsky, J., Silva, P., 2001. Why are children born to teen mothers at risk for adverse outcomes in young adulthood? Results from a 20-year longitudinal study. Dev. Psychopathol. 13, 377–397.

Jaffee, S.R., Moffitt, T.E., Caspi, A., Fombonne, E., Poulton, R., Martin, J., 2002. Differences in early childhood risk factors for juvenile-onset and adult-onset depression. Arch. Gen. Psychiatry 58, 215–222.

Keenan, K., Shaw, D., Delliquadri, E., Giovannelli, J., Walsh, B., 1998. Evidence for the continuity of early problem behaviors: application of a developmental model. J. Abnorm. Child Psychol. 26, 441–452.

Kessler, R.C., Davis, C.G., Kendler, K.S., 1997. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. Psychol. Med. 27, 1101–1119.

Kochanska, G., Friesenborg, A.E., Lange, L.A., Martel, M.M., 2004. Parents' personality and infants' temperament as contributors to their emerging relationship. J. Pers. Soc. Psychol. 86, 744–759.

Kovacs, M., MHS Staff, 2003. Children's Depression Inventory (CDI): Technical Manual Update. Multi-Health Systems, Inc., North Tonawanda, NY.

Kovacs, M., Feinberg, T.L., Crouse-Novak, M.A., Paulauskas, P., Finkelstein, R., 1984a. Depressive disorders in childhood: I. A longitudinal prospective study of characteristics and recovery. Arch. Gen. Psychiatry 41, 229–237.

Kovacs, M., Feinberg, T.L., Crouse-Novak, M.A., Paulauskas, P., Pollock, M., Finkelstein, R., 1984b. Depressive disorders in childhood: II. A longitudinal study of the risk for a subsequent major depression. Arch. Gen. Psychiatry 41, 643–649.

Kovacs, M., Gatsonis, C., Paulauskas, S.L., Richards, C., 1989. Depressive disorder in childhood. IV. A longitudinal study of comorbidity with and risk for anxiety disorders. Arch. Gen. Psychiatry 46, 776–782.

Launer, L.J., Forman, M.R., Hundt, G.L., Sarov, B., Chang, D., Berendes, H.W., Naggan, L., 1992. Maternal recall of infant feeding is accurate. J. Epidemiol. Community Health 46, 203–206.

Lewis, S.W., Murray, R.M., 1987. Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. J. Psychiatr. Res. 21, 413–421.

Liu, X., Gentzler, A.L., Tepper, P., Kiss, E., Kothencné, V., Tamás, Z., Vetró, A., Kovacs, M., 2006. Clinical features of depressed children and adolescents with various forms of suicidality. J. Clin. Psychiatry 67, 1442–1450.

Luby, J.L., Heffelfinger, A., Mrakotsky, C., Brown, K., Hessler, M., Spitznagel, E., 2003. Alterations in stress cortisol reactivity in depressed preschooler relative to psychiatric and no-disorder comparison groups. Arch. Gen. Psychiatry 60, 1248–1255.

Maziade, M., Côté, R., Bernier, H., Boutin, P., Thivierge, J., 1989. Significance of extreme temperament in infancy for clinical status in pre-school years. I: Value of extreme temperament at 4–8 months for predicting diagnosis at 4.7 years. Br. J. Psychiatry 154, 535–543.

Maziade, M., Roy, M.A., Fournier, J.P., Cliché, D., Merette, C., Caron, C., Garneau, Y., Montgrain, N., Shriqui, C., Dion, C., 1992. Reliability of best-estimate diagnosis in genetic linkage studies of major psychoses: results from the Quebec pedigree studies. Am. J. Psychiatry 149, 1674–1686.

Najman, J.M., Hallam, D., Bor, W., O'Callaghan, M., Williams, G.M., Shuttlewood, G., 2005. Predictors of depression in very young children: a prospective study. Soc. Psychiatry Psychiatr. Epidemiol. 40, 367–374.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., Weinberger, D.R., 2005. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat. Neurosci. 8, 828–834.

Preti, A., Cardascia, L., Zen, T., Pellizzari, P., Marchetti, M., Favaretto, G., Miotto, P., 2000. Obstetric complications in patients with depression – a population-based case-control study. J. Affect. Disord. 61, 101–106.

Reinherz, H.Z., Giaconia, R.M., Pakiz, B., Silverman, A.B., Frost, A.K., Lefkowitz, E.S., 1993. Psychosocial risks for major depression in late adolescence: a longitudinal community study. J. Am. Acad. Child Adolesc. Psych. 32, 1155–1163.

Reinherz, H.Z., Giaconia, R.M., Hauf, A.M.C., Wasserman, M.S., Silverman, A.B., 1999. Major depression in the transition to adulthood: risks and impairments. J. Abnorm. Psychology 108, 500–510.

Rothbart, M.K., Bates, J.E., 1998. Temperament, In: Damon, W., Eisenberg, N. (Eds.), Handbook of Child Psychology: Social, Emotional, and Personality Development, 5th ed. Wiley, New York, pp. 105–176.

Sanderson, M., Williams, M.A., White, E., Daling, J.R., Holt, V.L., Malone, K.E., Self, S.G., Moore, D.E., 1998. Validity and reliability of subject and mother reporting of perinatal factors. Am. J. Epidemiol. 147, 136–140.

Sherrill, J.T., Kovacs, M., 2000. Interview Schedule for Children and Adolescents (ISCA). J. Am. Acad. Child Adolesc. Psych. 39, 67–75.

Sigurdsson, E., van Os, J., Fombonne, E., 2002. Are impaired childhood motor skills a risk factor for adolescent anxiety? Result from the 1958 U.K. Birth Cohort and the National Child Development Study. Am. J. Psychiatry 159, 1044–1046.

Thomas, A., Chess, S., 1977. Temperament and Development. Brunner/Mazel, New York.

Tomeo, C.A., Rich-Edwards, J.W., Michels, K.B., Berkey, C.S., Hunter, D.J., Frazier, A.L., Willett, W.C., Buka, S.L., 1999. Reproducibility and validity of maternal recall of pregnancy-related events. Epidemiology 10, 774–777.

van Katwijk, C., Peeters, L.L.H., 1998. Clinical aspects of pregnancy after the age of 35 years: a review of the literature. Hum. Reprod. Updat. 4, 185–194.

van Os, J., Jones, P., Lewis, G., Wadsworth, M., Murray, R., 1997. Developmental precursors of affective illness in a general population birth cohort. Arch. Gen. Psychiatry 54, 625–631.

Vocisano, C., Klein, D.N., Keefe, R.S., Dienst, E.R., Kincaid, M.M., 1996. Demographics, family history, premorbid functioning, developmental characteristics, and course of patients with deteriorated affective disorder. Am. J. Psychiatry 153, 248–255.

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A GYERMEK EGÉSZSÉGES FEJLŐDÉSÉT BEFOLYÁSOLÓ TÉNYEZŐK

A gyermekpszichiátriai betegségek okai

Nagyon ritkán fordul elő, hogy gyermekpszichiátriai (továbbiakban GYIP) betegségben egy ok szerepel előidézőként. A pszichés kórforma nem alkot olyan "betegségegységet", mint pl. a vakbélgyulladás, hanem különböző faktorok együttesen befolyásolják az egyes kórképek kialakulását. Úgy is mondhatjuk, hogy a gyermekpszichiátriai kórképek létrejöttében biológiai, pszichológiai és szociális befolyások egyaránt és egy időben játszanak szerepet.

Genetikai hatások

A **kromoszómák**, és a bennük hordozott **génállomány** szabályozzák a szervezet működését, lassíthatják, vagy felgyorsíthatják a fejlődés ütemét, és meghatározzák azt, hogy a szervezet milyen módon fog reagálni a környezet egyes ingereire.

A gyermek későbbi viselkedése szempontjából fontos, hogy milyen adottságokkal jön a világra, milyen a súlya, bőrszíne, és hogy mindez a családjának mennyiben felel meg. Az egész gyermekkor, serdülőkor és felnőttkor folyamán állandó dinamikus együtthatás van a gének és a környezet között. Új stresszek új genetikai képességeket aktiválhatnak, amiket a szervezetnek előbb még meg is kell tanulni. Példa erre az inkompatibilis vérrel történő ismételt transzfúzió. Sok genetikailag determinált betegség csak a későbbi életkorokban manifesztálódik, és nem tudni, hogy a manifesztáció idejében mennyire van a környezeti stresszeknek szerepe.

Az eddigi vizsgálatok azt mutatták, hogy a gyermek jellemző tulajdonságai közül az **intelligencia** és a **temperamentum** az, ami a legerősebb genetikai befolyás alatt áll. A környezet befolyásoló hatása azonban ezekben az esetekben sem jelentéktelen.

A temperamentum

Már a születést követően megfigyelhető, hogy a csecsemők nem csak szomatikus és fiziológiai paraméterekben, viselkedésben (alvási, étkezési minták) különböznek egymástól, hanem spontán aktivitásuk is eltérő, a különböző ingerekre eltérően reagálnak. Ezek alapján a viselkedés három paramétere különböztethető meg. A **motivációs** része, azaz hogy valaki valamit **miért** tesz, a **tartalmi** része, azaz hogy valaki **mit** csinál, és a **formai** része, azaz, hogy valaki mit **hogyan** tesz. Ez a harmadik komponens az, ami a temperamentum befolyása alatt áll.

Temperamentumon leginkább az egyének közötti stílusbeli, formai különbözőséget értjük.

A temperamentum befolyását a későbbi adaptációra a Thomas és Chess által kifejlesztett kétpólusú /easy - difficult baby/ skálával vizsgálhatjuk. Segítségével megállapítható, hogy a 3-4 éves korban észlelt temperamentumbeli jellemzők hozhatók leginkább párhuzamba a serdülőkori majd fiatal felnőttkori beilleszkedéssel. Ezek és az ehhez hasonló vizsgálatok alátámasztják azt a feltételezést, hogy a temperamentumbeli jellemzők (nehéz természet), ha más tényezőkkel is interakcióba lépnek, elősegíthetik a gyermekeknél pszichiátriai betegségek létrejöttét.

A központi idegrendszer betegségei

A központi idegrendszer gyulladásai, sérülései - bakteriális és vírusfertőzései elsősorban enyhébb súlyosabb mentális retardációt, tanulási nehézségeket, figyelemzavart, és aspecifikus beilleszkedési zavarokat okozhatnak.

A pszicho-neuro-immunológia

Az agy és az immunrendszer közötti kapcsolat vizsgálatai arra utalnak, hogy az emberi viselkedés, a központi idegrendszer és az immunrendszer működése között szoros kapcsolat van.

Számos vizsgálat kimutatta, hogy a korai élet megrázó eseményei - mint pl. az anyától való korai elszakadás - több hypothalamus által regulált folyamatot befolyásol. Megváltozhat a testhőmérséklet, az alvás ritmusa, az autonóm idegrendszer érése. Ebből következett az a feltételezés is, hogy a korai anya gyermek kapcsolat megszakadása az immunfunkciók érésében, működésében is zavarokat okozhat.

Családi körülmények

A család nagysága befolyását a későbbi fejlődésre több kutató vizsgálta. Úgy tűnik, hogy a **sokgyermekes családok**ban a csecsemők gondos ellátása és a gyermekek továbbtanulásra való biztatása ritkább, mint a kisebb családokban. A nagyobb családok gyermekei elmaradást mutatnak a beszédfejlődés területén is, feltehetőleg a szülővel való verbális kommunikáció ritkasága miatt.

A ***testvérsorban elfoglalt hely*** is befolyásolhatja a szülő-gyermek kapcsolatot. A legidősebb gyermek iskolázottsági szintje általában a legmagasabb, de érzelmi zavar is esetükben alakul ki leggyakrabban, feltehetően a második, harmadik gyermek születése után bekövetkező mellőzés miatt. Az első gyermeket a legtöbb családban kiemelten kezelik, vele van a szülőknek a legszorosabb érzelmi kapcsolata, és a legerősebb kontroll alatt él. Így gyakran szorongóvá válik. A többi gyermek esetében a szülők már nem foglalkoznak annyit a neveléssel, kiegyensúlyozottabbak, jobban bíznak a szülői képességeikben, s a gyermek több szabadságot kap.

A szülői bűnözés szerepét a gyermekkori delikvencia kialakulásában minden vizsgálat egyértelműen bizonyította. A bűnöző szülők gyermekeinél már az iskolai beilleszkedéssel is komoly nehézségek vannak.

A ***szülők mentális betegsége*** is kedvezőtlenül hat az utódok pszichés fejlődésére. Minden mentális betegség fokozott rizikót jelent az utódok fejlődésére, de leginkább a személyiségzavar, és a súlyos cirkuláris depresszió vagy érzelmi zavar.

A ***szülői nevelői módszerek*** közül a meleg, korlátozó nevelői attitűd az, amelyben a gyermek függetlensége, önbizalma, szabálytartása, döntésképessége a legkedvezőbben fejlődik. A megértő, de ráhagyó nevelő mellett, ahol gyenge a kontroll, a gyermek otthon több agressziót mutat, és gyakoriak az indulatkitörései is. Ezekben a családokban a szülők türelmük fogytán gyakran inkonzekvens módon erősen büntetővé válnak, s így a gyermek önbizalmát veszti. A hideg, korlátozó nevelő mellett a gyermeknek nem lesz önbizalma, és gyakran visszahúzódóvá válik. Az elhanyagoló szülő gyermeke agresszívvá, alacsony önbizalmúvá fejlődik, akiben megfelelő önkontroll nem alakul ki.

Szociokulturális tényezők

A növekedés előrehaladásával a gyermek kikerül a családi környezetből, s az óvodában és az iskolában idegen felnőttekkel és gyermekekkel találkozik.

A család, az iskola, az óvoda integrálva van abba a kultúrkörnyezetbe, mely az adott társadalomra jellemző. A gyermekre hatnak a társadalom által alkotott szabályok, törvények,

értékrendszerek, a benne húzódó erővonalak, a szociális osztályhoz, vallási felekezethez, vagy etnikumhoz való tartozás. Ismeretei a világról amelyben él, már nemcsak a közvetlen tapasztalatok által bővülnek, hanem a tömegkommunikációs eszközök - a könyvek, a televízió, stb. - segítségével is gyarapodni kezdenek, s mindezek fejlődését nagymértékben befolyásolják.

A GYERMEKKORI DEPRESSZIÓ FEJLŐDÉSI ASPEKTUSAI

A depresszió megjelölést az életben igen gyakran használják mind orvosi-pszichiátriai értelemben, mind más szakmák szakkifejezéseként. Manapság a közgazdaságtan jelentéseiben is igen gyakran találkozunk vele. De még ha pszichiátriai értelemben is használjuk, a depresszió megjelölés mind egy tünet, mind egy tünetcsoport, azaz szindróma, mindpedig egy nozológiailag jól besorolható betegség meghatározására szolgál. A **depressziós tünet** a hangulat jellemzője. A rosszkedv, a szomorúság, a bánat kifejezésére szolgál. Ezek olyan átmeneti állapotok, amiket a legtöbb ember az élet különböző szakaszaiban érezhet. Tehát egyáltalán nem lehet patológiásnak tekinteni. Ha azonban a tünetek, vagy az olyan tünet, mint pl. a boldogtalanság nagyon intenzív, hosszú ideig fennáll, vagy a depressziós szindróma más tüneteivel együtt jelentkezik, akkor klinikailag már szignifikánsnak mondható. A **depressziós szindrómára** a rosszkedv, bánat mellett más tünetek is jellemzőek. Ilyen az alvászavar, az étvágytalanság, boldogtalanság, rossz koncentráció, alacsony önbecsülés, bűntudat, alacsony energetikai szint, pszichomotoros változások és szuicid ideációk. Ha ez a tüneti kép specifikus etiológiával, időtartammal, prognózissal és a kezelésre való hasonló reagálással együttesen fordul elő, akkor már nozológiailag **depresszió betegségnek** mondható.

Hosszú ideig vitatott volt maga az a kérdés is, hogy **létezik-e egyáltalán a gyermekkorban** a felnőttkorihoz hasonló depresszió. Az 1930 - 60- as évek között elsősorban a 1) *pszichoanalízis* hatására ezt erősen kétségbevonták. Úgy vélték, hogy igazi depresszió nem alakulhat ki addig, míg a szuperego teljesen ki nem fejlődött. 1970 - től aztán szélesedni kezdett a gyermekkori depresszió irodalma. Megjelentek a larvált depresszióról, 2) *depresszió ekvivalensekről* származó *klinikai* közlemények. (Márpedig az utánvizsgálatok azt mutatták, hogy ezek a maszkírozott tünetek nem a gyermekkori depresszió megjelenési formái, hanem inkább koegzisztálnak vele. A hasi fájdalomtól a szexuális promiscuitásig a teljes gyermek és felnőttkori pszichopatológiát felsorolták, mint ami a gyermekkori depresszió megnyilvánulási formájának tekinthető. Mindezekkel szemben a 3) D*SM IV és az ICD1O* szerint a depresszió betegség tünetei a csecsemő és a felnőtt korban sem különböznek egymástól.

A *fejlődési pszichopatológia* szerint mindhárom nézet csak feltételezéseken alapul, és nem a gyermek direkt megfigyelésén. A tetejében ezeket a feltételezéseket széles életkori intervallumokra terjesztették ki. A három megközelítés egyike sem végzett reprezentatív mintákon felméréseket, mellyel megállapította volna, hogy a depresszió megjelenésének feltételezett képe milyen gyakori is a különböző életkorokban, és hogy a megfigyelt tüneti kép kielégíti-e akár a szindróma, akár a betegség kritériumait.

A depresszióról a **fejlődési pszichopatológia** nem alkot teóriát, hanem direkt vizsgálatokat végez a gyermekekkel különböző életkorokban. Azt vizsgálja, hogy vajon más-e a különböző életkorokban a tünet ill. a betegség megjelenési formája. Van - e különbség a társuló tünetekben. Ha van, akkor ez az életkor következménye-e. Homogén-e a betegség, és ha igen vannak e alkategóriái. Úgy tűnik, hogy a szimptómás izomorphizmus az egész élet során nem valószínű. A felnőtt séma adolescensek számára kielégítőnek látszik, de minél fiatalabb a gyermek annál kevésbé. Ezért helyes lenne, ha minden életkorban kiválasztanának - a kognitív szintnek megfelelően - a depresszióra jellemző tüneteket (szégyen, reménytelenség,

stb). Ezek a felnőttkori depresszióban nem észlelhetők ugyan rendszeresen, de óvodás vagy iskolás gyermekeknél annál gyakrabban. Így egy többfokozatú diagnosztikai rendszert lehetne létrehozni, ahol az első sorban azok a tünetek szerepelnének, amik minden életkorban jellemzők a depresszióra, majd azok, amik gyermekkorban csak ritkán figyelhetők meg. Ezt követnék azok a tünetek, melyek nagy életkori variációt mutatnak. A diagnózis felállításához a különböző életkorokban különböző számú tünet együttállása lenne szükséges.

A jelenlegi diagnosztikus bizonytalanságot tükrözi az 1994-ben bevezetésre került ICD-10 is, ahol a fejlődési pszichopatológia kutatási eredményeit már igyekeztek figyelembe venni. Az ICD 10 szerint a hangulatzavarok közé (F30-F39) elsősorban a serdülőkorban észlelt tüneti kép osztályozható, bár még ez a rendszer is megemlíti, hogy a depresszió adolescensek esetében igen gyakran jelentkezik atípusos formában. Minél fiatalabb a gyermek, a teljes klinikai szindróma annál ritkább, és egyre gyakoribb a komorbiditás és a kevert tüneti kép. A fejlődési irányzatnak megfelelően a csecsemőkorban korábban anaklitikus depressziónak diagnosztizált kórformát a szeparációs szorongáshoz (F 93.0) kell osztályoznunk, a korai tartós érzelmi deprivációból (szeparáció, szülői agresszív nevelés, stb) eredő kapcsolatteremtési zavarokat az attachment zavaraihoz (F 94.1, F94.2). Az akut stresszre (hospitalizáció, szeretett személy halála, stb) bekövetkező, relatíve rövid ideig (1 évnél rövidebb) tartó depressziós jelenségeket az alkalmazkodási zavarokhoz (F 43.2) kell sorolnunk. Ide kerülnek azok a depressziós kórképek is, amikhez un. regresszív tünetek (enuresis, ujjszopás, stb. F 43.23), vagy agresszív, disszociális magatartászavar társulnak (F43.27). A gyermekkor folyamán gyakran számolhatunk a depresszió kevert tüneti megjelenési formáival is. Ilyen a depresszív viselkedészavar (F 92.O), ahol a magatartászavar és a depresszió egyéb tünetei koegzisztálnak. Hasonló koegzisztencia alapján jött létre a félelem és depresszió kevert zavara (F41.2) elnevezésű kategória. Ezekben az esetekben a depresszió tünetei közül a hangulatzavar a leggyakoribb, de a felnőtt szindróma valamennyi jellemzője előfordulhat, a gyermek kognitív és érzelmi fejlettségétől függően (2. táblázat).

A fenti diagnosztikai bizonytalanságból látható, hogy jelenleg a gyermekkori depresszió esetében sem egységes etiológiáról, sem patomechanizmusról, sem tüneti képről nem beszélhetünk. A diagnosztikus kategóriák felállítása is hol az etiológia alapján (pl. szeparációra bekövetkező reakció), hol a tüneti kép alapján (pl. depresszív viselkedészavar) történik.

Ezért a következőkben megpróbáljuk végigkísérni a leggyakoribb tünet - a depresszív hangulat –(szomorúság, bánat) életkori fejlődését, az esetleges kiváltó tényezőit, majd a depressziót indukáló folyamatokat, a feltételezett patomechanizmust. Végül kapcsolatot keresünk az egyes gyermekkori depressziós tünetek, és a felnőttkori depresszió betegség között.

A depressziós tünetek fejlődése

Az érzelmi fejlődés elméleti kutatói mind megegyeznek abban, hogy az érzelmi kifejezési módok az életkorral változnak. Míg egyesek már a születéskor megfigyelhetők, mások csak a későbbi életkorokban fejlődnek ki. Az életkor előrehaladtával az érzelmi kifejezés igen sokrétűvé válik, mind qualitativ, mint pedig qvantitativ értelemben, és a gyermek a szocializáció folyamán érzelmeinek kifejezésre juttatását megtanulja ellenőrizni is.

Úgy vélik, hogy a bánat alapérzelem, és mindenhol mindenkinél megfigyelhető. A kutatások azt mutatják, hogy a csecsemők nyolc jól megkülönböztethető érzelmet tudnak kifejezni, és a szomorúság is ezek közé tartozik.

A vizsgálatok azt bizonyítják, hogy a bánat az egyik legkorábbi érzelem, amelyet ki tudunk fejezni. Tisztázatlan, hogy vajon az érzelmi diszstressznek ez a korai kifejezése, amelyet a felnőtt megfigyelők szomorúságnak neveztek el, megfelel-e a későbbi fejlődés folyamán

megfigyelhető depressziónak. Hasonlóképp kérdéses, hogy vajon ezen szomorúság hátterében meghúzódó okok a fejlődés egész folyamán változatlanok-e? Vajon a bánat mennyiben tartozik hozzá a természetes érzelmi fejlődéshez? Mennyire, vagy milyen életkorban képesek a gyermekek mások szomorúságát felismerni, vagy saját szomorúságuk kifejezésre juttatását kontrollálni? Mikor képesek a bánat erősségét elkülöníteni önmagukban? Vannak-e olyan faktorok amelyek a fejlődés folyamán a szomorúsághoz társulnak? A következőkben erre szeretnénk röviden választ adni.

A depressziós érzelmek manifesztációja, felismerése és ellenőrzése

A tipegők és kisgyermekek inkább sírnak, ha szomorúak, vagy a kifejezés más non-verbális formáját használják, a nagyobb gyermekek és felnőttek inkább verbalizálják szomorúságukat, és a non-verbális kifejezésnek is számos különféle formáját alkalmazzák (pl.: mosolygás hiánya, szemkontaktus csökkenése).

Egyes kutatók úgy találták, hogy 10 éves korukra a gyermekek (főleg a lányok) arckifejezése csalódáskor mozdulatlanná válik, míg 4-6 éves korukban inkább sírtak. Tehát ahogy növekedtek, valódi érzelmeiket igyekeztek kontrollálni.

Már kis csecsemők is képesek felismerni és megkülönböztetni bizonyos érzelmi kifejezéseket. 10 hetes csecsemők észlelik, ha az anyjuk arckifejezése boldog, és ha szomorú. 1 éves csecsemők 3 alapérzelmet képesek megkülönböztetni: az örömöt, a szomorúságot, és a meglepetést. 3 hónapos csecsemők nyugtalanná válnak, ha az anyjuk arckifejezése szomorúságot mutat.

Ahogy a gyermeknél kezd a beszéd kialakulni, egyre fokozódik az a képessége, hogy az érzelmeket egymástól meg tudja különböztetni. Leghamarabb az öröm és a szomorúság megnevezését tanulják meg a gyermekek, és 4 éves korukban érzelmeik kifejezésére használni szokták az örülök, szomorú vagyok, mérges vagyok kifejezéseket. Az érzelmi viselkedés neveit, mint a sírás, nevetés még korábbi életkorban használják. Ahogy a gyermekek növekednek, képesek lesznek nemcsak felismerni más szomorúságát, de empátiás módon válaszolni is kezdenek rá. A vizsgálatok azt mutatják, hogy 2 éves gyermekek, ha látják, hogy a szülő szomorú, vigasztalni igyekeznek.

Összefoglalva elmondhatjuk, hogy a különböző fejlődési állapotokban a gyermekek szomorúságukat különbozőképp fejezik ki, és hogy a későbbi életkorokban igyekeznek kontrollálni szomorúságuk kifejezését. Épp így változik az életkorral az is, hogy fel tudják ismerni mások szomorúságát és hogy igyekeznek a másikat megvigasztalni.

A depresszió előfordulási gyakorisága

Epidemiológiai tanulmányok azt mutatták, hogy a depresszió gyakorisága az életkor növekedésével változik. A különbség attól is függ, hogy vajon a tünetet, vagy a betegséget vizsgáljuk-e, és hogy a depresszió megjelölésére milyen mutatókat használunk. Fiatal gyemekkorban ugyanis a teljes depressziós szindrómát csak ritkán találhatjuk. Ennek ellenére viszont már 6 hónapos csecsemőnél is megfigyelhető a szomorúság átmeneti kifejezése.

Ha a szomorúság kritériumául az állandó rossz érzést használjuk, akkor azt találjuk, hogy a 10-14 évesek 13 %-ban depressziós hangulatról számolnak be, 17 %-nál hiányzik a mosoly, és 9 %-uk depressziósnak tűnik. Ha ugyanezeket a gyermekeket azután 14-15 éves korukban újra vizsgálták, azt állapíthatták meg, hogy az adolescensek több mint 40 %-a panaszkodik depressziós érzésekről, és 7-8 %-uk öngyilkosságra is gondolt már. A szülők és a tanárok, a serdülők depressziójának szintjét már kevésbé tudták megbecsülni.

A depressziós tünet kiváltó tényezői

Negatív életesemények

Elég nehéz egy olyan életeseményt találni, amely csakis és kizárólagosan szomorúságot okoz. Még a szeparáció is, amelyet a szomorúság elsődleges okának említenek, kezdetben szorongást vált ki az újszülöttből. Ehhez hasonlóan az életesemények egész sora (gyász, életet fenyegető betegség, stb.) elsősorban erős szorongást okoz, és csak amellett szomorúságot.

Interperszonális veszteség és szeparáció

A szomorúságot előidéző szituáció prototípusa a szeretett személytől való szeparáció, vagy annak elvesztése. Az interperszonális veszteség, a kapcsolatok megszakadása, vagy a csalódás, éppúgy mint a szeretett személy betegsége, a felnőttkori depresszió kialakulásával a legszorosabb összefüggésben van. Talán kevésbé ismert ezeknek az életeseményeknek a gyermekkori depresszióval való kapcsolata (3. táblázat).

A szeretett személy elvesztése után kialakuló depresszió mind csecsemőknél, mind tipegőknél, mind pedig a főemlősök utódainál megfigyelhető. A gondozótól való szeparáció az érzelmi reakciók egész sorát váltja ki, kezdve a kezdeti tiltakozástól a csalódottságon át a szociális kapcsolatok későbbi zavaráig.

A veszteség és szeparáció mellett számos más olyan interperszonális helyzet van, amely szomorúságot válthat ki. Ehhez tartozik az, hogyha a szeretett személy az illetőt elutasítja, ha fontos személy az illetőt nem veszi figyelembe, nem értékeli, vagy egyik fontos kapcsolatában súlyos konfliktusok vannak. Igen fontos, hogy mind egy szoros pozitív kapcsolat hiánya, mind pedig annak elvesztése egyaránt depresszióhoz, szomorúsághoz vezethet.

Fizikális betegségek

A balesetből, betegségből eredő károsodások szintén gyakran vezethetnek szomorúsághoz. Főleg azok a betegségek tartoznak ide, amik kifejezett változásokat idéznek elpő a testi képességekben, a megjelenésben vagy az intellektuális teljesítményben.

Önértékelés csökkenése

Mind az önbizalom hiánya mind elvesztése egyformán igen fontos tényező lehet.

Elmondhatjuk, hogy bár az életesemények számtalan kategóriája okoz bánatot, ezen események egyike sem okoz szükségszerűen, vagy miden személynél minden időben. Lehetnek olyan események is, amelyeket nem említettünk, de bizonyos embereknél mégis depressziós hangulatot hívhatnak elő. Elmondhatjuk, hogy a szomorúság erőssége és tartama nagy individuális variabilitást mutat, amely az egyénben és a környezetben rejlő tényezőknek egyaránt függvénye.

Családi hatások

Depressziós anyákat vizsgálva azt állapították meg, hogy gyermekeik 25 %-ánál 5 vagy több depressziós tünet figyelhető meg, szemben avval a kontroll csoporttal, ahol egy sem volt. Az utódok 7%-a kimerítette a DSM III Major depresszió kritériumait, míg a kontroll csoportban senki. Általában elmondható, hogy a depressziós szülő emelkedett rizikót jelent az utódok hangulatzavara, és depressziója szempontjából is. A vizsgált gyermekek állapota szorosabb összefüggést mutatott a szülő depressziójának aktuális állapotával, s kevésbé a betegségtörténetével. A nem krónikus, de kezeletlen betegek gyermekei több pszichiátriai zavart mutattak, mint a krónikus beteg, de kezelt szülőké.

Depressziós szülők esetén a családban halmozódnak a negatív életesemények. Csökken az anya és gyermeke között a biztonságos attachment kialakulásának lehetősége. A családban

kicsi a kohézió, szervezetlenség uralkodik, és több a konfliktus, mint az egészséges családokban.

A **depressziós gyermekek** családját vizsgálva megállapították, hogy a szülők gyakran elutasítók, sokat és agresszív módon büntetnek. Ezek a gyermekek anyjukkal szemben kevesebb pozitív érzelmet mutattak, s ritkábban kommunikáltak vele. Az anyák a gyermekek elé magasabb követelményeket állítanak, az apák pedig csak a kiemelkedő teljesítményeket jutalmazzák. Ezekre a családokra jellemző, hogy az autonómiát nagymértékben elnyomják, és ehelyett abszolút kontroll és dominancia uralkodik bennük.

Az életeseményre való reakció változása a gyermek fejlődésével

Megfigyelték, hogy ugyanarra az eseményre a gyermekek az életkoruk változásával párhuzamosan másként reagálnak. A szeparációra bekövetkező klasszikus választ (tiltakozás-elkeseredettség-szociális kapcsolat zavara) a gyermekek leginkább 1/2 és 4 éves koruk között mutatják. 6 hónapos kor előtt ez a reakció nem jelentkezik, mivel a gyermeknél a szelektív attachment még nem alakult ki. 4 éves kor után már szintén kevésbé viseli meg a gyermeket a szeparáció, mivel már képes megérteni, hogy időleges is lehet, tehát nem érzi magát örökre elhagyatottnak.

A szeretett személy halálát követő **gyászreakció** is változik az életkorral. Meglepő, hogy fiatal gyermekek gyakran úgy tűnik, észre sem veszik a szeretett személy elvesztését. Ez abból adódik, hogy nem képesek felfogni sem a veszteség irreverzibilitását, sem annak következményeit. Azonban ahogy az idő múlik, a gyermek egyre inkább rádöbbenhet a halál visszafordíthatatlanságára és elhúzódó szomorúsággal reagálhat, amelyhez más érzelmi és viselkedésbeli tünetek is társulhatnak. Ez az elhúzódó gyászreakció azonban sokkal inkább a haláleset következményeire adott válasza a gyermeknek, semmint magára a halálra.

Szintén megfigyelhető, hogy a gyermekek másként reagálnak a **szülők válására** nemüktől, temperamentumuktól és fejlődési szintjüktől függően. A vizsgálatok azt mutatták, hogy a fiatalabb gyermekek a válási procedúrát nehezen tolerálják, mivel szociális és kognitív képességeik még fejletlenek, és így nehezebben birkóznak meg azokkal a stressz-szituációkkal amelyek a válást kísérik. Természetes tehát, hogy a reakciók az életkorral különböznek. Bár a szomorúság is része ezeknek a reakcióknak, de más érzelmek is (szorongás, bűntudat, harag) jelen vannak.

A gyermekek reakciói a **testi betegségekre** szintén változnak az életkorral. Serdülőkorú égési sérültek sokkal nehezebben tudtak megbirkózni testi hibájukkal, mint náluk fiatalabbak.

A kívánságok és a lehetőségek közötti diszkrepancia 18-24 éves korban válik érezhetővé a gyermek számára, és a hiány-állapotok ekkor jelentenek először stressz-szituációt.

Összefoglalva elmondhatjuk, hogy számos olyan negatív életesemény van, amely nagy valószínűséggel társul, társulhat depressziós tünettel, vagy magával a depresszió szindrómával. Bizonyos faktorok, mint az életkor, a kognitív érettség, a szociális támogatás, a személyiség befolyásolhatják a szomorúság intenzitását, vagy tartamát, illetve a vele való megbirkózást. A következő fejezetben néhány olyan lehetséges mechanizmust fogunk tárgyalni, amelyek által a negatív életesemények depressziót okozhatnak.

Depressziót indukáló folyamatok

Számos olyan teória van, amely depressziót indukáló folyamatokat tárgyal, ezek közül azonban csak néhányra térünk ki.

A **behaviorista (un. kísérletező) modell** szerint a negatív életesemény *aktuális átélése*, vagy a pozitív megerősítés hiánya, ill. alacsony szintje depressziós érzéseket válthat ki, de a

depresszió valamennyi tünetét is létrehozhatja. Selingman (1974) un. *tanult tehetetlenség* elmélete szerint a személy nem veszi észre, hogy saját viselkedésével a kellemetlen környezeti eseményeket enyhíteni tudja.

Ezzel szemben mind a **kognitív perspektíva** (Beck 1967) mind a **pszichoanalítikus nézőpont** úgy véli, hogy a depressziót mind a valódi, mind pedig az elképzelt negatív életesemények létrehozhatják. A kognitív folyamat a korábban megtörtént rossz eseményeket felidézheti, észlelheti a jelenlegi kedvezőtlen helyzetet, vagy mérlegelheti egy jelen helyzet rossz következményeit. Ezúton szomorúságot eredményezhet. Ezek az elméletek szerint egyáltalán nem szükséges, hogy aktuálisan átéljük a negatív életeseményt. A kognitív átélés, a kognitív folyamat önmagában is elegendő a depressziós hangulat kiváltásához. Sőt egyes kognitív teoretikusok egyenesen úgy vélik, hogy a negatív életesemények önmagukban egyáltalán nem elégségesek ahhoz, hogy szomorúságot hozzanak létre. Sokkal fontosabbak azok a kognitív tartalmak, amelyek egy-egy eseményhez kapcsolódnak, azaz az egyes események kognitív értékelése. A kialakult kognitív triád (a negatív önértékelés, az élmények negatív interpretációja és a negatív jövőkép) azután reménytelenséghez, tehetetlenséghez és így depresszióhoz vezet.

A rossz hangulat létrejöhet **helyettesítő** módon is. Ez történhet direkt megfigyelés, elképzelés, vagy a médiák által való közvetítés (újság, könyv, film) útján. A helyettesítő folyamat, amely a szomorúságot létrehozza az *empátia*, vagy beleélés. Egyes szerzők az empátiát a megfigyelő helyettesítő aorusaljának tartják, amely "nem a személy saját helyzetére bekövetkező reakció, hanem egy más személy helyzetére bekövetkező helyettesítő válasz". Az empátia lényege, hogy a személy egy másik személy helyébe képzeli magát. Úgy vélik, hogy az empátia a fejlődés folyamán változásokon megy át, és csak akkor alakul ki, amikor a gyermek számára lehetővé válik, hogy saját személyét másoktól képes legyen elkülöníteni. Ezért a reflexes érzelmi rezonancia bizonyos formái, mint például az empátiás sírás, sosem figyelhető meg csecsemő-korban.

A empátiás beleélés különösen könnyű olyan esetekben, ha a másik személy helyzete életszerűen ábrázolt (jól megrendezett film, vagy részletező regény), ha a megfigyelő helyzete hasonlít a megfigyeltéhez, ha hasonló jellemvonásai vannak a megfigyelt személynek, azaz a megfigyelő számára könnyű saját magát a másik helyébe beleképzelni. A kísérletes vizsgálatok mind gyermekekkel, mind felnőttekkel azt mutatták, hogy ha a megfigyelő úgy érzi, hogy a helyzet olyan "mintha" Ő volna ugyanabban a helyzetben, mint az ábrázolt személy, az sokkal könnyebben vezetett empátiás aorusalhoz, mint amikor az illető a másikat egy bizonyos távolságból volt képes szemlélni (3. táblázat).

Megállapíthatjuk, hogy mindegyik leírt folyamat képes arra, hogy jelentős mértékű rosszkedvet okozzon. Mi lehet az a lehetséges mehanizmus aminek a révén ezek a különböző folyamatok hatnak? Lehetséges-e hogy ugyanaz a mechanizmus útján hat mind a három. Például lehet, hogy mind a behavior, mind a helyettesítő módszer kogníciókat mozgósít, vagy mind a három folyamat azonos biológiai mechanizmusokat indít el, amelyek azután a rossz hangulatot eredményezik? Meg lehet-e magyarázni a kognitív, vagy biológiai mechanizmusokkal azokat a különbségeket, amelyeket az egyes személyek válaszaiban találtak?

A depresszív érzelmek hátterében meghúzódó mechanizmusok

Számos szerző vizsgálta általában az érzelmek és a bánat hátterében meghúzódó mechanizmusokat. A jelen fejezetben három teóriát tárgyalunk részletesebben. Hozzá kell fűznünk, hogy a depresszió kialakulását önmagában egyik sem tudja megmagyarázni, feltehetően együttesen működnek közre annak létrehozásában (4. táblázat).

Evolúciós elméletek

Már Darwin (1872) megfigyelte, hogy a különböző kultúrákhoz és nemzetekhez tartozó emberek arckifejezése, ha sírnak, akkor hasonló, és ezért úgy vélte, hogy létezik egy veleszületett univerzális alap-érzelmi kifejezés. Az is feltételezhető, hogy más személyek érzelmet tükröző arckifejezését a csecsemő képes felismerni, és erre reagálni, és ezért ez a képesség is veleszületett.

Új Guineában végzett vizsgálatok Darvin megfigyeléseit alátámasztották. Kimutatták, hogy az ott élő gyermekek, akik soha nem kerültek kapcsolatba a nyugati kultúrával, fényképekről a nyugati ember arckifejezését helyesen tudták megítélni. Az esetek 79 %- ában fel tudták ismerni a szomorúságot. Hasonlóképpen jó teljesítményt nyújtottak a boldogság, a düh, az elégedetlenség felismerése alkalmával is. Valamivel kevésbé voltak képesek elkülöníteni a meglepetést és a szorongást. Ezek az eredmények azt mutatják, hogy legalábbis bizonyos arckifejezésekben van bizonyos fokú univerzalitás.

A kutatók azt találták, hogy már nagyon fiatal csecsemők is képesek differenciált arckifejezésekre. Bár bizonyos arckifejezések univerzálisnak mondhatók, attól az még nem jelenti feltétlenül azt, hogy veleszületettek. Imitációs tanulás révén az újszülöttek képesek már néhány napos, vagy hetes korban arckifejezéseket utánozni.

A szomorúság mint adaptív válasz

Az evolúciós elméletek azt feltételezik, hogy az érzelmeknek adaptív szerepük van. Úgy vélik, hogy a diszstressznek kommunikatív motiváló és összetartó funkciója van. A diszstressz kifejezése azt közli másokkal, hogy valaki rosszul érzi magát, és segítséget igényel. A diszstressz arckifejezések - főként gyermeknél - másokban tipikusan *szimpátiát és empátiát* váltanak ki. Azon fiatal bűnelkövetők bírói ítélete pl., akik szomorúságot és megbánást mutattak a tárgyaláson, lényegesebb enyhébb volt, mint azoké, akik dühösnek, vagy boldognak mutatkoztak, jóllehet ugyanazt a bűntényt követték el.

Másrészről a szomorúság, a bánat érzése az egyént arra motiválja, hogy olyan viselkedéseket mozgósítson, amellyel *le tudja győzni* a stressz-helyzetet. A bánat idején az egyénnek lehetősége van, hogy átdolgozza a bonyolult helyzeteket, és meg tudja oldani őket. Megbirkózhat magával a stresszet indukáló helyzettel, vagy annak következményeivel, máshogy értékelheti a helyzetet, vagy szociális támogatást kereshet.

Harmadrészt a diszstressz erősítheti a család, a szűkebb közösség, vagy a fajta összetartását. Egyes kutatók szerint a "gyász biológiai reakció, amelynek a fejlődés folyamán az a szerepe, hogy a fajtán belül biztosítsa a *csoport összetartást*, amely a túlélés szempontjából igen fontos". Azt is feltételezik, hogy a csoportkohéziót az tartja fenn, hogy a csoporttól való szeparáció mind pszichológiai, mind fiziológiai értelemben egyaránt rendkívül stresszt okozó élmény. Ezért a szeparációnak, akár az élménye, akár az elképzelése olyan stresszt jelent, amely arra késztet mindenkit, hogy szorosan a szeretett személy mellett maradjon, és így a fajta túlélése a csoport összetartása miatt örökre, vagy folyamatosan biztosítva van.

A szomorúság mint maladaptatív válasz

Bár a szomorúságnak mint említettük számos adaptív funkciója is van, megfigyelhetők maladaptatív következményei is. A bánat ideje alatt *csökkenhet a kognitív teljesítmény*, és a tanulás. Embergyűlölet alakulhat ki, csökken az ellenállás a csábításokkal szemben. Jobban emlékezünk a szomorúságot okozó eseményekre, amely elhúzódóvá teheti az állapotot, szemben azokkal a korábbi megállapításokkal, hogy a szomorúság segíthet a negatív életesemény legyőzésében. A depressziós gyermekek inkább visszahúzódóak, és problémáikon kevésbé aktívan dolgoznak, mint azok akik nem depressziósak.

Összefoglalva tehát azt mondhatjuk, hogy bár a szomorúság és a gyász lehet, hogy a faj-fejlődés szempontjából adaptív, de az már kevésbé tisztázott, hogy az egyén szempontjából mennyire mondható adaptívnak.

Biológiai elméletek

A vizsgálatok azt mutatták, hogy az érzelmek fontos forrása a **thalamus**. Az érzelmek átélése a thalamusból a kortexbe futó idegpályák épségének a függvénye, s így az érzelmek kifejezése a thalamusból a motoros központba küldött idegi impulzusok függvénye.

Kutatások bebizonyították, hogy az érzelmek kifejlődésében mind a thalamusnak, mind a **hypothalamusnak** egyaránt szerepe van, s további kutatások azt bizonyították, hogy az érzelmeket, és az érzelmek kialakulását nem lehet az agy egy-egy pontjára fókuszálni, sokkal inkább szó van itt az agykéreg különböző területén lévő struktúrák rendszeréről.

A **limbikus rendszer** szervezi az érzelmek megélését. A hypothalamus a perifériát a kéreggel köti össze. A teljes limbikus rendszer részt vesz az érzelmek létrehozásában, de nincs olyan specifikus mechanizmus, amely az egyes érzelmek kialakulásáért felelős lenne.

Az érzelmek az idegsejtek aktivációja útján váltódnak ki, és az érzelmek minőségét ennek az aktivációnak az iránya és erőssége fogja megszabni. Például akkor alakul ki félelem, ha a neurális aktiváció pozitív és igen erős. Közeledés pedig akkor alakul ki, ha az ingerlés pozitív, de gyenge.

A legtöbb kutatás, amely az érzelmek által kiváltott pszichofiziológiával foglalkozik, általában vizsgálta az érzelmeket. Bár egyre több az olyan közlemény, amely a gyermekkori depresszió kutatására koncentrál (hypothalamicus, hypophysis, adrenális tengely diszfunkciója, dexamethazon supressiós teszt, növekedési hormon vizsgálat, alvási EEG), ezek a tanulmányok inkább a depresszió szindrómára és a betegségre fókuszálnak, nem a bánatra, mint a depresszió egy tünetére. Ezért ezeket a depresszió betegségnél elemezzük bővebben. Kevéssé ismert a bánat pszichofizológiája gyermeken, és ez a jövő kutatásának egyik fontos területe lehet. Másik fontos kérdés, hogy vajon a depresszió szindróma és betegség különféle biológiai tünetei megfigyelhetők-e, ha valaki szomorú, vagy bánatos, vagy csak a teljes depressziós szindróma esetén észlelhetők.

Kognitív szociális tanulás elmélete

Míg a biológiai és a fejlődési perspektívák az érzelmek állandó és univerzális vonatkozásait vizsgálják, addig a szociális tanulás elmélete az érzelmek átélésének és kifejezésének egyéni aspektusaira koncentrál. Bár a szocializáció elmélete elismeri az organikus tényezők fontosságát, hasonlóan lényegesnek tartja a tanulás szerepét az érzelmek fejlődésében. Hogyan magyarázza meg a szocializáció az emóciók individuális különbségét? Az érzelmek milyen aspektusa alakul ki a szocializáció folyamán, melyik az a folyamat, ahol a szocializáció hat? A következő részben ezzel fogunk foglalkozni. Itt próbáljuk megvilágítani azokat a kognitív és szocializációs folyamatokat, amelyek a bánat kifejlődésében szerepet játszhatnak.

Az érzelmek szocializációja

Az érzelmek vizsgálatára irányuló irodalom azt mutatja, hogy a gyermekek a fejlődés folyamán megtanulják hogyan, mikor és mivel kontrollálják érzelmeik kifejezésre juttatását, és így érzelmeik külső megnyilvánulása különbözni fog a belső érzelmi állapotuktól. "Ahogy a gyermek egyre idősebb lesz, kortársai és a szülők gátolják abban, hogy valódi érzelmei az arcán kifejezésre jussanak".

A szocializáció folyamán, különösen az erős érzéseket igyekszik a környezet befolyásolni, bár a laboratóriumi vizsgálatok a kevésbé intenzív érzelmek, mint például a csalódottság

vizsgálatára korlátozódnak. A szocializáció folyamán a fiúknál igyekszik a környezet a bánat kifejezését elnyomni, míg lányoknál a dühét. A düh kifejezése helyett a környezet lányok esetében a bánat kifejezésre juttatását erősítette. Tehát úgy tűnik, hogy a szocializáció nyomására főleg fiúknál a szomorúság kifejezése, kifejezésre juttatása különösen gyakran sérül.

Az irodalom alapján általánosságban elmondhatjuk, hogy a gyermekek a tulajdonságokról, hiedelmekről, erkölcsről, értékekről tanulási folyamat kapcsán nyernek információkat, és hogy ezek bevéződése a direkt instrukció, a modellezés és a kívánatos viselkedés megerősítése révén történik. Azt is elmondhatjuk, hogy bizonyos specifikus szocializációs körülmények negatív kognitív sémákhoz vezethetnek, amelyek aztán szomorúság kifejlődését eredményezheti. Ebből következik, hogy a gyermek-szülő interakció negatív képet alakíthat ki a gyermekben önmagáról, a világról és a jövőről egyaránt.

A kognitív teóriákat az a kritika érte, hogy bizonyos érzelmeket már akkor is megfigyeltek a csecsemőknél, mielőtt azok bármiféle kogníciót is társíthattak volna a bánattal. Ezért úgy vélik, hogy a szomorúság az egyike az alapérzelmeknek, és már nagyon korai csecsemőkorban is megfigyelhető mások azonban azonban úgy vélik, hogy a szomorúság, bánat, csak akkor jelentkezik a gyermek értelmi fejlődésében, amikor a gyermek az anyát, az anya személyét képes önmagától eldifferenciálni (6-9 hónapos életkor). Ezek szerint vagy kell egy bizonyos fokú kognitív érettség a szomorúság érzéséhez, vagy a korai formája a diszstressznek, amelyet szomorúságnak neveznek, az nem ugyanaz a szomorúság, mint ami később észlelhető. Az lehetséges, hogy a csecsemő arckifejezése úgy tűnik, hogy szomorú, de ez még nem jelenti feltétlenül azt, hogy a csecsemő szomorúságot is él át. Az a tény, hogy a szomorúság kifejezése már csecsemőnél is megfigyelhető, már akkor, mielőtt szomorúsághoz társuló kogníciói kifejlődhettek volna (a jövő felé irányuló elvárások, az énről alkotott vélemény), nem jelenti azt, hogy ezek a kogníciók nem játszanak-e nagyon fontos szerepet a szomorúság kifejezése és megélése szempontjából a fejlődés későbbi idején. Sokan úgy vélik, hogy a diszstressz ”non-kognitív" kifejezése lehetséges csecsemőknél. Ez a precursora, vagy prototípusa a szomorúság későbbi lényegesen érettebb formájának.

Összefoglalva megállapíthatjuk, hogy a kogníciók igen fontos szerepet játszanak abban, hogy a szomorúság mikor, és hogyan fejeződik ki, és társulását is szabályozzák bizonyos életeseményekkel. Abban, hogy milyen kogníciók fognak egy gyermekben kialakulni, igen fontos szerepe van a gyermek környezetében élő személyeknek (szülőknek, tanároknak, kortársaknak).

Az érzelmek tanulása

Alapvetően az érzelmeket éppúgy tanuljuk, mint bármilyen más viselkedést, beleértve a direkt (klasszikus kondicionálás, instrumentális tanulás, didaktikus tanulás) és indirekt módszereket (obszervációs tanulás, imitáció és média útján). Watson (1919) klasszikus kísérletében bemutatta, hogy egy kicsi gyermeknél korábban neutrális stimulus hogyan okozhat félelmet. Csak kevés vizsgálat van azonban arra, hogy klasszikus kondicionálással bánat létrehozható-e. Wolpe (1971) jutott legközelebb a vizsgálatokhoz, amikor kimutatta, hogy a depresszió klasszikusan társul súlyos félelmi állapotokkal.

Az instrumentális kondicionálás tehát szerepet játszik az érzelmek és azok kifejezésének a szocializációjába. A gondozóknak számos lehetőségük van arra, hogy instrumentális kondicionálás segítségével befolyásolják a csecsemők érzelmeit. A fiú és lány kisdedek érzelmi kifejezésében mutatkozó különbségek a környezeti megerősítés különbözőségére vezethetők vissza. Jóllehet az anyák mindkétnemű gyermeküknek bemutatják és megerősítik a

legkülönfélébb pozitív érzelmeket, lány gyermekeiknek az érzelmi kifejezés nagyobb skáláját mutatják be.

Kiemelt személyek (szülők, tanárok) tanítása, szintén direkt hatással van az érzelmek szocializálására. A szülő például ilyen szabályt állíthat a gyermek elé: "Egy nagy fiú nem sír!", "Ha így nézel rám, tudom, hogy mérges vagy!", "Ha valami bajod van, megkönnyebbülsz, ha beszélsz róla!". Így direkt instrukciók segítségével a gyermekek meg tudják tanulni az érzelmi kifejezés szabályait, az érzelmek elnevezését, és az érzelmek szabályozását.

A szociális tanulás sokkal indirektebb módja mások megfigyelése. A gyermekek ilyen módon megtanulhatják, hogy mik azok, amik bizonyos érzelmeket kiváltanak, hogyan kell kifejezni és szabályozni az érzelmeket, és az egyes érzelmi kifejezéseknek mik a következményei.

Tudják-e a csecsemők utánozni anyjuk szomorú arckifejezését? A vizsgálatok azt mutatják, hogy jóllehet a csecsemők nem képesek ugyanarra a szomorú arckifejezésre, mint depressziós anyjuk, mégis tisztán felismerhető negatív reakciójuk, ha anyjuk arca szomorú. Azok a tanulmányok, amelyek depressziós anyák csecsemőit vizsgálták szintén arra utaltak, hogy azok gyermekei visszahúzódóbbak, kevésbé tartanak szemkontaktust, kevesebbet játszanak, gyakrabban tiltakoznak és ritkábban mutatnak pozitív érzelmeket. Depressziós anyák csecsemői a korábbihoz hasonlóan reagáltak akkor is, ha anyjuk azt az instrukciót kapta, hogy "nézzen depressziósan", míg a nem depressziós anyák utódai a dezorganizáció és diszstressz ugyanolyan tüneteit mutatták, ha anyjuk depressziót szimulált, mint a klinikailag depressziós anyák csecsemői.

A "kölcsönös regulációs modell" magyarázza a csecsemőknek anyjuk depressziójára kialakult zavart reakcióját. A modell szerint a depressziós anya a csecsemő érzelmi regulációs jeleire nem képes válaszolni, ami rosszul koordinált interakciókat eredményez, és a csecsemőkben további diszstresszt hoz létre. Jóllehet a csecsemő kezdetben állandóan megpróbál anyjától segítséget kérni, hamarosan viselkedése önszabályozóvá válik (tekintet elfordítás) acélból, hogy negatív interakciókat alakíthasson ki. A depressziós anyák csecsemőjének érzelmi zavara tehát nem az anya direkt utánzásának az eredménye, nem az anya táplálja bele valamilyen úton-módon a gyermekébe saját érzelmét. "Ez sokkal inkább a csecsemő normális reguláló képességének az eredménye, amely fokozatosan fejlődik ki, mivel az anya arckifejezése nem képes ellátni normális külső reguláló szerepét."

Vajon idősebb korban képes lesz-e arra a gyermek, hogy utánzás révén megtanulja a szomorúságot a depressziós felnőttől? Bár egyre több arra vonatkozó irodalom van, hogy a depressziós szülők utódai sokkal gyakrabban depressziósak, mint a nem depressziósaké, kevéssé ismert az a folyamat, ahogy ez a depresszió létrejön. Számos mehanizmust feltételeztek, amely révén ez a folyamat hathat (szülői érzés hiánya, a depresszív tünetek modellálása, stressz-szituáció megosztása a szülővel, a gyermek elhanyagolása, bántalmazása, érzelmi hidegség).

Összefoglalva elmondhatjuk, hogy az érzelem számos aspektusa, beleértve kifejezését, megjelölését, szabályozását, kiváltóit a szocializáció folyamán tanulható. A szociális tanulási folyat mind direkt kondicionálás, mind indirekt megfigyelés útján létrejöhet. Van néhány kísérleti bizonyíték arra, hogy a depresszió létrejöttéért is ilyen szocializációs élmények tehetők felelőssé.

A csecsemő- gyermek- és serdülőkori depresszió kapcsolata

Sokan keresik a választ arra, hogy a szomorúság korai kifejezése, manifesztációja, a csecsemőkorban megfigyelt depresszió, és a későbbi gyermekkorban, vagy felnőttkorban megfigyelt depresszió között van-e folyamatos átmenet?

Prospektív tanulmányok szerint- praepubertásban lévő gyermekeket vizsgálva, akik a DSM III szerint a major depresszió, dysthymiás zavar, alkalmazkodási zavar depresszióval és az egyéb pszichiátriai zavar depresszió nélkül kategóriákba voltak sorolhatók, - megállapítható, hogy az alkalmazkodási zavar depresszióval relatíve gyorsan remisszióba kerül, és csak ritkán tér vissza. A nem depressziós pszichiátriai betegek esetében is utánkövetés során csak ritkán fejlődik ki depresszió. A major depresszió gyorsabban javul, mint a dysthymiás forma, de mindkettő relatíve hosszú lefolyású volt, és hajlamos a kiújulásra. További utánkövetés lenne szükséges ahhoz, hogy a felnőttkori kimenetelről nyilatkozni lehessen.

Összefoglalva azt mondhatjuk, hogy úgy tűnik, van kapcsolat a gyermekek és a felnőttek depressziója között. A serdülőkori depresszió és a felnőttkori depresszió viszonylatában még bizonyos tüneti hasonlóságról is beszélhetünk.

„A gyermekkori depresszió rizikótényezői" kutatás megtervezése, megvalósítása, lefolyása

13 év története: Pályázat-előkészítés, -írás és a kutatásszervezés tapasztalatai egy amerikai NIMH kutatási támogatás kapcsán

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Összefoglalás: A szerzők a közleményben összefoglalják a kutatásszervezés területén szerzett 13 évnyi tapasztalatukat. Először azokat az elővizsgálatokat ismertetik, melyek egy nagy összegű külföldi pályázat elnyeréséhez szükségesek. Azután részletezik, hogy milyen hatalmas adminisztratív apparátust igényel – a jól képzett szakemberek mellett – egy ilyen több helyen folyó kutatás felépítése, megszervezése, az adatok kezelése, azok állandó ellenőrzése és feldolgozása, értékelése. Végül ismertetik, hogy milyen tudományos eredmények vannak születőben a több mint egy évtizedes kutatómunka után.
Kulcsszavak: gyermekkori depresszió; kutatás leírása; szervezeti felépítés; közlemények

Summary: The authors summarize their experiences in research organization accumulated during 13 years. At first they outline preliminary studies which are prerequisites of high prestige international grants. Then they describe the huge administrative apparatus dedicated – besides skilled professionals – for the construction and organization of the research, the management, continuous checking and evaluation of data in such a multisite study. Finally, they report on the scientific results obtained after 13 years of hard work.
Key words: childhood onset depression; research design; organizational construction; publications

Húsz éve, hogy első alkalommal kapcsolatba léptem *Kovács Máriával*. Olvastam a nemzetközi kutatásokban igen gyakran alkalmazott „Gyermekkori depresszió" kérdőívéről (továbbiakban GYD), és kértem, küldje el, és engedélyezze magyarra fordítását és klinikai használatát. Ő angol levelemre angolul válaszolt, de kérte, hogy a továbbiakban én nyugodtan írjak neki magyarul, mondván, hogy 1956-ban gyermekként távozott családjával hazánkból, s így olvasni és beszélni jól tud nyelvünkön, de a magyar nyelvű írás már nem erőssége.

Ekkor néhány levélváltás után megszakadt a kapcsolatunk, de ő 1994-ben Magyarországra érkezett egy nagy amerikai–magyar kutatási projekt tervével „a gyermekkori depresszió rizikótényezőinek" kutatása területén. Az 5 évesre tervezett kutatást a National Institute of Mental Health (továbbiakban NIMH) támogatásával képzelte el, de mint nagy tapasztalatokkal rendelkező kutató tudta, hogy egy ilyen volumenű projekt elnyeréséhez és külföldi lebonyolításához rendkívüli erőfeszítéseket kell tenni.

Előkutatás

Először is meg kell győzni az NIMH-t, hogy miért fontos ez a téma. Miért kell ezt Magyarországon és nem az USA-ban végezni. Magyarországon megfelelő kutatóbázis kialakítható, és a kutatásban résztvevők alkalmasak arra, hogy a kutatást lefolytassák.

Ahhoz, hogy mindezt bebizonyíthassuk, egy kisebb előkutatást kellett megtervezni és elvégezni, amihez a Fogarty International Research Collaboration Award támogatását kértük a „Depression and Suicidal Behaviors in Hungarian Children (5 R03 TW00459-02)" című pályázatban, melynek a koordinátora *Csorba János* volt.

Támogatási összeg: 14 895 dollár

A kutatás fő célja: Megvizsgálni, és adatokkal alátámasztani, hogy Magyarországon vegyes gyermekpszichiátriai klinikai betegcsoportban milyen a gyermekkori depresszió és öngyilkossági viselkedés pont prevalenciája.

Ehhez három gyermekpszichiátriai intézet együttműködése volt szükséges. A kutatásban a Semmelweis Egyetem Pszichiátriai Klinika Ifjúságpszichiátriai Szakrendelése, a Vadaskert Alapítványi Kórház Gyermekpszichiátriai Osztály és Szakambulancia és a Szegedi Tudományegyetem Gyermek- és Ifjúságpszichiátriai Önálló Osztály fekvő- és járóbeteg részlegei vettek részt.

A felmérés a következőkből állt: Olyan strukturált interjú (Detailed Evaluation Schedule for Children and Adolescents – DESCA) felvétele, mely tartalmazza az öt gyermekpszichiátriai részlegen az újonnan jelentkezett gyermekek és családjuk szocio-demográfiai paramétereit, nagyobb életeseményeit, pszichoszomatikus fejlődési adatait és pszichopatológiai tüneteit. Az interjút részben a szülővel, részben a gyermekkel arra kiképzett gyermekpszichiáterek és pszichológusok készítették. Emellett egy nemzetközi kutatásokban gyakran alkalmazott önkitöltős kérdőívet vettek fel a szülővel a gyermek általános pszichopatológiai tüneteiről Childhood Behavior Checklist (továbbiakban CBCL), és a gyermekkel kitöltették a GYD feladatlapot, mely specifikusan a depresszió tüneteire kérdez.

A kutatás négy fázisa

Instrumentáció: a DESCA magyarra fordítása, visszafordítása angolra, majd a magyar változat további finomítása egy bilingvis pszichológus segítségével. A GYD feladatlap és a CBCL hiteles magyar fordítása már rendelkezésre állt.

Interjúkészítők kiképzése: 10 gyermekpszichiáter és 2 pszichológus kiképzése a következőkből állt: DESCA itemenkénti elemzése, szerepjáték a résztvevőkkel, és 2–2 interjú a beteggel a kiképző, *Kovács Mária* jelenlétében.

Interrater reliabilitás: 68 betegnél 2 interjúkészítő volt jelen az interjú felvételénél: az egyik az interjút készítette, a másik tőle függetlenül pontozta az interjút. Az interrater reliabilitás elfogadhatónak bizonyult (Kappa≥0,85) a DESCA itemek 80%-ánál.

Fő tanulmány: 1996. október és 1997. október között a három betegfelvételi iroda szűrte a betegeket. A gyermek bekerülhetett a kutatásba, ha 7–17 év közötti volt, nem volt mentálisan retardált, nem volt krónikus gyermekgyógyászati/neurológiai betegsége, legalább egy biológiai szülővel élt együtt, aki a gyermekről megbízható információt tudott nyújtani. A szülőt és gyermeket, ha a vizsgálatba bekerülési kritériumoknak megfelelt, felvilágosítottuk a kutatás lényegéről, és beleegyezését kértük a vizsgálat lefolytatásához. A DESCA interjú felvétele és az önkitöltős kérdőívek a beteg és a szülő számára kb. 1–1,5 órás elfoglaltságot jelentett. Cserébe a beteg és a szülő egy szokásosnál részletesebb, a gyermek lelkiállapotát jobban tükröző gyermekpszichiátriai vizsgálatot kapott.

A klinikai diagnózist (depressziós vagy más pszichiátriai betegség) a strukturált interjú, a szülő és gyermek által kitöltött önkitöltős kérdőívek, valamint egy nyitott interjú alapján a vizsgálatot végző gyermekpszichiáterek véleményének figyelembevételével állapítottuk meg.

Az adatokat a projekt statisztikusához küldtük, ahol az interjúk és kérdőívek ellenőrzésen mentek át, a kihagyott válaszokat a szülővel/gyermekkel telefonon pótoltattuk.

Eredmény

90%-os beleegyezési arány mellett 490 beteg került a kutatásba, ami igen jónak mondható. Általában az anyák voltak az informátorok. A gyerekek 58%-a élt érintetlen családban, szemben

az USA-ban észlelt 26–36%-os aránnyal. A gyermekek 83,9%-ának volt legalább egy testvére.

A következő, a támogatás szempontjából fontos szempontnak (7–14 éves életkor közötti résztvevők) felelt meg 392 gyermek. A DESCA interjúra alapozva 34,4%-uk merítette ki a major depresszió DSM-IV szerinti diagnosztikus kritériumait. Ebben a fiatalabb depressziós alcsoportban a nemi megoszlás, a testvérszám és az intakt családok száma a nagyobb csoporthoz hasonló volt. A depressziós gyermekek testvérei és unokatestvérei között lényegesen gyakoribb volt a depressziós anamnesztikus adat, mint a nem depressziós betegek esetében (chi-négyzet=6,67; p=0,01 chi-négyzet 11,15, p=0,001).

Ezek alapján az NIMH-nek bebizonyíthattuk, hogy Magyarországon magas a major depresszióban szenvedő gyermekek száma, akik közül többen élnek biológiai szüleikkel együtt, mint az Egyesült Államokban, és különböző intézetek között létrehozható olyan kutatói együttműködés, mely biztosítja az adatok egyöntetű felvételét, a kidolgozott protokoll betartását.

A gyermekkori depresszió rizikótényezői (NIMH PO1–MH 56193) kutatás 1998. december 1.– 2007. június 31.

A fenti – Fogarthy-kutatás – adataiból kiindulva elkezdhettük az előbb három évre tervezett depresszió kutatás pályázatának megírását, melyet az 1998-as tavaszi benyújtás után revízióra visszaküldtek, de az ismételt beadást követően, majd a 2007-ig történő meghosszabbítás kérelmezésekor (competing renewal application) azonnal elfogadták, mely szinte példa nélkül álló ilyen nagy pályázati összegnél az NIMH történetében.

A támogatás összege 1998. december 1.–1999. november 30. között: 499.975 dollár, majd 1999. december 1.–2007. június 3. között: 2.255.797 dollár.

A kutatás célja: A gyermekkori depresszió pszichoszociális és genetikai kockázati tényezőinek vizsgálata. Megvalósítása lényegesen nagyobb szervezési feladatot (23 gyermekpszichiátriai intézet és három genetikai anyag izolálására alkalmas laboratórium együttműködését) igényelt, mint a megelőző Fogarthy-pályázat.

Etikai bizottsági vélemények kikérése: A teljes kutatási dokumentációt benyújtottuk az ETT-hez, majd engedélye birtokában valamennyi kutatóhelyen a helyi etikai bizottságokkal évente elbíráltattuk a helyben folyó kutatást.

Kutatóhelyek kiválasztása:

1. Meglátogattunk minden, egy nap alatt Budapestről vagy Szegedről elérhető gyermekpszichiátriai osztályt és ambuláns rendelést. Számba vettük a rendelő betegforgalmát, a szakorvosokat, pszichológusokat, motivációjukat a kutatásban való aktív vagy passzív részvételre. Ismertettük a kutatás céljait, és lehetőségeiket a kutatás különböző szintjein való részvételre. A kutatóhelyek feladata volt valamennyi, az ambulancián megjelenő betegnek – aki a vizsgálatba bekerülés kritériumainak megfelelt – és szülőjének elmagyarázni a kutatás lényegét, majd beleegyezésüket kérni a teljes kutatási folyamatba (két alkalommal részletes ISCA-D interjú, s amennyiben ezen depressziósnak bizonyul, vérvétel DNS-minta vételére). A bekerülési kritériumok a következők voltak: 7–14 év közötti életkor, mentálisan nem retardált, nem szenvedett krónikus belgyógyászati betegségben, legalább egy biológiai szülőjével együtt élt, volt 7–16 év közötti vér szerinti testvére, és a szülő és gyermek által kitöltött rövid depresszió szűrőteszten depresszióra gyanúsnak bizonyult.

A szűrési folyamatra a vállalkozó kutatóhely adminisztrátorait kiképeztük, majd évente emlékeztető tréninget tartottunk számukra.

Ugyancsak kiképeztük a kutatóhelyen dolgozó kezelőorvosokat a beleegyeztetési folyamatra.

2. Három genetikai laboratórium került be a kutatásba, melyek feladata a családtagoktól levett vérből a DNS izolálása, majd Torontóba – a Clarck Intézetbe – küldése volt. Torontóból *Cathy Barr* és *Jim Kennedy* meglátogatta a kiválasztott laboratóriumokat, és a DNS kivonáshoz egységes protokollt állítottak össze.

3. Mivel az NIMH szokatlanul hosszú időn át igen nagy összeggel támogatta USA-n kívüli országban a pályázatot, 3 vezető adminisztrátor

jött el Magyarországra, és személyesen meglátogatott 5 kutatóhelyet, 1 genetikai laboratóriumot, hogy képet kapjon a nagy volumenű tervek megvalósíthatóságáról.

Interjúk és kérdőívek kiválogatása, interjúkészítők kiképzése, szinten tartása, ellenőrzése

Az első lépésben 2 fő Pittsburgh-be utazott, és ott 2 hetes kiképzést kapott a féligstrukturált interjú (Kiddi-SAD) készítéséből. Ezután *Kovács Mária* és *Hartwin Sadowsky* jött Magyarországra, és angol nyelvű képzést tartott 14 főnek (közülük kerültek ki később a további interjúképzők, interjú szupervizorok, értékelő szakorvosok). Ezt követően lefordítottuk, majd bilingvis pszichológus segítségével angol nyelvre visszafordítottuk az Interview Schedule for Children and Adolescents: Diagnostic változatot (ISCA-D) és a többi kérdőívet. A korábbi Fogarthy Studyban használt DESCA interjút a kutatás jelenlegi céljának megfelelően átalakítottuk General Information Sheet (GIS) néven. Az ISCA-D felvétele – mely a pervazív zavarok kivételével valamennyi pszichiátriai betegségre rákérdez – kb. 2–2,5 órát vesz igénybe a gyermek életkorától és tünetei számától függően. Mind a szülő, mind a gyermek interjúja alapján az interjúkészítő dönt abban, hogy a kérdezett gyermeknél a tünet küszöb feletti, küszöb alatti mértékben van jelen, vagy egyáltalán nem áll fenn. (Az alkalmazott interjúk és kérdőívek felsorolását lásd az 1. táblázatban). Ezt követően azon gyermekpszichiáterek és klinikai szakpszichológusok számára, akik azt vállalták, 2 hetes interjúkészítő tanfolyamot tartottunk meghatározott tematika szerint, majd 5–5 db interjút kellett munkahelyükön elkészíteni és a szupervizorokkal megbeszélni. A továbbiakban, amennyiben a szupervizorok az 5 interjú alapján az interjúk minőségét megfelelőnek tartották, az interjúkészítők kevésbé szoros kontroll (rekalibrációs képzések) mellett elkezdhették az interjúzást.

A kutatás folyamán a kieső interjúkészítők miatt (GYED, külföldre távozás stb.) még három alkalommal tartottunk kurzus-szerű képzést, és egy egyéni, illetve kiscsoportos képzési protokollt is kidolgoztunk. Az eltelt 9 év alatt összesen 58 interjúkészítőt képeztünk ki.

A kutatásban dolgozó interjúkészítők félévente rekalibrációs továbbképzésen vettek részt, hogy a pontozásuk egységes maradjon minden kutatóhelyen.

Minden interjúról hangfelvétel készült, és az interjú szupervizorok évente randomizált módon minden interjúkészítőtől 5 hangfelvételt ellenőriztek. Ha az interjú minősége nem volt megfelelő, az interjúkészítő egyéni továbbképzésen vett részt.

Adatbeviteli rendszer kiépítése

A felvett interjúkat az interjúkészítők – a regionális irodák közvetítésével – eljuttatták a központi irodába, ahol az adatokat rögzítették egy előre elkészített adatbázisba a megfelelő adatbeviteli felület alkalmazásával. Az adatok pontosságának biztosítása érdekében a beviteli rendszer úgy működött, hogy az első bevitel után a teljes adatmennyiséget újra bevitte egy második adatbevivő (Double-check). A két bevitel során jelentkező különbségeket a rendszer végleges tárolás előtt listázta, amin végighaladva a második bevivő ellenőrizhette az eltéréseket, és meggyőződhetett a bevitt adatok pontosságáról.

A már bevitt adatokat a kutatás alatt folyamatosan ellenőriztük, egymást kizáró adat-párok, és szúrópróbaszerű ismételt adatbevitellel. Az így kapott eredmények ismeretében biztosak lehetünk benne, hogy az adatbázisban tárolt adatok kevesebb mint 0,5% adatbeviteli hibát tartalmaznak.

Pilot fázis

Mikor az összes interjú fordítása és az adatbeviteli rendszer összeállt, az első 5 bekerült eseten kiértékeltük a szűrés, az interjúkészítés, adatbevitel, vérvétel folyamatát, és a tapasztalatok alapján, ahol szükséges volt, megváltoztattuk a menetet.

1. táblázat
Az adatgyűjtés folyamata

AZ ADAT TÍPUSA	A VIZSGÁLAT IDEJE				A VÁLASZADÓ			PONTOZÁS	
	Szűrés	Bevétel		FU	Szülő	Proband	Testvér	Önkitöltős	Klinikus
		I.	II.						
Pszichiátriai tünetek									
Előszűrés	+				+	+		+	
Klinikai szűrő	+			+	+	+			+
ISCA-D hangulat modul		+			+	+	+		+
ISCA-D			+		+	+	+		+
FIGS-M		+			+				+
CASFI-M		+			+				+
Gyerek tünetlista (CSC)		+		+	+			+	
CBCL		+		+	+			+	
BDI			+		+			+	
CDI		+		+		+	+	+	
Gyerek Reménytelenség Skála		+		+		+	+	+	
Spielberger Vonás/állapot Szorongás Skála			+		+			+	
Demográfiai és életesemények									
Bekerülési Általános Információk Kérdőív (GIS)		+			+				
Utánkövetéses GIS (FU-GIS)				+	+				
Életminőség (QL)		+		+	+	+	+	+	
Érzelmi reguláció									
EAS Temperamentum Kérdőív		+		+	+			+	
Érzések és a Gyermekem			+		+			+	
Felnőtt Attachment Skála (AAS)			+					+	
PANAS-X		+		+		+	+	+	
PANAS-M		+		+		+	+	+	
Érzelmi válasz depresszióra (RDQ-Y)		+		+		+	+	+	
Élet Orientáció (LOT-Y)		+		+		+	+	+	
Érzések és Én		+		+		+	+	+	
Milyen vagyok (Harter's önértékelési profil gyermek vagy serdülő változat)									

FU=follow-up; **ISCA-D**=Interview Schedule for Children and Adolescent-Diagnostic Version; **FIGS-M**=Family Interview for Genetic Screening-Modified Version; **CASFI-M**=Child-Adolescent Screen for Family Interview-Modified Version; **CSC**=Child Symptom Check List; **CBCL**=Child Behavior Check List; **BDI**=Beck Depression Inventory; **CDI**=Children's Depression Inventory; **GIS**=General Information Sheet; **AAS**=Adult Attachment Scale; **PANAS**=Positive and Negative Affect Schedule **RDQ-Y**=Responses to Depression Questionnaire for Youngsters; **LOT-Y**=Life Orientation Test for Youngsters

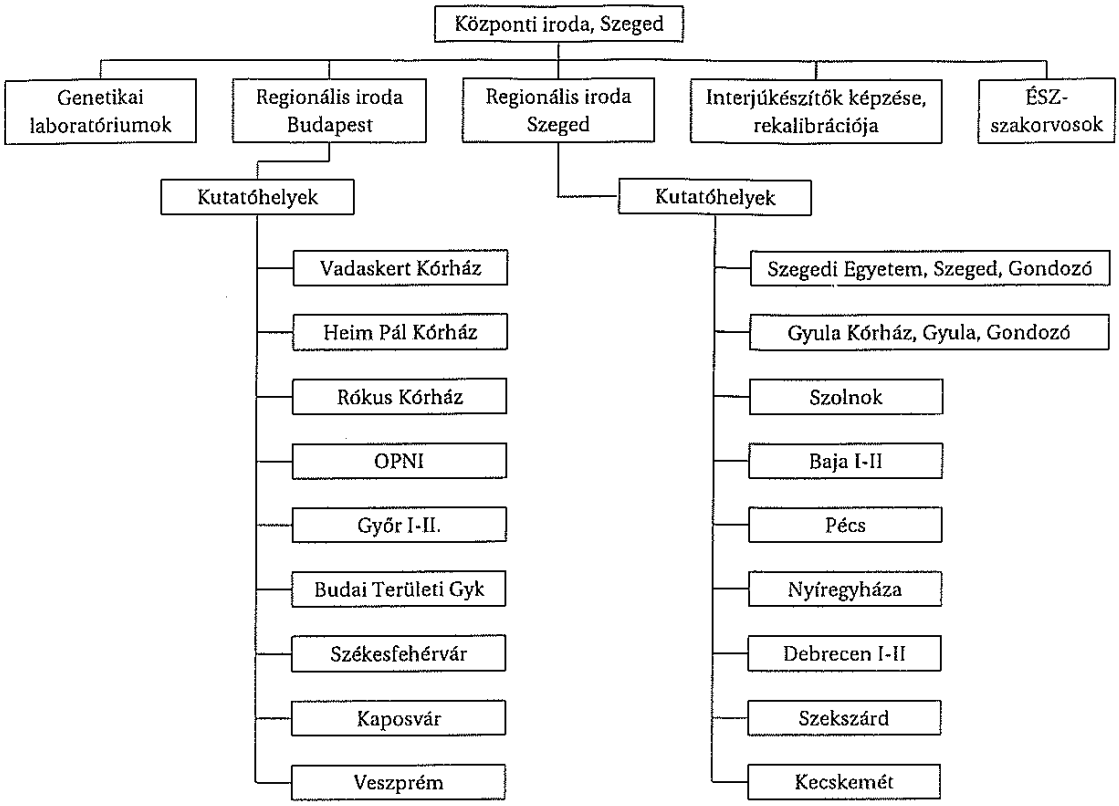
Adminisztratív infrastruktúra megszervezése

Ezt követően, hogy a szűrés, interjúkészítés, vérvétel stb. mindenütt egységesen történjen, minden folyamatot írásos protokollban rögzítettünk. A protokollok írása, a protokoll szerinti működések monitorizálása, a kutatás összefogása egy központi iroda felállítását tette szükségessé. A kutatás szervezeti felépítése az alábbi volt. (1. ábra)

Kutatóhelyi adminisztrátor feladatai

A 23 kutatóhelyen valamennyi megjelent betegen ellenőrizni, hogy megfelel-e a bekerülési

1. ábra
A kutatás szervezeti diagramja



kritériumoknak, és ezt az adott táblázatba a betegek kezdőbetűit alkalmazva feljegyezni. A táblázatot naponta telefaxon elküldeni a regionális központba. Ha a beteg a bekerülési kritériumoknak megfelelt, akkor odaadni neki a beleegyező nyilatkozatot, majd tájékoztatásra és beleegyezésre a kezelőorvoshoz küldeni. Ha a szülők és a gyerek a kutatásban való részvételbe beleegyeztek, jelenteni a regionális központba, és elküldeni a beleegyező nyilatkozatot. Ezután biztosítani, hogy a központ által szervezett interjúkészítőnek a megszervezett időpontban legyen a kutatóhelyen helye az interjú elkészítéséhez, és vigyázni a gyermekre, amíg a szülő interjúja folyik. A szűrésen átesett gyermekeket regisztrálni a kezelőlapon, és a negatívakat félévente ismét szűrni depresszió szempontjából. Évente két alkalommal rendelkezésére kell állnia a központból kiküldött monitor számára, aki ellenőrzi, hogy a szűrési protokollt megfelelően betartják-e. A regionális központ és a kutatóhelyek közötti kapcsolat folyamatosságának biztosítására minden kutatóhelyre önálló telefont és telefaxot telepítettünk.

Regionális központok

Két regionális központot alakítottunk ki, egyet a Szegedi Tudományegyetemen, egyet Budapesten a Vadaskert Alapítványi Kórházban. A regionális központok feladata volt, hogy a hozzájuk tartozó kutatóhelyekkel napi kapcsolatban legyenek, a szűrések adatait számítógépen rögzítsék. Itt szervezték meg a területükön dolgozó interjúkészítők és a kutatásba beleegyezett családok találkozásait az interjúk lebonyolítása céljából, valamint itt történt az elkészült interjúk formai és szakmai ellenőrzése, majd az interjúk elküldése a központi irodába. Minden munkafolyamatot számítógépen rögzítettek. A feladatok elvégzésére egy-egy regionális alközpontve-

zetőt, egy-egy adminisztrátort, és egy-egy interjú szupervizort alkalmaztunk.

Mindkét regionális iroda rendszeresen tartotta a kapcsolatot a hozzájuk tartozó interjúkészítőkkel. Vigyáztak, hogy ugyanahhoz a családhoz a második interjúra másik interjúkészítő legyen beosztva.

Központi iroda: Szegedi Tudományegyetem

Itt történt a kutatás valamennyi fázisának adminisztratív összefogása, az ellenőrzött interjúk adatainak számítógépre vitele, a munka elosztása.

Működtetésére manager team állt össze a kutatás általános vezetője, a kutatási koordinátor, az interjúképzési és ellenőrzési koordinátor, a gazdasági koordinátor, és az információs technológiai manager részvételével. Ez a csoport kéthetente ülésezett, megbeszélte az elvégzett feladatokat vagy a felmerült nehézségeket, és megszabta a következő 2 hétben elvégzendőket, és azok fontossági sorrendjét.

A központi iroda végezte a diagnosztikus munka utolsó fázisát is: az *Értékelő Szakorvosi folyamatok* (továbbiakban *ÉSZ*) *szervezését:* A kutatás folyamán minden betegről két interjú készült 2 hét–6 hónapon belüli időszakban 2 független interjúkészítővel. Az első alkalommal az ISCA-D-nek csak az affektív zavarok modulját vettük fel, és csak ha a gyermek ott depressziósnak bizonyult, akkor került sor a második – ekkor már a DSM-IV csaknem valamennyi betegségét felölelő teljes ISCA-D – interjúra. Az adatbevitel után az interjúkat kinyomtattuk és 2 értékelő szakorvos (gyakorlott gyermekpszichiáterek) a beszerzett egyéb betegdokumentációval együtt megkapta azokat. Mindketten önálló diagnózist hoztak a DSM-IV alapján, majd konszenzus konferencián döntöttek a beteg végleges diagnózisaiban, valamint abban, hogy valóban volt-e major depresszió vagy bipoláris betegsége. Ha a döntés pozitív volt, a gyermek proband státuszt kapott.

Ezután kerülhetett sor a *biológiai mintavételre,* melyet szintén a központi iroda szervezett. Minden betegtől, és lehetőleg mindkét szülőjétől szájnyálkahártya kenetet és vért is vettek, s a központban generált kódszámmal látták el azokat, így biztosítva azok teljes anonimitását. Ha egy testvér depressziósnak bizonyult, tőle is vettünk biológiai mintát. A szájnyálkahártya mintát azonnal Torontóba küldték, míg a vért valamelyik hazai genetikai laboratóriumba DNS izolálásra, elkerülendő a feldolgozás során a családon belüli vizsgálati anyagok esetleges összecserélését.

A kutatás utolsó fázisa az *utánkövetéses vizsgálat* volt, szintén a központi iroda szervezésében. Minden major depressziós betegnek és 7–16 éves testvérének évente kiküldtünk egy önkitöltős tesztcsomagot, amelyben a szülő és a gyermekek által kitöltendő, a depressziót és a bipoláris betegséget szűrő tesztek voltak. Célja az volt, hogy megtudjuk van-e visszatérő depressziós epizódja a probandnak, vagy nem csapott-e át bipoláris betegségbe. Emellett, ha a testvérnél a depresszió gyanúja merült fel, akkor őt is a probandnál leírt diagnosztikus folyamatnak vetettük alá, s ha major depresszió betegség vagy bipolaritás igazolódott, tőle is DNS-mintát vettünk.

A kutatás menete és eredményei

Szűrés, bevonás, beleegyezés: A lehetséges probandok szűrését 1999. november 1. és 2005. július 1. között végeztük. Összesen 28 533 gyermeket szűrtünk, akik közül 1299 adott a szűrőkérdésekre a határértéknél magasabb pontszámot, és 840-en egyeztek bele a kutatásban való részvételbe. További 403 eset került be a kutatásba alternatív úton. Ezekről a betegekről a kezelőorvosok gondolták, hogy depressziósak és irányították a kutatáshoz őket. Ebből a 403 esetből 256-an egyeztek bele a részvételbe.

Diagnosztikus folyamat: Összesen 1023 pozitív szűrési eredménnyel rendelkező gyermeknek 1127, míg 406 testvérnek 474 első interjúja volt az interjúzási fázis végéig. A fenti csoportból 762 probandnak 768, míg 222 testvérnek 233 második interjúja volt. 756 probandot és 200 testvér adatait értékelték az Értékelő Szakorvosok (1127 és 267 ÉSZ értékelés). Az értékelések eredmé-

nyeként 723 probandnál és 182 testvérnél igazolódott a depresszió. (Az eltérő számok egyrészt abból adódnak, hogy voltak olyan betegek, akiket az eltelt évek során 2–3 alkalommal is interjúvoltunk, mivel első, illetve második alkalommal nem merítették ki a major depresszió DSM-IV diagnosztikus kritériumait. Másrészt abból, hogy relapszus, rekurrencia, esetleg bipolaritás gyanúja esetén a proband ismét interjúra került). Kontrollcsoportként 104 olyan 18 éven felüli testvért is bevontunk a kutatásba, akiknél a fentebb említett részletes diagnosztikai folyamat egész életükre vonatkozóan kizárta major depressziós epizód fennállását.

Interjúban adott diagnózisok ellenőrzése: A kutatásban résztvevő interjúkészítők által felvett interjúk minőségét rendszeres rekalibrációs találkozókkal biztosítottuk. Évente két alkalommal országos találkozót szerveztünk az interjúkészítőknek. Ezeken a találkozókon az Értékelő Szakorvosok is esetmegbeszéléseket tartottak a magyarországi vezető kutató irányításával, így biztosítva az ÉSZ értékelések egyöntetűségét.

Minden elkészült interjút egy héten belül formailag és tartalmilag ellenőriztünk. Telefonon nem megoldható probléma, hiba esetén az interjút visszaküldtük javításra a készítőjének. A szupervízorok rendszeresen ellenőrizték az interjúkat a magnókazetták visszahallgatásával.

Elvesztett alanyok: 74 gyermeket/családot elvesztettünk még az első interjú előtt, 210 eset vált a kutatás számára nem megfelelővé, mivel nem volt érzelmi problémájuk, vagy teljesült náluk valamilyen kizárási kritérium. 130 probanddal vesztettük el a kapcsolatot, 83 esetet kizártunk, míg 23 esetben megszakítottuk a folyamatot, mivel nem kooperáltak a beleegyezést követően, és 1 gyermek meghalt a kutatás ideje alatt. 15 családdal vesztettük el a kapcsolatot költözésük miatt. 7 család esetén minden kapcsolatunk megszakadt. Ezeket az eseteket minden harmadik hónapban megpróbáltuk ismét elérni a háziorvosokon, illetve az előzetesen megadott kapcsolattartó személyen keresztül.

Vér-, nyálminta gyűjtés: Azokon a kutatóhelyeken, ahol nem volt elérhető helyi vérvevő, mobil vérvevőt alkalmaztunk, aki a vérvételt a család lakásán végezte el.

A kutatás kezdetétől vér- vagy nyálmintát 686 probandtól és 180, 18 éven aluli depressziós és 104, 18 éven felüli egészséges testvértől vettünk le. A minták családonkénti összetétele a következő: proband és két szülő (nincs érintett testvér) 339 család; proband, egy vagy több érintett testvér és 1 vagy két szülő: 251 család; proband és egy szülő: 96 család. Az összesített depressziós testvérek aránya 22,06%, ami magasabb, mint a kutatás kezdetén várt 20%.

A vér- és nyálmintákból DNS izolálás történt a helyi kutatólaboratóriumokban. Az anyag felét Torontóba küldtük további vizsgálatokra, fele pedig a hazai kutatás számára maradt meg.

Utánkövetés: Azok a gyermekek, akik az első vizsgálat során nem elégítették ki a probanddá válás kritériumait (kockázati csoport), a depressziós probandok és testvéreik mindannyian évente levélben küldött önkitöltős tesztet kaptak. A kutatás kezdetétől 904 proband+ kockázati csoportban lévő gyerek, valamint 1151 testvér kapott önkitöltős kérdőívet, az évek során összesen 5044 levelet küldtünk ki. 888 proband + kockázati csoportban lévő gyermek és 1112 testvér mindösszesen 4688 alkalommal küldte vissza a kérdőívet. Az összesített visszaküldési arány 92,9% volt. A válaszok értékelése után összesen 382 utánkövetési interjút készítettünk probandokkal és 65-öt testvérekkel.

Kapcsolattartási célból 2008. augusztus 1–31. között 1077 utánkövetéses önkitöltős kérdőívet küldtünk ki, 2008. december 31-ig a kérdőívek 78%-a érkezett vissza.

Adat-integritási folyamat: A kutatás ideje alatt 2 teljes állású és 1 félállású adatbevivő dolgozott a kutatásban. Egy monitorizáló csapat biztosította az adatok integritását, valamint a különböző folyamatokban észlelhető hibáknak a felderítését. Az adatellenőrzési csapatot 1 teljes állású és 3 félállású adminisztrátor alkotta.

Felmerülő problémák, megoldások, megelőzések

Három hónapos célokat állítottunk fel a levélben küldött utánkövetési folyamat optimalizálására és az adattisztításra. Az eredményeket minden

három hónap végén, országos megbeszéléseken átnéztük, értékeltük ez előző 3 hónap eseményeit és újabb feladatokat tűztünk ki a következő 3 hónapra.

Megpróbáltuk minimalizálni az elvesztett családok/gyermekek számát, ezért több lépcsős eljárást dolgoztunk ki az elvesztett családok követésére. Ennek keretében próbáltuk elérni a családot telefonon, telefonszám és címkeresési eljárásokat, ajánlott levelek küldését alkalmaztuk, valamint a Népességnyilvántartóból próbáltuk megtudni az elvesztett családok elérhetőségét. Minden elvesztett családot 3 havonta próbáltunk a fenti módszerekkel a kutatásba visszahozni. Erre a folyamatra külön csoportot szerveztünk.

Főbb eredmények

Együttműködés: A sok éves együttműködés és együttgondolkodás a csaknem egész Magyarországot felölelő gyermekpszichiátriai ellátásban és gondozásban részt vevő kollegákkal javította és egységesítette diagnosztikai munkánkat a mindennapi betegellátásban, és szellemi erőforrást jelentett mindenkinek, de főleg az izoláltan, nehéz körülmények között dolgozó, de fejlődni kívánó munkatársainknak.

Standardizált tréning: Magyar nyelvre adaptáltunk egy korábban hazánkban nem alkalmazott féligstrukturált pszichiátriai diagnosztikus interjút (ISCA-D), mely a legtöbb pszichiátriai betegség DSM-IV szerinti lehető legpontosabb diagnózisát adja. Kidolgoztunk egy standardizált tréningprogramot a féligstrukturált diagnosztikus interjúkészítéshez. Ennek felépítése: 2 hetes bevezető tréning (elméleti és gyakorlati jártassággal rendelkezőknek a pszichiátriai diagnosztikában és a féligstrukturált interjútechnikában) majd 3 napos gyakorlatokat szerveztünk 3 havonként.

Infrastruktúra, informatika: Megterveztünk és kiviteleztünk egy komplex informatikai megoldást az ország 3 kutatási irodájában, felállítottunk egy egyedülálló adatbázist, és egy webes felületet az adatok tárolására, kezelésére, valamint az interjúk szervezéséhez. Az adatok integritását kettős adatbevitellel és folyamatos adattisztítással biztosítottuk. Komplex tűzfal rendszer és Virtuális Magánhálózatok (VPN) biztosították a kódolt, biztonságos kommunikációt az irodák között. Napi mentés készült az adatbázisról, és a mentéseket a szerver háttértárolóján, egy különálló backup tároló szerveren, valamint heti rendszerességgel CD-re/DVD-re mentve tároljuk.

Adatbázis és biobank: A kutatás folyamán olyan adatbázist állítottunk össze a gyermekkori kezdetű depresszió területén, mely világviszonylatban is egyedülálló, mind a kivizsgálás és *diagnosztika precizitása,* mind a *probandszám nagysága* miatt. Biobankunkban a DNS-minták mellett számos pszichoszociális kockázati tényező vizsgálatára is van mód, mely lehetővé teszi a genetikai eltérések összekapcsolását a betegség kialakulásában résztvevő egyéb faktorokkal.

Publikálás

2003 decemberétől kezdve rendszeres, havi kutatási találkozókat tartottunk. A megbeszélések célja volt, hogy elősegítsék és felügyeljék a publikációs munkákat. A szupervíziót a kutatás magyarországi vezetője – *Vetró Ágnes* – és a helyettese – *Gádoros Júlia* – tartották.

Számos tudományos cikket publikáltunk, vagy van jelenleg bírálat alatt, és számos előadást tartottunk országos és nemzetközi konferenciákon, jóllehet az adatoknak még csak egy kis töredékét sikerült elemeznünk. Két kollegánk PhD fokozat eléréséhez szükséges abszolutóriumot szerzett, s téziseinek megvédése előtt áll. Három kollegánk elkezdte PhD témája kidolgozását.

Genetika

Számos, főként a szerotonin anyagcserében szerepet játszó gént vizsgáltunk (Lásd tudományos közlemények). Vizsgálataink szerint a gyermekkori kezdetű depresszió kialakulásában az ESR1, NTRK3, MTHFR, AVPR1B géneknek és a BDNF-nak lehet szerepe.

Pszichoszociális kockázati tényezők

A nehéz temperamentum a major depresszió és az első internalizációs kórkép korábbi jelentkezésére hajlamosít, de csökken ez a hatás, ha a gyermek teljes családban él a korai gyermekkorban. A nehéz temperamentumnak ez a hatása az életkor előrehaladásával csökken.

Magas diszfunkcionalitás és alacsonyan funkcionáló érzelmi regulációs tendencia növeli az öngyilkossági hajlam esélyét depressziós gyermekeknél, míg a negatív jellegű emocionalitásnak nincs semmi hatása.

Összehasonlítva az anyától és a gyermektől kapott válaszokat a gyermek depressziós tüneteiről, azt találtuk, hogy a lányok sokkal súlyosabb tünetekről számolnak be mint a fiúk, ugyanakkor az anyák válaszában nincs nemenkénti eltérés. A szülő–gyermek egyezés a tünetekben függött a gyermek életkorától. A depressziós anyák sokkal súlyosabb problémákról számoltak be gyermekükkel kapcsolatban, mint a nem depressziósak.

Major depresszió és a komorbid szorongási zavar növeli az alkoholfogyasztás esélyét. A legmagasabb kockázat a generalizált szorongáshoz köthető (OR=8,4). Komorbid viselkedési zavarok növelik a dohányzás kockázatát (OR=3,72).

A projekt ideje alatt a kutatáshoz a betegektől vagy a kutatóhelyektől panasz, vagy etikai kifogás nem érkezett.

Összefoglalva elmondhatjuk, hogy amikor elkezdtük írni a pályázatot még magunk sem gondoltuk, hogy ilyen szerteágazó, komplex, nagy volumenű lesz a kutatás, melyet lefolytatunk. A pályázat megvalósításán 14 teljes munkaidőben dolgozó munkatárs dolgozott, de az eseti interjúkészítőkkel, részmunkaidős kollegákkal együtt voltak olyan hónapok, mikor 114 embernek számfejtettünk bért. Mindez természetesen az NIMH hatalmas támogatása nélkül nem valósulhatott volna meg, amelyért köszönetünket fejezzük ki.

Köszönetnyilvánítás

Megköszönjük a kutatásban résztvevő intézetek dolgozóinak munkáját, mely hozzásegített bennünket a gyermekkori depresszió kockázati tényezőinek jobb megismeréséhez.

Irodalom

1. I BAJI, NL LOPEZ-DURAN, M KOVACS, CJ GEORGE, L MAYER, K KAPORNAI, E KISS, M VUGA, J GADOROS, Á VETRÓ: Age, sex, somatic complaints, and the symptom presentation of childhood depression in a Hungarian clinical sample. Psychiatr Res, under review (2, 298)

2. L MAYER, NL LOPEZ-DURAN, M KOVACS, C GEORGE, I BAJI, K KAPORNAI, E KISS, Á VETRÓ: Stressful life events in a clinical sample of depressed children in Hungary. J Affect Disord (közlésre elfogadva, 2008. okt. 7. online). (IF:3, 144)

3. E KISS, K KAPORNAI, I BAJI, L MAYER, Á VETRÓ: Assessing quality of life: mother-child agreement in depressed and non-depressed Hungarian samples. Eur Child Adolesc Psychiatry, In press (IF:1.992)

4. MILL J, WIGG K, BURCESCU I, VETRÓ Á, KISS E, KAPORNAI K, TAMÁS Z, BAJI I, GÁDOROS J, KENNEDY JL, KOVACS M, BARR CL AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Mutation screen and association analysis of the glucocorticoid receptor gene (NR3C1) in childhood-onset mood disorders (COMD). Am J Med Genet B (Neuropsychiatr Genet). In press (IF:4, 463)

5. GOMEZ, WIGG K, FENG Y, KISS E, KAPORNAI K, TAMÁS Z, MAYER L, BAJI I, DARÓCZI G, BENÁK I, OSVÁTH KOTHENCNÉ V, DOMBOVÁRI E, KACZVINSZKY E, BESNYŐ M, GÁDOROS J, KING N, SZÉKELY J, KOVACS M, VETRÓ Á, KENNEDY JL, BARR CL: 72/G30 (DAOA) and Juvenile-onset mood disorders. Am J Med Genet B (Neuropsychiatr Genet). In press (IF:4,463)

6. VL MISENER, L GOMEZ, KG WIGG, N KING, E KISS, G DARÓCZI, K KAPORNAI, Z TAMÁS, L MAYER, J GÁDOROS, I BAJI, LJ KENNEDY, M KOVACS, Á VETRÓ, CL BARR AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Tagging SNP association study of the IL-1("beta")gene (ILB1) and childhood-onset mood disorders. Am J Med Genet B (Neuropsychiatr Genet), in press (IF:4, 463)

7. KG WIGG, Y FENG, L GOMEZ, E KISS, K KAPORNAI, Z TAMÁS, L MAYER, I BAJI, G DARÓCZI, BENÁK I, OSVÁTH KOTHENCNÉ V, DOMBOVÁRI E, KACZVINSZKY E, BESNYŐ M, GÁDOROS J, KING N, SZÉKELY J, KOVACS M, VETRÓ Á, KENNEDY JL, BARR CL: Genome scan in sibling pairs with juvenile-onset mood disorders: evidence for linkage to 13q and Xq. Am J Med Genet B (Neuropsychiatr Genet), in press (IF:4, 463)

8. VL MISENER, L GOMEZ, KG WIGG, P LUCA, N KING, E KISS, G DARÓCZI, K KAPORNAI, Z TAMÁS, L MAYER, J GÁDOROS, I BAJI, LJ KENNEDY, M KOVACS, Á VETRÓ, CL BARR AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Cytokine genes TNF, IL1A, IL1B, IL6, IL1RN and IL10,and childhood-onset mood disorders. Neuropsychobiology, 2008; 58:71-80 (IF:1, 992)

9. MILL J, KISS E, BAJI I, KAPORNAI K, DARÓCZY G, VETRÓ Á, KENNEDY J, KOVACS M, BARR C; THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDER: Association study of the estrogen receptor alpha gene (ESR1) and childhood-onset mood disorders. Am J Med Genet B (Neuropsychiatr Genet), 2008 Oct 5; 147B(7):1323-6 (IF:4, 463)

10. SHAIKH SA, STRAUSS J, KING N, BULGIN NL, VETRÓ A, KISS E, GEORGE CJ, KOVACS M, BARR CL, KENNEDY JL; INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Association study of serotonin system genes in childhood-onset mood disorder. Psychiatr Genet, 2008, 18:47-52. (IF:2, 14)

11. Y FENG, Á VETRÓ, E KISS, K KAPORNAI, G DARÓCZI, L MAYER, ZS TAMÁS, I BAJI, J GÁDOROS, N KING, JL KENNEDY, K WIGG, M KOVACS, C BARR, AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Association of the neurotrophic tyrosine kinase receptor (NTRK3) gene and childhood-onset mood disorders. Am J Psychiatry, 2008; 165:610-616 (IF:8, 25)

12. KAPORNAI K, VETRÓ A: Depression in children. Curr Opin Psychiatry, 2008 Jan;21(1):1–7. (IF:2, 599)

13. Y FENG, K WIGG, N KING, Á VETRÓ, E KISS, K KAPORNAI, L MAYER, J GÁDOROS, JL KENNEDY, M KOVACS, C BARR, AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: GPR50 is not associated with childhood-onset mood disorders in a large sample of Hungarian families. Psychiatr Genet 2007; 17:347–350 (brief report) (IF:2, 257)

14. E DEMPSTER, I. BURCESCOU, K WIGG, E KISS, I BAJI, J GÁDOROS, ZS TAMÁS, JL KENNEDY, Á VETRÓ, M KOVACS, CL BARR, AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Evidence of an association between the vasopressin V1b receptor gene (AVPR1B) and childhood-onset mood disorders. Arch Gen Psychiatry, 2007; 64(10):1189–1195 (IF:13, 936)

15. EL DEMPSTER, E KISS, K KAPORNAI, G DARÓCZI, L MAYER, I BAJI, ZS TAMÁS, J GÁDOROS, JL KENNEDY, Á VETRÓ, M KOVACS, C BARR, AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: No evidence of association between a functional polymorphism in the MTHFR gene and childhood-onset mood disorders. Mol Psychiatry, 2007; 12:1063–1064 (IF:10.9)

16. ZS. TAMAS, M. KOVACS, A. GENTZLER, P. TEPPER, J. GÁDOROS, E. KISS, K. KAPORNAI, Á. VETRÓ AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDER: The Relations of Temperament and Emotion Self-Regulation with Suicidal Behaviors in a Clinical Sample of Depressed Children in Hungary. J Abnorm Child Psychology, 2007, 35(4):640–652 (IF:2.4)

17. KISS E., BAJI I., MAYER L., SKULTÉTI D., BENÁK I., VETRÓ Á.: Életminőség kérdőív validitása és pszichometriai jellemzői magyar gyermekpopuláción. Psychiatr Hung, 2007, 22(1):33–42.

18. E. KISS, A. GENTZLER, C. GEORGE, K. KAPORNAI, ZS. TAMÁS, M. KOVACS, Á. VETRÓ AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Factors influencing mother-child reports of depressive symptoms and agreement among clinically referred depressed youngsters in Hungary. J Affect Disord, 2007, 100(1-3): 143–151 (IF:3, 138)

19. K. KAPORNAI, A. GENTZLER, P. TEPPER, E. KISS, L. MAYER. ZS. TAMÁS, M. KOVACS, Á. VETRÓ: Early development and features of Major Depressive Disorder in a child clinical sample in Hungary. J Affect Disord, 2007, 100(1–3): 91–101 (IF:3,138)

20. X. LIU., D.J. BUYSSE, A. GENTZLER, E. KISS, L. MAYER, K. KAPORNAI, Á. VETRÓ, M. KOVACS: Insomnia and hypersomnia associated with depressive phenomenology and comorbidity in childhood depression. Sleep, 2007, 30(1):83–90 (IF:5, 126)

21. KISS E., PIKÓ B., VETRÓ Á.: Dohányzás és szerhasználat előfordulása és kapcsolata a pszichiátriai komorbiditással depressziós gyermek- és serdülőpopulációban. Psychiatr Hung, 2006, 21(3):219–226.

22. MAYER L., KISS, E., BAJI I., SKULTÉTI D., VETRÓ Á.: Depressziós tünetek és az életesemények összefüggésének vizsgálata általános iskolás populációban. Psychiatr Hung, 2006, 21(3): 210–218.

23. MAYER L, KISS E, BAJI I, SKULTÉTI D, VETRÓ Á: Életesemények minőségi elemzése és kapcsolata a depressziós tünetekkel általános iskolás populációban. Psychiatr Hung, 2006; 5: 360–370.

24. X. LIU, M. KOVACS, A. GENTZLER, P. TEPPER, E. KISS, V. OSVATH KOTHENCZNÉ, ZS. TAMÁS, Á. VETRÓ: Clinical features of depressed children with various forms of suicidality. J Clin Psychiatry, 2006, 67:1442–1450 (IF: 5, 53)

25. I. BURCESCU, K. WIGG, L. GOMEZ, N. KING, Á. VETRÓ, E. KISS, K. KAPORNAI, J. GÁDOROS, J. KENNEDY, M. KOVACS, C. BARR, AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Association study of the adrenergic receptors and Childhood-Onset Mood Disorders in Hungarian families. Am J Med Genet B (Neuropsychiatr Genet), 2006, 141B:227–233 (IF: 4,463)

26. V MISENER, L GOMEZ, K WIGG, P LUCA, N KING, Á VETRÓ, E KISS, Z TAMÁS, J KENNEDY, M KOVACS, C BARR: Association of the IL-10 receptor 1 gene with childhood onset mood disorders. Am J Med Genet B (Neuropsychiatr Genet), 2006, 141B(7):724 (IF: 4, 463)

27. J. ADAMS, K. WIGG, N. KING, I. BURCESCU, Á. VETRÓ, E. KISS, L. BAJI, C. GEORGE, J. KENNEDY, M. KOVACS, C. BARR, AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Association study of Neurotrophic Tyrosine Kinase Receptor Type 2 (NRTK2) and Childhood-Onset Mood Disorders. Am J Med Genet B (Neuropsychiatr Genet), 2005, 132B:90–95 (IF: 3, 521)

28. I. BURCESCU, K. WIGG, N. KING, Á. VETRÓ, E. KISS, L. KÁTAY, J. KENNEDY, M. KOVACS, C. BARR, AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Association study of CREB1 and Childhood-Onset Mood Disorders. Am J Med Genet B (Neuropsychiatr Genet), 2005, 137B:4550 (IF: 3, 521)

29. J. STRAUSS, C. BARR, C. GEORGE, B DEVLIN, Á. VETRÓ, E. KISS, I. BAJI, N. KING, S. SHAIKH, M. LANKTREE, M. KOVACS, J. KENNEDY, AND THE INTERNATIONAL CONSORTIUM FOR CHILDHOOD-ONSET MOOD DISORDERS: Brain-derived neurotrophic factor variants are associated with childhood-onset mood disorder: confirmation in a Hungarian sample. Mol Psychiatry, 2005, 10:861–867 (9.335)

30. MAYER L., KISS E., BAJI I., SKULTÉTI D., VETRÓ Á.: Demográfiai jellemzők és pszichopathológiai rizikótényezők összefüggésének vizsgálata általános iskolás populációban. Fejlesztő pedagógia, 2005, 16(5–6):49–54.

31. J CSORBA J, S RÓZSA, J GÁDOROS, A VETRÓ, E KACZWINSZKI, E SARUNGI, J MAKRA, K KAPORNAI: Suicidal depressed vs. Non-suicidal depressed adolescents: differences in recent psychopathology. J Affect Disord 2003, 74: 229–236 (3.078)

32. J CSORBA, S RÓZSA, Á VETRÓ, J GÁDOROS, J MAKRA, E SOMOGYI, E KACZVINSZKY, K KAPORNAI: Family and School – related stresses in depressed Hungarian children. Eur Psychiatry, 2001, 16:18–26 (IF:1,273)

Characteristics of and Risk Factors for Childhood-onset Depression in Clinically Referred Hungarian Children and Adolescents

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Abstract

This article reports on the genetic and psychosocial risk study of childhood-onset depression (COMD) in a very large clinically referred sample in Hungary. The sample included 723 children with major depressive disorder (mean age 11.26 years, standard deviation [SD] 2.09, range seven to 14.9 years) recruited from 23 clinical sites across the country. Psychiatric evaluations were conducted via a semi-structured interview and diagnoses were assigned by *Diagnostic and Statistical Manual of Mental Disorders-IV* (DDSM-IV) criteria. Developmental and life events were queried via a structured questionnaire. Children and parents also completed self-rated questionnaires that assessed various symptoms, aspects of temperament, emotion regulation and quality of life. We report on clinical and depressive symptom presentation as a function of age, suicidality and types of sleep disturbance. We summarise findings on the relations of: emotion regulation and temperament to suicidal behaviours; early developmental characteristics and the onset-timing and severity of COMD; life events and COMD status; psychiatric co-morbidity and health risk behaviours such as smoking and drinking; mother–child agreement about depressive symptoms and quality of life of depressed children; and putative genetic contributors to COMD. Systematic and reliable empirical data and information on the defining characteristics of and risk factors associated with COMD can inform the design of preventative interventions and can also be useful to clinicians who treat children with these conditions.

Keywords

Childhood-onset depression (COMD), risk factors, symptom, severity

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This study was designed to investigate genetic and psychosocial risk factors in a large clinically referred sample of children who had their first depressive episode before 15 years of age. Cases were recruited between 1 December 1998 and 31 June 2007. Patients were screened at 23 child psychiatry centres in Hungary, the catchment areas of which covered about 80% of all referred patients in the nation. Altogether, 28,533 children presenting with various psychiatric problems were screened and 1,702 passed further screens (using pre-determined cut-off on self- and proxy-reported mood questionnaires). Consent was obtained from 1,096, of whom 905 had major depressive disorder (MDD) according to *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV) criteria. We obtained samples for genetic analyses from 866 children and their parents.[1] Yearly follow-ups (across five years) were conducted via mailed questionnaires to monitor new episodes or onset of MDD. Across all years, a total of 92.9% of the monitored cases returned the questionnaires based on which subjects with probable new/recurrent episodes entered the evaluation and diagnostic process.

In this article we summarise published findings to date. Subjects in the various articles are subsamples of the total study sample; the varying sample sizes reflect the data that were available. For details, please see each of the original articles, referenced at the end of the article.

Method

Children were considered to be potential subjects if they met the following eligibility criteria: between seven and 14.9 years of age, presence of DSM-IV MDD, one available biological parent, sibling between seven and 16.9 years of age, not mentally retarded and free from major systemic medical disorders. We obtained signed informed consent from the parent and assent from the child before initial evaluation. The total sample included 723 children. Mean age at initial examination was 11.26 years (standard deviation [SD] 2.09) and 45.8% were girls. Mean age at the onset of depression was 10.11 years (SD 2.33). The average number of MDD episodes was 1.33 (SD 0.61, range one to six). Altogether, 19.5% had mild depression, 46.9% had moderate depression and 33.6% had severe depression. Twenty-eight per cent had a history of inpatient psychiatric hospitalisation and 61% had been prescribed psychotropic medication. The age of the biological mothers was 36.7 years on average (SD 6.0), they had a mean of 11.4 years of education (SD 4.3) and 37.8% came from broken families. Parent-reported financial situation was average in 59.3% of cases, below average in 31.5% of cases and above average in 9.1% of cases.

Measurements

Subjects were evaluated by a semi-structured psychiatric interview, the Interview Schedule for Children and Adolescents – Diagnostic

Version (ISCA-D).[2] It includes most DSM-IV axis I diagnoses and some DSM-III disorders. The clinician first interviews the parent about the child's symptoms and then the child, then generates an overall rating for each symptom based on the information provided by each informant. Final diagnoses were reached by consensus diagnostic procedure by best-estimate diagnosticians.[3] Psychiatric evaluations were conducted by trained child psychiatrists and psychologists. The Intake General Information Sheet (IGIS), completed based on an interview with the parent, is a comprehensive data form covering demographic, family, developmental issues, physical health, psychosocial history and life events. Parents and children also completed a variety of questionnaires. In this article, we report findings based on the following instruments: parent-rated Emotionality Activity Sociability (EAS) Temperament Questionnaire,[4] which measures four temperament dimensions: emotionality, activity, sociability and shyness; self-rated Feelings and Me child questionnaire,[5] which served as an index of children's self-regulatory responses to dysphoria and distress; child- and parent-rated Invertars zur Erfassung der Lebensqualität bei Kindern und Jugendlichen (ILK), which inquires about quality of life in seven domains;[6] and parent-rated Beck Depression Inventory (BDI),[7] which measured maternal depressive symptoms.

Results

One of the enduring questions about childhood depression is whether symptoms differ as a function of age and sex. We addressed this topic[8] given that few studies had sufficiently large samples to examine developmental differences in rates of specific symptoms. Since many depressed youths also have anxiety disorders[9] and there is an association between somatic symptoms and anxiety in childhood,[10] we also looked at the relationship between somatic complaints and depression.

Consistent with previous studies,[11,12] we found that the frequency of several neuro-vegetative symptoms, including hypersomnia, psychomotor retardation and fatigue, increased with age. This pattern was accompanied by a significant increase in depressed mood, thoughts of death and suicidal ideation and a reduction in rates of psychomotor agitation. Specifically, our results indicate that the presentation of depression becomes more neuro-vegetative as children transition from childhood into adolescence. Our findings are not entirely consistent with DSM-IV criteria, according to which irritability can substitute for depressed mood as a required symptom[13] in childhood. Depressed mood and irritability were relatively frequent across all ages, with more than 60% of patients displaying them. In contrast, anhedonia was relatively infrequent across all age groups, with rates below 50%. This suggests that anhedonia, and not depressed mood, is the least frequent core symptom in depression among children and adolescents, while irritability is significantly more common, often occurring in conjunction with rather than as a substitute for depressed mood.

Approximately 90% of depressed adults[14] and at least two-thirds of depressed children have sleep complaints,[15–17] but it is not clear whether sleep-disturbed children differ from sleep-undisturbed peers in terms of clinical presentation of the illness and whether these features differ across depressed children with insomnia, hypersomnia or both. In addressing this issue[18] we found that 72.6% of our sample had experienced sleep problems during the past month: 53.5% had insomnia, 9.0% had hypersomnia and 10.1% had both, the prevalence being significantly higher in girls. Youths with both sleep disorders were more likely to have recurrent depressive episodes, longer illness duration and highest depression severity compared with children with one disturbance only. Sleep-disturbed children had more co-morbid anxiety disorder and less oppositional defiant disorder. Depressed children with both sleep disorders may represent a severe subtype of depression with circadian rhythm disorders or sleep–wake cycle abnormalities, which may cause or worsen other depressive symptoms.

Although the relationship between suicidal behaviour and depression have been extensively studied across the age span, little is known about gradations of suicidality as specified in the DSM-IV. Therefore, we examined the prevalence of recurrent thoughts of death, suicidal ideation, suicidal plans and suicide attempts in our sample and their relationship to various clinical characteristics of the MDD episodes.[19] Lifetime prevalence were the following: recurrent thoughts of death 67.5%, suicidal ideation 47.6%, suicidal plans 29.8% and suicide attempt 11.6%. For girls, all four suicidal behaviours tended to increase with age, while for boys none had significant differences across age groups. Suicidal youths were more severely depressed, showed more feelings of worthlessness and inappropriate guilt and showed a more distinct intensity of depressed mood. Suicide attempters were most likely to have a history of psychiatric hospitalisation. The highest prevalence of depressed mood was found in attempters (94.5%), followed by youths with suicide ideations (88%), recurrent thoughts of death (74.5%) and suicide plan (73.5%). Suicidal youths were more likely to evidence anxiety disorders and conduct disorder than non-suicidal peers. There were no differences in co-morbid disorders across various forms of suicidality. Depressed mood, psychomotor agitation, feelings of worthlessness, co-morbid anxiety and conduct disorder were independent and significant correlates of at least one form of suicidal behaviour. Worthlessness was the only symptom related to all four suicidal behaviours, which suggests that it may play a central role in increasing suicidality.

Although many (but not all) depressed youths exhibit some form of suicidal behaviour at some point in their lives, a logical further question is whether there are particular personality characteristics of depressed youths that increase the risk of suicidal behaviour. We explored this possibility[20] by examining the relationship between temperament and emotion self-regulation with DSM-specified suicidality.[13] Depressed non-suicidal and suicidal children had similar levels of negative emotionality. Non-suicidal children and children with recurrent thoughts of death were very similar on the four dimensions of temperament (emotionality, activity, sociability and shyness). Depressed children characterised by many maladaptive ways of regulating their own dysphoria were likely to have definite suicidal behaviours (ideation, plans or attempts). In contrast, a more extensive repertoire of adaptive regulatory responses to dysphoria signalled a decreased likelihood of specific suicidal behaviours. Youngsters who had attempted suicide had considerably higher maladaptive emotion regulation than other children. We detected interaction terms between emotion regulation and shyness as well as sociability for suicide attempters. These findings may suggest that when some temperament traits become extreme, emotion regulatory competence (or the lack thereof) has little impact on the odds of suicide attempt, but in the absence of extreme traits adaptive emotion regulation skills appear to serve as protective factors and lower the odds of attempted suicide.

As we noted above, about one-third of the children in our sample were rated by clinicians as having severe depression. Since depression severity has been implicated in the disorder's course and in treatment response, we examined whether early infant physiological characteristics could partly explain eventual MDD severity.[21] Specifically, we investigated whether peri-natal problems, developmental delay and difficult infant temperament render children vulnerable to earlier onset and more severe episodes of depression. However, we also took into consideration that the effects of risk factors may not be specific to MDD onset, but might also relate to the earliest internalising disorder (MDD, dysthymia or anxiety disorder). We found that difficult temperament predicted earlier onset of MDD and first internalising disorder, but its effect was ameliorated if the family was intact during early childhood. Its importance decreased as a function of age time. Peri-natal problems and developmental delay did not affect onset ages of disorders and none of the early childhood characteristics were associated with MDD episode severity. Difficult temperament was also associated with earlier dysthymia or anxiety disorder as well as MDD, indicating lack of specificity to MDD. Our findings highlight that even in a vulnerable sample, the putative negative effects of early infant characteristics are not immutable but can be ameliorated by family resources.

Another one of the enduring questions in the field has concerned the contribution of life events and stresses to childhood depression. Although we could not investigate causal relationships because our entire sample had MDD, we did examine developmental trends in life events and compared our sample's life event history with that of a comparison group of peers who we recruited from public schools.[22] The comparison sample included 724 children (399 girls); mean age was 10.8 years (SD 2.2 years). We queried both samples for 26 stressful life events. We examined both individual life events and five life-event groups (parental health, death, sociodemographic, intra-familial life events and a miscellaneous group containing abuse, teasing, police contact and suspension from school).

Depressed children experienced twice as many life events as the normative group. The number of life events increased with the age of the child in the normative group, while it was independent of age in the depressed group. Almost all individual life events were experienced significantly more often in the depressed group. Three life event groups increased the odds of MDD significantly: parental illness doubled the odds, intra-familial life events almost tripled the odds regardless of the child's age and death increased the odds by almost one-fifth. Repeated teasing and abuse increased the odds of MDD regardless of the age and gender of the child. Natural disaster, mother's serious somatic illness, father's psychiatric hospitalisation and the death of a close relative increased the chance of depression in children ≤11 years of age. Parental unemployment proved to be a risk factor in the older age group. Parental divorce increased the odds by five to 10 times in younger girls, but this effect decreased in older girls. Family arguments increased the chance of developing MDD with increasing age.

The association between mood disorders and certain risk behaviours such as smoking, drinking and drug abuse also deserves further attention.[23,24,25] We investigated these behaviours in a sample that, besides depressed probands, also included siblings with mood disorders.[26] MDD was present in 51%; the rest had minor depression, adjustment disorder or mood disorder not otherwise specified. The rate of co-morbid disorders were 76%. Thirty per cent had anxiety disorder, 18.4% had attention-defecit–hyperactivty disorder (ADHD), 14.7% had enuresis, 11.8% had tic disorder and 11% had dysthmia. The prevalence of smoking and drinking was 19.9 and 24%, respectively. The frequency of drug use was between 7 and 9.4% depending on the type of drug. Alcohol consumption was more frequent among girls. The presence of MDD increased the odds of drinking (odds ratio [OR] 2.7), while co-morbid anxiety disorder increased it further (OR 3.48). Generalised anxiety disorder and social phobia increased the odds most (OR 8.4 and 3.84, respectively). Co-morbid behavioural problems, most notably conduct disorder, enhanced the likelihood of smoking (OR 3.55).

It is unambiguous in the literature that physical illnesses reduce quality of life (QoL) in children. The effect of psychiatric illnesses was not extensively studied in this age group. Furthermore, few studies investigated parent–child agreement on children's quality of life. We compared mother- and child-reported QoL of the depressed sample with a group of non-depressed peers recruited from public schools.[27] Subjects of the comparison sample included 1,695 youngsters without clinically significant depressive symptoms. We refer to the original article for precise demographic characterisations of the samples.

QoL scores were lower in the depressed sample regardless of the reporter. Mothers of depressed children rated lower satisfaction for their children in the areas of school, family, peer relations and mental health than their offspring. Mothers of non-depressed children scored significantly higher on the QoL of all domains than their children. Presence of depression in the child decreased mother–child agreement, while older age had only a tendency for improved concordance. The total QoL scores of mothers and children correlated more closely in the non-depressed sample. Our results support the tendency of parents to relate more serious negative effects to depressive disorder than their children and to undervalue their non-depressed offspring's problems compared with non-depressed children.

As we noted previously, agreement is generally low to moderate between symptom reports of mothers and children, which might present as difficulty during the assessment process. Factors that influence individual reports and agreement have also been of interest.[28,29] We aimed to investigate and compare mother- and child-reported severity of child depressive symptoms.[30] Mothers reported higher symptom severity for boys, while parent-reported severity did not differ significantly from self-reports in girls. At the same time, girls endorsed significantly higher severities in self-reports than boys. Child-reported severity was associated with child sex, age and maternal depression and severity increased as girls got older. Mother-reported symptom severity increased with higher maternal depression scores; more educated mothers reported more severe cognitive symptoms for children and less severe vegetative symptoms for girls. Mother–child agreement was predicted only by the age of the child: older children and their mothers were more likely to agree than younger ones. Even though more depressed mothers reported more severe depressive symptoms in children, children of more depressed mothers themselves reported higher levels of mood symptoms for themselves, suggesting that they are at an increased risk of depression themselves.

The role of genetic deficits in the aetiology of childhood-onset mood disorders (COMD) is supported by compelling evidence. The genetic part of our study intended to replicate earlier findings and investigate new possibilities. Deficits in neural plasticity have been suggested to underlie the development of depression. The receptor neurotrophic tyrosine kinase B and its ligand, brain-derived neurotrophic factor (BDNF), play essential roles in neural plasticity. Messenger RNA (mRNA) expression of both of these genes has been shown to be influenced by stress and chronic antidepressant treatment. Markers in BDNF[31] and the neurotrophic tyrosine kinase receptor 3 (located on 15q25.3–q26.2, a region linked to early-onset mood disorders) were significantly associated with COMD in this sample;[32] however, the neurotrophic tyrosine kinase receptor 2 (NTRK2) was not.[33]

Results for cAMP-responsive element-binding protein (a transcription factor that increases the expression of key growth factors involved in synaptogenesis and neurogenesis) do not support previous evidence for this gene as a major factor contributing to depression.[34] Disturbances in stress hormones have been implicated in mood disorders, in particular in the hyperactivity of the hypothalamic–pituitary–adrenal axis (HPA). A G-protein-coupled receptor, vasopressin V1b, was found to be implicated in the aetiology of mood disorders, particularly in females.[35]

The existence of sex-specific aetiological factors in depressive disorders related to oestrogen was examined by genotyping 11 single nucleotide polymorphisms (SNPs) spanning the oestrogen receptor alpha gene. Three of the examined SNPs were found to be associated with COMD.[36] No evidence for association was observed with the adrenergic receptor genes (a1B, b3, a2C, a2A and b1) in this sample.[37] Genes involved in the regulation of inflammatory cytokine activity are considered to be strong candidates for involvement in genetic susceptibility to depressive disorder. Six key genes were tested (tumour necrosis factor [TNF], interleukin [IL]1A, IL1B, IL6, IL1RN and IL10); however, no association was observed.[38,39] Result of a genome scan using 405 microsatellite provided evidence for linkage with markers on two chromosomes (13q and Xq).[40] Within the 13q linkage region, we found suggestive evidence for association with markers in G72/G30,[41] genes previously associated with mood disorders. The gene for the X-linked orphan G-protein-coupled receptor in the X-linage region was not found to be associated with COMD.[42] No evidence of association was found between a functional polymorphism in the 5,10-methylenetetrahydrofolate reductase gene (MTHFR, an enzyme involved in the metabolism of folic acid) and COMD.[43] Polymorphisms in two serotonin receptor genes were investigated (HTR1B and HTR2A, and the serotonin transporter r SLC6A4) but no association was found with COMD.[44]

Conclusion

In this article we have summarised published findings from our study of the risk factors of childhood-onset depression (COMD). Knowledge of risk factors enables psychiatrists to pay special attention to vulnerable populations. By applying effective preventative methods early on, some of these disadvantages might be decreased and adoptive mechanisms initiated. It is important to imply and integrate the results of ongoing research into everyday practice. ■

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1. Vetró Á, Baji I, Benák I, et al., Planning, implementing, and course of the study Childhood-Onset Depression: the story of 13 years; experiences of grant preparation, writing, and research coordination in relation to an American NIMH research grant, *Psychiatr Hung*, 2009; in press.
2. Sherill J T, Kovacs M, Interview Schedule for Children and Adolescents (ISCA), *J Am Acad Child Adolesc Psychiatry*, 2000;39:67–75.
3. Maziade M, Roy M A, Fournier JP, et al., Reliability of best-estimate diagnosis in genetic linkage studies of major psychoses: results from the Quebec pedigree studies, *Am J Psychiatry*, 1992;149(12):1674–86.
4. Buss A H, Plomin R, *Temperament: Early developing personality traits*, Hillsdale, NJ: Lawrence Erlbaum Associates, Inc., 1984.
5. Kovacs M, The Feelings and Me emotion regulatory strategy utilization questionnaires, Unpublished manuscript, University of Pittsburgh School of Medicine, 2000.
6. Mattejat F, Jungmann J, Meusers M, et al., Das inventar zur erfassung der lebensqulität bei kindern und jugendlichen (ILK) – eine pilotstudie, *Z Kinder Jugendpsychiat Psychother*, 1988;26:174–82.
7. Beck AT, Steer RA, Garbin MG, Psychometric Properties of the Beck Depression Inventory: Twenty-Five Years of Evaluation, *Clin Psychol Rev*, 1988;8:77–100.
8. Baji I, Lopez-Duran NL, Kovacs M, et al., Age, sex, somatic complaints, and the symptom presentation of childhood depression in a Hungarian clinical sample, *Clin Psychiatry*, 2009; in press.
9. Kovacs M, The course of childhood onset depressive disorders, *Psychiatr Ann*, 1996;26:326–30.
10. Ginsburg GS, Riddle MA, Davies M, Somatic symptoms in children and adolescents with anxiety disorder, *J Am Acad Child Adolesc Psychiatry*, 1994;33:1223–35.
11. Ryan N D, Puig-Antich J, Ambrosini P, et al., The clinical picture in major depression in children and adolescents, *Arch Gen Psychiatry*, 1987;44:854–61.
12. Mitchell J, McCauley E, Burke PM, et al., Phenomenology of depression in children and adolescents, *J Am Acad Child Adolesc Psych*, 1988;27:12–20.
13. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (4th edition)*, Washington, DC, 1994.
14. Tsuno N, Besset A, Ritchie K, Sleep and depression, *J Clin Psychiatry*, 2005;66:1254–69.
15. Ivanenko A, Crabtree VM, Gozal D, Sleep and depression in children and adolescents, *Sleep Med Rev*, 2005;9:115–29.
16 Dahl RE, Ryan ND, Matty MK, et al., Sleep onset abnormalities in depressed adolescents, *Biol Psychiatry*, 1996;39:400–410.
17. Gruber R, Brouillette RT, Towards an understanding of sleep problems in childhood depression, *Sleep*, 2006;29: 418–20.
18. Xianchen L, Buysse DJ, Gentzler AL, et al., Insomnia and hypersomnia associated with depressive phenomenology and comorbidity in childhood depression, *Sleep*, 2007;30(1): 83–90.
19. Xianchen L, Gentzler AL, Tepper P, et al., Clinical features of depressed children and adolescents with various forms of suicidality, *J Clin Psychiatry*, 2006;67:1442–50.
20. Tamás Zs, Kovacs M, Gentzler AL, et al., The relations of temperament and emotion self-regulation with suicidal behaviour in a clinical sample of depressed children in

Hungary, *J Abnorm Child Psychol*, 2007;35(4):640–52.
21. Kapornai K, Gentzler AL, Tepper P, et al., International Consortium for Childhood-Onset Mood Disorders, Early developmental characteristics and features of major depressive disorder among child psychiatric patients in Hungary, *J Affect Disord*, 2007;100(1–3):91–101.
22. Mayer L, Lopez-Duran NL, Kovacs M, et al., Stressful life events in a clinical sample of depressed children in Hungary, *J Affect Disord*, 2008
23. Rao U, Ryan ND, Dahl RE, et al., Factors associated with the development of substance use disorder in depressed adolescents, *J Am Acad Child Adolesc Psychiatry*, 1999;38: 1109–17.
24 Hanna EZ, Yi H, Dufour MC, The relationship of early-onset regular smoking to alcohol use, depression, illicit drug use, and other risky behaviours during early adolescence: results from the youth supplement to the Third National Health and Nutrition Examination Survey, *J Subs Abuse*, 2001;13:265–82.
25 Silberg J, Rutter M, D'Onofrio B, Eaves L, Genetic and environmental risk factors in adolescent substance use, *J Child Psychol Psychiatry*, 2003;44:664–76.
26. Kiss E, Pikó B, Vetró Á, Frequency of smoking, drinking and substance use and their relationship to psychiatric comorbidity in depressed child and adolescent population, *Psychiatr Hung*, 2006;21(5):371–8.
27. Kiss E, Kapornai K, Baji I, et al., Assessing quality of life: mother-child agreement in depressed and non-depressed Hungarian populations, *Eur Child Adolesc Psychiatry*, 2009; in press.
28. De Los Reyes A, Kazdin AE, Measuring informant discrepancies in clinical child research, *Psychol Assess*, 2004;16:330–34.
29. De Los Reyes A, Kazdin AE, Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendation for further study, *Psychol Bull*, 2005;131:483–509.
30. Kiss E, Gentzler AL, George C, et al., Factors influencing mother-child reports of depressive symptoms and agreement among clinically referred depressed youngsters in Hungary, *J Affect Disord*, 2007;100(1–3):143–51.
31 Strauss J, Barr CL, George CJ, et al., Brain-derived neurotrophic factor variants are associated with childhood-onset mood disorder: confirmation in a Hungarian sample, *Mol Psychiatry*, 2005;10:861–7.
32. Feng Y, Vetró A, Kiss E, et al., International Consortium for Childhood-Onset Mood Disorders, Association of the Neurotrophic Tyrosine Kinase Receptor 3 (NTRK3) Gene and Childhood-Onset Mood Disorders, *Am J Psychiatry*, 2008;165:610–16.
33. Adams JH, Wigg KG, King N, et al., Association Study of Neurotropic Tyrosine Kinase Receptor Type 2 (NRTK2) and Childhood-Onset Mood Disorders, *Am J Med Genet*, 2005;132B:90–95.
34. Burcescu I, Wigg K, King N, et al., Association study of CREB1 and childhood-onset mood disorders, *Am J Med Genet B Neuropsychiatr Genet*, 2005;137B:45–50.
35. Dempster EL, Burescu I, Wigg K, et al., Evidence of on association between the vasopressin V1b receptor gene (AVPR1B) and Childhood-onset mood disorders, *Arch Gen Psychiatry*, 2007;64:1189–95.
36. Mill J, Kiss E, Baji I, et al., The International Consortium for Childhood Onset Mood Disorders, Association study of the estrogen receptor alpha gene (ESR1) and childhood-onset mood disorders, *Am J Med Genet B Neuropsychiatr Genet*, 2008;147B:1323–6.
37. Urcescu I, Wigg K, Gomez L, et al., International Consortium for Childhood-Onset Mood Disorders, Association study of the adrenergic receptors and childhood-onset mood disorders in Hungarian families, *Am J Med Genet B Neuropsychiatr Genet*, 2006;141(3):227–33.
38. Misener VL, Gomez L, Wigg KG, et al., The International Consortium for Childhood-Onset Mood Disorders, Cytokine Genes TNF, IL1A, IL1B, IL6, IL1RN and IL10, and Childhood-Onset Mood Disorders, *Neuropsychobiology*, 2008;58:71–80.
39. Misener V, Gomez L, Wigg KG, et al., Association of the IL-10 receptor 1 gene with childhood onset mood disorders, *Am J Med Genet B Neuropsychiatr Genet*, 2006; 141B(7):724.
40. Wigg K, Feng Y, Gomez L, et al., Genome scan in sibling pairs with juvenile-onset mood disorders: Evidence for linkage to 13q and Xq, *Am J Med Genet B Neuropsychiatr Genet*, 2008;
41. Gomez L, Wigg K, Feng Y, et al., G72/G30 (DAOA) and juvenile-onset mood disorders, *Am J Med Genet B Neuropsychiatr Genet*, 2008
42. Feng Y, Wigg K, King N, et al., GPR 50 is not associated with childhood-onset mood disorders in a large sample of Hungarian families, *Psychiatr Genet*, 2007;6:347–50.
43. Dempster E, Kiss E, Kapornai K, et al., No evidence of association between a functional polymorphism in the MTHFR gene and childhood onset-mood disorders, *Mol Psychiatry*, 2007;12:1063–4.
44. Shaikh SA, Strauss J, King N, et al., International Consortium for Childhood-Onset Mood Disorders, Association study of serotonin system genes in childhood-onset mood disorder, *Psychiatr Genet*, 2008;18(2):47–52.