Emotion regulation in children and adolescents with major depressive disorder and comorbid anxiety disorder

Ph.D. Thesis

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3. Bylsma LM, Yaroslavsky I, Kiss E, Kapornai K, Halas K, **Dochnal R**, et al. Familiality of mood repair responses among children and adolescents with and without histories of depression. *Cogn Emot* (2015) 10:1–10. (IF:2.688)

ABSTRACTS RELATED TO THE THESIS

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ABSTRACT

Introduction and aims

Major depressive disorder (MDD) is a common disorder in children and adolescents. MDD significantly impairs school performance, and social relationshis, enhances substance abuse, and importantly suicidal behavior. Several etiological factors play a complex role in the development of childhood-onset depression. A specific individual factor that has been attracting interest for its role in depressive disorder is the way an individual self-regulates negative emotions.

We aimed to explore the role of emotion regulation (ER) in the development of childhood-onset depression and the effect of comorbid anxiety disorders on the ER profile of patients with depression histories. As a first step, we examined the possible relationship between ER and depression comparing the ER repertoire of depressed and healthy control groups of youngsters. Since the presence of comorbid anxiety disorders is clinically significant in terms of prevention, therapy, and prognosis, we extended our research to test whether comorbid anxiety has an effect on the ER profile of depressed individuals. We specifically aimed to compare the adaptive and maladaptive ER repertoires of youngsters with histories of MDD with and without comorbid anxiety and to examine whether certain ER response clusters (Cognitive, Social, Behavioral/Physical) characterize comorbid children and adolescents.

We hypothesized that 1) depressed youths will evidence ER deficits relative to controls. Then, we aimed 2) to compare the adaptive and maladaptive ER repertoires with histories of MDD with and without comorbid anxiety and 3) to examine whether certain ER response clusters (Cognitive, Social, and Behavioral/Physical) characterize comorbid children and adolescents.

Materials and Methods

We analyzed data on 181 healthy controls and 217 youth (11–18 years old) with depression history: 85 subjects with lifetime anxiety comorbidity (comorbid group) and 132 without lifetime anxiety (non-comorbid group). Psychiatric diagnosis was established by a comprehensive *Diagnostic and Statistical Manual of Mental Disorders* (DSM) IV-based diagnostic procedure. ER strategies were examined *via* the self-rated “Feelings and Me” Child version questionnaire (FAM-C).

Results

In the first part of our study, we analyzed the ER strategies of youths with history of MDD compared to healthy, never depressed controls. We found that our probands with depression histories reported higher rates of maladaptive and lower rates of adaptive ER responses compared to controls across all ER response domains (Total, Cognitive, Social, Physical/Behavioral). Another aim of our study was to examine whether anxiety disorder as a comorbid condition further worsens the impaired ER in youngsters with histories of depression. The comorbid group used maladaptive ER strategies significantly more frequently than the non-comorbid youngsters. The Behavioral/Physical and Social ER skills, especially those reflecting social withdrawal and self-harm, were responsible for the higher maladaptive scores.

Conclusion

The results of our current study extended previous findings in several ways: 1) we examined adaptive and maladaptive ER strategies in multiple domains; 2) we used a large clinical sample of youngsters with childhood-onset depression, which was carefully diagnosed by trained psychiatrists and psychologists. The ability to use adaptive cognitive strategies to regulate emotion in case of dysphoria may play a role in the development of childhood-onset depression. Furthermore, anxiety comorbidity leads to a more impaired profile in the social and behavioral/physical emotional regulation domains. Our research also shows that the ER repertoire is influenced not only by the underlying psychopathology but also by sex and the presence of an internalizing disorder.

1. Introduction

1.1. The burden of Major Depressive Disorder

Major depressive disorder (MDD) is a highly prevalent, recurrent, and potentially chronic disorder (Ferrai et al, 2013). Furthermore, MDD is associated with reduced adaptive functioning and lower quality of life (Kessler et al, 2005, 2003, 1998). The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for MDD episode include a sustained, at least a 2-week period of time, where five of the following symptoms are present most of the day, nearly every day: depressed mood (may be an irritable mood in children), loss of interest or pleasure, increased or decreased appetite, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, excessive guilt, decreased concentration, and suicidal thoughts. At least one of the symptoms must be either depressed/irritable mood or loss of interest. The symptoms must cause significant distress or impairment in functioning (APA, 2013).

Notably, MDD is the leading cause of disability worldwide and is a major contributor to the overall global burden of disease (Lopez and Murray, 1998). Indeed, according to the Burden of Disease List major depression is at third place and it is projected that, MDD might become higher on the list, with one of the greatest burden of disease in Europe by 2030 (WHO, 2011). Moreover, as Berndt et al. (2000) summarized: earlier onset of major depression seems to have severe consequences in adulthood in different domains such as greater symptom severity, more impaired familial, social, and occupational functioning, poorer quality of life, greater medical and psychiatric comorbidity, more lifetime depressive episodes and suicide attempts.

1.2. Childhood-onset MDD

Major depressive disorder has become more common in children and adolescents. It significantly impairs school performance, and social relationships, enhances substance abuse, and importantly suicidal behavior (Ryan, 2005; Birmaher et al., 1996, WHO 2011). The prevalence of MDD increases with age, with a lower point prevalence in childhood (0.4-2.5%) and higher in adolescence (0.4-8.3%) (Birmaher et al. 1996), and a lifetime prevalence of 4-5% in children and 13-15% in adolescents (Vetró et al. 1997). A European survey found that 5%

of 16-year-old girls and 1.3% of boys met the criteria for MDD (Kopp et al. 1997). By the age of 18, 20-25% of adolescents have had an episode of MDD (Lewinsohn et al. 1993). Several national and international studies also confirm that adolescent lifetime prevalence is almost the same as in adulthood (17-20%), suggesting that adult depression often begins in adolescence (Szádóczky 2000, Wittchen et al. 1998). Depression in youth on average lasts several months and tends to be recurrent. Within 2 years of MDD recovery, approximately 40% of child and adolescent patients will experience a recurrent episode (Kovacs et al, 1984). Based on clinical studies 60% of depressed kids/adolescents will have MDD in adulthood as well (Birmaher et al. 1996).

Similarly, in community population aged 21 21.4% of individuals with mood disorders experienced an MDD episode in their life earlier. 50% of adolescents with MDD will have at least 1 more MDD episode by age 24.

There are few studies on the general mental health of young people in Hungary, so there is little data available on the prevalence of depressive symptoms in childhood, despite the fact that the Child Depression Questionnaire (CDI) has been validated in Hungary as well (Csorba et al. 1994a, Rózsa et al. 1999, Pikó and Fitzpatrick 2001, Vetró et al. 1997). In particular, there are few studies on the prevalence and pathomechanism of depressive symptoms in children under 11 years of age. The school-age population (11.5-17.5 y.o.) has been regularly surveyed since 1985 by the WHO at international level including Hungary (Health Behavior of School-Aged Children, HBSC). In the 2002 survey, 18% of boys and 30% of girls had high scores on the CDI short version questionnaire indicating the presence of depressive symptoms (Aszmann, 2003). Data from two further studies represent the school-age children (Hungarostudy) conducted in 1988 and 1995 were obtained exclusively from the Hungarian population aged 15 years and older. A significant increase was found in the prevalence of major depressive symptoms, particularly in those requiring treatment in the 1995 survey, compared with the previous survey in 1988 (Kopp et al. 1997). Data from the Hungarostudy 2002 showed no significant change in the prevalence of depressive symptoms between 1995 and 2002 (Purebl and Kovacs, 2006).

Indeed, according to international data, youths with depression have a high incidence of suicidal behavior (Harrington, 2001, Pfeffer, 1991). The number of non-fatal suicide attempts in this age group is at least 10-100 times the number of completed suicides (Shain, 2007). In a Hungarian depressed, 7-14 y.o. population the proportion of suicidal ideation was 43.7% among girls and 36.5% among boys (Baji et al, 2009).

Based on all the above major depressive disorder imposes a major burden on individual families and societies as well, thus better understanding the factors that might be involved in the development and recurrence of MDD would be crucial in terms of individualized early intervention.

1.3. Emotion Regulation and Major Depression

Several etiological factors play a complex role in the development of childhood-onset depression, including genetic, biochemical, endocrine, social, socioeconomic, psychologic, and environmental factors (Birmaher et al, 1996; 2007, Paykel, 2003, Kapornai and Vetró, 2008). Indeed, children may have a pre-existing vulnerability (eg. genetic, biochemical, temperament) that interacts with different environmental, and psycho-social stressors (eg. family disharmony, separation, domestic violence, abuse, school difficulties, social isolation, chronic illness) leading to the onset of the disorder (Charles and Fazeli, 2017).A specific individual factor that has been attracting interest for its role in depressive disorder is the way an individual self-regulates (modulates) negative emotions (Adrian et al, 2011, Davidson et al, 2002, Gross, 1998). Emotion regulation (ER) refers to maintaining or accentuating, as well as inhibiting or subduing emotional arousal, by modifying the dynamic and temporal features of a given emotion (Thompson, 1994). Also, regulatory processes or strategies are anchored in internal neuro-biologic systems, occur in a social context, and include learned strategies of self-management as well as control of the external environment. (Thompson, 1994). Sadness and dysphoria - the crucial symptoms of major depression – are the predominant negative emotions experienced by the individuals. The impaired to reduce sadness and dysphoria is a key problem for depressed and depressed-prone individuals (Kovacs and Yaroslavsky, 2014). According to Cole et al. (2004), ER serves to attenuate, diminish, maintain, or prolong and strengthen the given emotion (Cole et al., 2004). ER involves interrelated self-regulatory response domains (cognitive, behavioral, and social) that can change the activated emotion by modulating its valence, intensity, or time course. Emotion self-regulation responses start to develop in early childhood, and build up over time being shaped by several factors: temperament of the child, parent-child relationship, social interactions and experiences, and the child's cognitive capacity (Gross et al, 1995). The ER profile includes different regulatory domains (eg. social cognitive, behavioral). The social domain of ER has been studied in mother-infant interactions among humans and animal species (Hofer, 1994). For example, mothers who are generally aware of and positively responsive to their child's emotions facilitate the development of adaptive

regulatory skills (Calkins, 1994). Social agents are important sources of ER. Experiences of early regulatory interactions are integrated into a network of mental representations, which then influence the general patterning of social relationships and serve as prototypes for interpersonal contact to regulate emotions in later years. (Hofer, 1994). The cognitive and behavioral domains of ER involve diverse processes and strategies. In infancy, certain cognitive processes serve regulatory functions in general ways (Thompson, 1994). With maturation, cognitive processes become more complex, increasingly psychological oriented, and are involved in learning emotion display rules. Children become aware that distress can be regulated by thinking about positive events, electing to engage in some behavior, or re-interpreting the meaning of stimuli (Thompson, 1994). By late childhood, at around age 12 or so, cognitive features become stable predictors of youngsters' emotional well-being (Nolen-Hoeksema et al, 1992).

The ability to regulate emotions and attenuate negative emotions has been shown to play an important role in adjustment and is considered fundamental to healthy child development and functioning (Gross and Thompson, 2007, Gross and John, 2003, Calkins and Dedmon, 2000, Cole et al, 2004, Thompson, 1994, Zeman 2006). In general ER strategies have been categorized as adaptive or maladaptive (Aldao et al., 2010). Appropriate (adaptive) ER strategies (e.g., distraction, cognitive reappraisal, and seeking interpersonal support) might lead to the emergence of adequate emotions, attenuate dysphoria, contribute to mental and physical health, to the development and maintenance of peer relationships and social functioning (Joormann et al., 2007, Kovacs et al., 2009, Zeman at al 2006, Yaroslavsky et al., 2013). Adaptive ER skills increase in number parallel to cognitive development and socialization process during mid to late childhood (Yap, 2007). Maladaptive ER strategies or responses exacerbate rather than ameliorate the dysphoric mood, prolong and aggravate dysphoria and are risk factors in the development and maintenance of several psychiatric disorders (Schafer et al, 2016, Joormann and Gotlib, 2010, Kovacs et al., 2009). Again, ER – both adaptive and maladaptive - can involve cognitive processes, overt behaviors, interpersonal interactions, or different physical senses (see: Kovacs and Yaroslavsky., 2006).

During the development of the child, ER repertoire can be easily operationalized, instructed, and modified. Therefore, early intervention is the key to treating depressed youths.

There is a large body of work on adults on the emotion-cognition link and its role in coping with distress (eg. Bower, 1981, Lazarus, 1991). Failure to regulate emotions by resorting to dysfunctional cognitive strategies has been theorized to be a specific risk factor for depressive disorders (Nolen-Hoeksema, 1995, Persons and Miranda, 1992). These are more and

more research results regarding the connection between ER and depression in the pediatric population as well. It is documented that, depressed youngsters utilize ineffective ER repertoires using a greater number of maladaptive strategies and fewer adaptive ones than healthy controls (Aldao et al., 2010, Bylsma et al., 2015). The study by Kovacs et al. (2009), based on a clinical sample, indicated that maladaptive skills are correlated with a worsening of depression symptoms and increase the probability of recurrent depressive episodes. ER difficulties can persist even after depression has remitted. Our research group previously showed that both remitted and currently depressed young adult probands reported a greater number of maladaptive ER responses to sadness than did controls (Kovacs et al, 2009). In addition, younger depressed children (kindergarten to eighth grade) have been found to use maladaptive responses to regulate emotions more frequently than non-depressed children (Garber et al, 1995). Furthermore, the maladaptive response style to depressed mood also appears to increase the risk of suicidal behavior (Kovacs and George, 2020, Liu et al, 2009).

Learning about the emotion regulation profile of depressed and depression-prone children and adolescents may serve as important information in designing effective prevention and therapeutic interventions in childhood-onset depression.

1.4. Depression and anxiety comorbidity

Research has shown that depression and anxiety are highly correlated and are the most common comorbid mental disorders. Based on comprehensive epidemiological data, the estimated rate of comorbid anxiety disorders with depression in children and adolescents ranges from 30% to 75% (Angold et al, 1993, Cummings et al, 2014). Comorbidity estimates in clinical samples can be as high as 86% (Birmaher et al, 1996, Essau, 2008, Geller et al, 1985). According to studies reviewed by Angold et al (1999), each condition is more likely to occur in the presence of the other than alone.

Understanding the etiology, and the co-occurrence is important because the level of distress tends to increase in these patients (Essau, 2003). Research on the impact of comorbidity on depression and anxiety disorder suggests that patients with both disorders have a greater impairment and symptom severity, more chronic course of illness, and decreased response to treatment relative to patients with these conditions in isolation (Fichter et al, 2010, Franco et al, 2007, Masi et al, 2000, Strauss et al, 1988). Furthermore, youths with both anxiety and depressive disorder had a high risk of suicide attempts (Pawlak et al, 1999).

Several theoretical models have been proposed to explain these mechanisms. One opinion on the phenomenology of comorbidity states that anxiety and depression, two distinct disorders share common risk/etiological factors. Moreover, one disorder could be a risk factor for the other one (Klein and Riso, 1993, Seligman and Ollendich, 1988).

Depression and anxiety have been associated with difficulties in downregulating negative affect and deficits in the ability to upregulate or maintain positive affect (Wante et al, 2018, Jazaieri et al, 2013). Poor emotion regulation might play an important role in the etiology of depression and anxiety, and in the development of comorbidity between these disorders.

1.5. Emotion Regulation in Anxiety

ER also seems to be impaired in individuals with anxiety symptoms (Klemansky et al., 2017, Schafer et al., 2016). A growing body of literature suggests that anxiety, similar to depression, is associated with the decreased use of adaptive regulation responses and increased use of maladaptive responses, in both youth and adults (e.g., Carl et al., 2013, Cisler and Olatunji, 2012, Suveg et al., 2010, Turk, 2005). For example, Suveg and Zeman (2004) found that children with anxiety disorders were less successful in controlling negative emotions than healthy controls. Anxious children had lower levels of emotional understanding and more difficulty in regulating worry, sadness, and anger (Zeman et al., 2006). According to Carthy et al. (2010), children with anxiety disorder have greater negative emotionality and more deficits in using reappraisal in negative emotional situations. Mennin and colleagues (2005) found in an adult population sample that patients (mean age 19.5 years) with generalized anxiety disorder (GAD) had low self-soothing ability following a negative emotional experience.

In our project, we view ER as a major pathway that links innate vulnerability to depression to the development of the phenotype. Therefore, dysfunctional or impaired ER strategies increase the risk of developing depressive symptomatology and subsequent full-blown depressive episode. In addition, maladaptive ER strategies are likely to be more pronounced in depression and anxiety comorbid patients. Although there is a large body of evidence about the causal relationship between ER process and depression, to our knowledge ER strategies, and specifically its characteristic subdomains have not yet been empirically verified in a large, precisely diagnosed clinically depressed pediatric population.

1.6. Aims

To explore the role of ER in the development of childhood-onset depression and the effect of comorbid anxiety disorders in order to further clarify the above-mentioned questions, we aimed to investigate the association between ER, childhood-onset depression, and comorbid anxiety disorders in youngsters with histories of MDD.

As a first step, we examined the relationship between ER and depression. As the next step we extended our research to the etiological role of ER in comorbid depressed and anxious youths because the comorbidity of anxiety disorders is clinically significant in terms of prevention, therapy, and prognosis.

Specifically,

1) We hypothesized that in case of dysphoria, probands with histories of MDD will evidence more frequent use of maladaptive strategies and less frequent use of adaptive strategies relative to their control peers.
2) Our research question was whether anxiety comorbidity has an additional negative effect on already impaired emotion regulation of probands with histories of MDD.
3) Finally, we aimed to answer our research question regarding specific ER profile of probands with histories of MDD. Specifically, we tested whether certain ER response clusters (Cognitive, Social, and Behavioral/Physical) will differentiate non-comorbid vs. comorbid probands with histories of MDD.

2. Methods

My research is related to two parts of a large joint research project conducted in collaboration between the University of Pittsburgh and the University of Szeged about childhood-onset major depression. The research has been an ongoing project for more than 20 years as a multidimensional study of the risk factors and course of childhood-onset major depression (Kapornai et al, 2020 PH). The cooperation between the University of Pittsburgh and the University of Szeged began with the project entitled *"Risk Factors in Childhood-Onset Depression"* (COD Study) on the 1st of October, 1999 with the financial support of the American National Institute (NIH Grants # MH-084938) (Fig. 1.). The primary objective of the COD study was to investigate the genetic and psychosocial risk factors of early-onset MDD.

To investigate the possible genetic etiology every child who entered the study with early onset MDD (proband) had at least one sibling. Siblings can be considered a population at risk for MDD. *"Biobehavioral Inflexibility and Juvenile Onset Depression"* (Biobehavioral Study) was the research phase launched in 2009 as a continuation of the original COD project. (Fig. 1). In this research phase, we conceptualized depression as a condition marked by bio-behavioral inflexibility. According to this view, depression involves reduced variability and flexibility in emotions, in their management, and in handling environmental demands.

My research was conducted in two parts (Study 1. and Study 2.) (Fig. 1.). In my present dissertation, I report on a subsample of depressed *probands* and *siblings* originally enrolled in the COD study, while *control* subjects in my investigation were enrolled in the Biobehavioral Study.

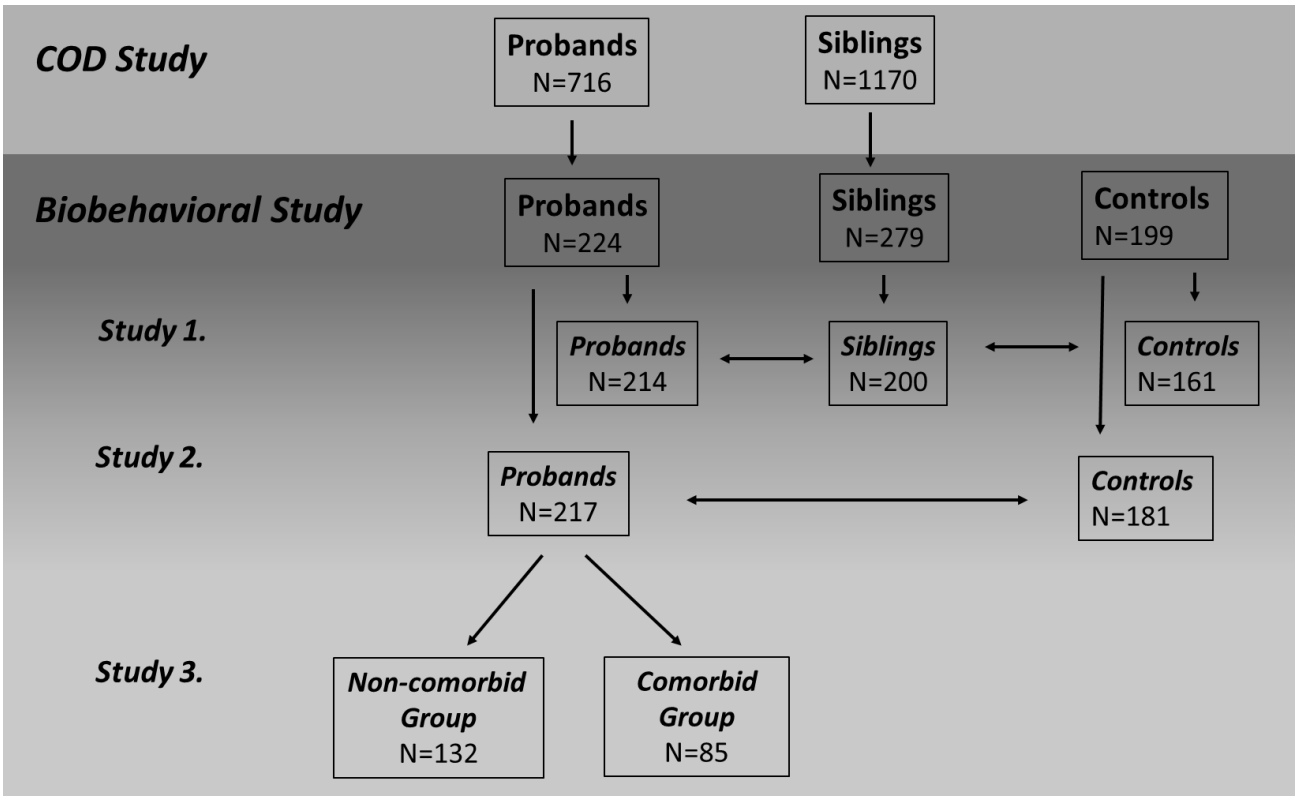

Fig. 1. Study samples COD Study, Biobehavioral Study, Study1. and Study 2.

2.1. Enrollment and assessment procedures

2.1.1. Study 1

2.1.1.1. Probands and Unaffected Siblings in Study 1.

For the COD study 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). 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 the 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). 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, following 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 the administration of the "Mood Disorder Module" of a diagnostic interview, as well as the Intake General Information Sheet, a comprehensive demographic and anamnestic data form. Participants also completed self-rated scales. To set a proper longitudinal overview, evaluations started with a "timeline" for the patient from birth to the date of the assessment. The timeline anchors included major "public" events with the corresponding dates (e.g., Christmas, the 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 timeline ("chronograph") served to identify the times when the child's symptoms became problematic and to date disorder onsets and offsets.

If the child met DSM - IV criteria for mood disorder at the first assessment, he/she continued the second part of the evaluation with the full diagnostic interview and the

completion of additional self-rated scales. If a child met the diagnostic criteria of major depressive disorder and became MDD proband in the COD study, his/her siblings 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. Similar to the probands in both the COD and the Biobehavioral Study, siblings were followed up to at least 18 years of age by sending yearly mail-follow-up test packets. The packets included: a) parental report of interim medical and psychosocial events and a 26-item DSM depressive symptom checklist and b) children's self-rated depression scale. In case of positive screening based on this packet, the sibling was scheduled for the diagnostic assessment procedure. Unaffected siblings were the participants who have never been depressed up to 18 years of age.

By the end of the COD study, the research was in contact with 716 depressed probands, 1170 siblings, and one or both parents of these probands (Fig. 1). During the Biobehavioral Study, which started in 2009 we recruited probands and unaffected siblings who lived within commuting distance of our three research hubs located in the north (Budapest), the southeast (Szeged), and the southwest (Pécs) regions of Hungary. We contacted previously diagnosed probands aged 12-18 years, and 11-17 years old siblings who never had depressive disorder before. As an initial step in our prescreen and recruitment, we relied on information from MFU (described previously). We selected families with probands and potentially unaffected siblings in the required age range. We sent a letter, followed by a phone call, to ascertain the family's willingness to participate, and if was appropriate we scheduled the first assessment, at which time the written consent was signed. Probands (N=214) and unaffected siblings (N=200) in my Study 1. were selected from the above described, carefully assessed Biobehavioral Study samples (Fig. 1.).

2.1.1.2. Control subjects in Study 1.

Controls recruited in the Biobehavioral Study became controls in Study 1. Control subjects were recruited from medium size public elementary and secondary schools in all three research cities (Szeged, Budapest, Pécs) where most of the probands resided. After permission was obtained from the school principals, trained research staff visited the regular parent's meeting in every class. They described the study to the parents, and handed printed summary and pre-screen tests to those parents who agreed to be contacted. The screening questionnaires were used to check for signs of depression or chronic medical illness. The families mailed the

completed forms back to the research staff. Based on the received screening forms we selected eligible children randomly and invited them to participate. Controls (N=199) were recruited to approximate the sex and age distribution of probands, and only those subjects were included in the control pool who had no history of any psychiatric disorder (Fig.1).

2.1.2. Study 2 and 3

During the Biobehavioral Study, the enrollment of the control subjects was continuous. 181 healthy controls were enrolled at the time point of Study 2, which was 20 more than in Study 1. Accordingly, the Control Group with the increased subject number was compared with the Proband Group (N=217)

In Study 3. we compared data of 217 probands children with lifetime MDD (N=132, Non-Comorbid Group) with probands with MDD and any lifetime anxiety disorder (Comorbid Group, N=85) (Fig.1).

2.2. Measurements

The psychosocial assessment battery had two main components: clinical psychiatric evaluation and diagnosis, and self-rated questionnaires.

2.2.1. Psychiatric evaluation: Interview Schedule for Children and Adolescents– Diagnostic Version (ISCA-D)

The psychiatric assessment entailed the administration of a semi-structured, DSM – IV (American Psychiatric Association, 2000) based psychiatric interview (ISCA-D).

ISCA-D is an extension and modification of the Interview Schedule for Children and Adolescents (ISCA) (Sherill and Kovacs 2000). It is a semi-structured interview assessing lifetime psychiatric disorders and current psychiatric status along with the onset and offset dates of each disorder in youths based on DSM-IV (American Psychiatric Association, 2000). Psychiatric diagnoses were evaluated over the subject's lifetime. The intake interviews were assessed during the original COD study and covered the time frame from birth to the time of the interview. The probands who participated in the present study were re-evaluated by the follow-up version of ISCA-D (FU-ISCA-D) to assess their current diagnoses and also their psychiatric histories since the previous interview. Therefore, the diagnostic evaluation covered

the time from birth to the current assessment. All diagnoses, number of episodes, and age at first depressive disorder were also evaluated from birth till the timepoint of the actual assessment. In the case of control subjects, the intake version was administered. Diagnostic evaluations were carried out by trained child psychiatrists and psychologists, who completed three months of didactic and practical training in the ISCA-D semi-structured interview technique, and rendered the best-estimate psychiatric consensus diagnosis. As reported elsewhere, interviewers have achieved satisfactory inter-rater reliability (Baji et al., 2009, Kiss et al., 2007, Tamás et al., 2007).

2.2.2. Self-rating questionnaires

Self-rating scales for the present study were administered at the time of the Biobehavioral Study, after the ISCA-D interview, on the same day. Interviewers were available to help younger children as needed.

2.2.2.1. "Feelings and Me" Child version (FAM-C)

ER strategies were examined via the self-rated *"Feelings and Me" Child (FAM-C*) version questionnaire which evaluated the use of emotion regulatory responses to depressed, dysphoric mood (Bylsma et al, 2015, Kovacs, 2000, Tamás et al., 2007). We presumed that there was a trait-like characteristic style of the use of the ER response repertoires. Therefore, there was no timeframe for this questionnaire.

The FAM-C is a questionnaire, which surveys the use of responses to depressed, dysphoric mood, focusing on those often reported in the literature to maintain or to attenuate those affects. It is suitable for ages 7-17, and lists a total of 54 depression-relevant mood repair strategies focusing on coping with sadness: 32 strategies that are "adaptive" (i.e. serve to down/regulate sadness, e.g. listen to music) and 22 strategies which are "maladaptive" (i.e. serve to exacerbate sadness, e.g. hit myself). Besides the Total Adaptive and Maladaptive scores, the items reflect three regulatory domains: Behavioral/Physical (24 items), Social-Interpersonal (12 items), and Cognitive (18 items), with adaptive and maladaptive strategies in each. Respondents rate from "0=not true of me" to "2=many times true of me" the extent to which items characterize them when feeling sad or upset. The cognitive subscale includes items *"think about things being bad forever"* (maladaptive) or *"think of something fun"* (adaptive). Behavioral subscale items include *"pick my skin, pull my hair, or bite my fingers"* (maladaptive) or *"listen to fun music"*

(adaptive). Social subscales include items such as *"yell or scream at my family"* (maladaptive) or *"look for a teacher or other adult to talk to"* (adaptive).

The FAM-C demonstrated good psychometric properties in the present sample and in prior work with clinical and non-clinical samples in the US and in Hungary (Kovacs et al., 2009; Tamás et al., 2007). The FAM-C total scores were highly internally consistent in the present study (α's=.85–.87), mirroring prior reports (Kovacs et al., 2009; Tamás et al., 2007). Internal consistency was adequate for most sub-scale scores (Adaptive Behavioral α=.73, Cognitive α=.74, Social α=.71; Maladaptive Behavioral α=.58, Cognitive α=.80, Social α=.63). Test-retest reliability of total scores over one year has been satisfactory in youth (Tamás, et al., 2007). Mirroring construct validity, FAM-C maladaptive scores were shown to correlate with depression symptoms (r=.64, p<.0001) and rumination (r=.71, p<.0001; Tamás, et al., 2007) in a large clinical sample of youths. A previously conducted confirmatory factor analysis using n=2,558 school-based youths supported the validity of the 3 subdomains: our research group obtained excellent fit for the Adaptive subscales (CFI=0.95, RMSEA=0.07) and adequate fit for the Maladaptive subscales (CFI=.91, RMSEA=.06) (Bylsma et al, 2015, Kovacs et al., 2009).

2.2.2.2. Child Depression Inventory (CDI)

In order to control for depressive symptoms, the Child Depression Inventory (CDI) was administered. CDI is a 27-item, self-rated, symptom-oriented scale suitable for youths aged 7 to 17, sensitive to changes in depressive symptoms over time, and is a useful index of the severity of the depressive episode. It measures depressive symptoms in the last two weeks. The 27 items are grouped into five areas, including "Negative mood", "Interpersonal Problems", "Ineffectiveness", "Anhedonia", and "Negative Self Esteem". Items are scaled in three statements, from 0 to 2 based on symptom severity (Kovacs, 1992).

The studies analyzing the psychometric characteristics of the test reported internal consistency reliability coefficients in the low to upper 0.80s (Kovacs et al, 1983) and test-retest reliability coefficients ranging from 0.38 to 0.87 (Kovacs, 1992, 2003).

2.3. Samples

2.3.1. Description of samples in Study 1.

2.3.1.1. Proband, Sibling, and Control Groups

The depressed group included 214 *probands* with histories of childhood-onset MDD established previously in the COD study. Of the 214 probands, 10 had 2 siblings, 86 had 1 sibling, and 118 had no siblings. Another group of youth included 200 high-risk *siblings* of probands, who had no history of depressive disorders, selected from the COD study as well. The final group of youth also included 161 normal controls who never had any major psychiatric disorder (Bylsma et al, 2015).

Ages of subjects ranged from 11- to 19 years (probands: M=16.9, SD=1.4; siblings: M=15.9, SD=2.1; controls: M=15.8, SD=2.1) and males constituted 64% of the probands, 47% of the siblings, and 65% of the controls. Consistent with the racial distribution in Hungary, probands were 96% Caucasian, 2% biracial (or other), and 2% Roma; siblings were 96% Caucasian, 2% biracial (or other), and 3% Roma; controls were 99% Caucasian, and 1% biracial (or other) (Bylsma et al, 2015).

At the diagnostic assessment for the current study, 59% of probands had one MDD episode, 32% had two episodes, and 10% had three or more episodes; 184 subjects were in full remission from their most recent MDD episode, while 30 (14%) were currently in a depressive episode. The mean age at onset of the first MDD episode in the proband youth was 9.04 years (SD=1.89 years). The characteristics of the three groups are shown in Table 1.

Table 1. Study 1. Sample description

	Probands (N=214)	**Siblings (N=200)**	**Controls (N=161)**
Age (mean year)	16.99 (SD:1.41)	15.91 (SD:2.16)	15.85 (SD:2.14)
Gender distribution	Male: 64%	Male: 47%	Male: 65%
Nr. of MDD episodes	one MDD ep.: 59% two MDD ep.: 32% three or more MDD ep.:10%	-	-
Nr. of youths currently in depressive episode	30 (14%)	-	-
Age of onset of first MDD episode (year)	9.04 (SD:1.89)	-	-

2.3.2. Description of different samples in Study 2 and 3

2.3.2.1 Non-comorbid and Comorbid Proband Groups

The same proband sample was used in Study 2 and 3 as in Study 1. Since the enrollment was continuous through Study 1 and 2 proband number increased by 3 probands at the time point of Study 2, which did not change significantly the characteristics of the proband sample. The final sample in Study 2 included 217 children (ages: 11–19 years; mean age: 17.01; SD: 1.39; gender distribution: 139 male and 78 female) who had had at least one lifetime MDD episode: 54.8% had one, 30% had two, and 15.2% had three or more MDD episodes. Of the whole sample, 13.4% were currently in depressive episode. The characteristics of the comorbid and non-comorbid groups are shown in Table 2.

Table 2. – Sample description Non-comorbid and Comorbid group

	Non-comorbid group (N=132)	**Comorbid group (N=85)**
Age (mean y.o.)	17.04 (1.4)	16.97 (1.3)
Gender distribution	Male: 63.63%	Male: 64.7%
Nr. of MDD episodes	1.53 (0.7)	1.78 (0.8)
Nr. of youths currently in depressive episode	13 (9.8%)	16 (18.8%)
Age of onset of first depressive episode (y.o.)	9.21 (1.8)	8.75 (1.8)
Age of onset of earliest anxiety disorder (y.o.)	-	8.08 (3.69)

2.4. Statistical analysis

2.4.1. Statistical analysis – Study 1

Differences in FAM scores between probands, siblings, and controls were examined utilizing multilevel models to consider within-family clustering. ICCs ranged from .06 to .20 for offspring Adaptive FAM scores, and from .03 to .11 for the Maladaptive FAM scores. Age and sex of subjects were included in these models, as we have previously found these variables to relate to FAM scores. Significant group effects were examined using post-hoc tests that controlled for multiple comparisons. (Bylsma et al, 2015).

2.4.2. Statistical analysis - Study 2, 3

We used SPSS Statistics 22.0 package for all the performed statistical analyses.

The percentage of missing data was very low: 0.4% in the whole dataset. By default, SPSS treated missing values as "missing", and these items were not included in the statistical analysis. To examine possible differences between groups on baseline characteristics, we used independent *t-test* for continuous and *Chi square* test for categorical variables. GLM-univariate analysis was used to explore the differences in the ER responses between the groups. False Discovery Rate (Benjamini-Hochberg Procedure) was used to control for multiple comparisons.
The dependent variables were: Total Adaptive, Total Maladaptive, Adaptive Cognitive, Maladaptive Cognitive, Adaptive Social, Maladaptive Social, Adaptive Behavioral/Physical, and Maladaptive Behavioral/Physical scores as measured by the FAM-C.
The independent variable was group membership. The two groups were: youth with any lifetime depression disorder and any lifetime anxiety disorder (comorbid group), and youth with any lifetime depression disorder and no lifetime anxiety disorder (non-comorbid group)
The two groups did not differ in gender and age distribution (p=0.73), age of onset of first MDD episode (p=0.08), or the number of youths currently in MDD episode (p=0.06). However, the CDI-R scores (p=0.02), age of onset of first mood disorder (MDD or dysthymia) (p=0.03), and the number of MDD episodes (p=0.03) showed statistically significant differences in the two groups. Therefore, we used these variables as *covariates* in our group analyses, because these parameters might have had an influence on our hypothesis, namely the relation between anxiety comorbidity and ER in depressed youths. Patients with bipolar disorder (n = 6) were excluded from the statistical analysis.

2. Results

3.1. Study 1

In the first part of our research, we examined whether the ER strategies differed among depressed probands, unaffected siblings, and healthy controls. Importantly, the groups differed on all FAM-C scores as we hypothesized (Table 3, *p*s<.01). Pairwise post-hoc LSD tests showed that probands reported lower Adaptive and higher Maladaptive FAM-C scores relative to controls across all mood repair response domains (*p*s<.001). Specifically, the Total Adaptive score of the probands was 19.2 % less compared to the control group. The largest difference was in the Adaptive Cognitive subdomain (6.63±3.38 in probands vs. 8.65±3.38 in controls). Total Maladaptive score was higher in probands by 28.29%. The Maladaptive Cognitive subdomain was showing the largest difference (4.07±3.58 in probands vs. 2.89±2.49 in

controls). Interestingly, with a few exceptions, siblings' mean FAM-C scores fell midway between the mean scores of proband and controls, with many of these differences being statistically significant (Table 3).

Table 3. FAM scores in Probands, Siblings, Control groups

FAM-C Score	**Group Mean (SE)**			***F*** (***ps<.01***)	**Pairwise LSD Comparison** (***ps<.05***)
	Probands	**Siblings**	**Controls**		
Adaptive Total	**19.52 (8.64)**	**22.79 (8.80)**	**24.16 (8.73)**	**13.38**	**Control > Sibling > Proband**
Adaptive Cognitive	6.63 (3.38)	7.89 (3.37)	8.65 (3.38)	16.60	Control > Sibling > Proband
Adaptive Social	3.44 (2.61)	4.20 (2.70)	4.46 (3.14)	7.57	Control, Sibling > Proband
Adaptive Behavioral	9.43 (4.69)	10.70 (4.54)	11.05 (4.24)	5.57	Control, Sibling > Proband
Maladaptive Total	**10.59 (7.09)**	**9.88 (6.26)**	**7.52 (5.07)**	**13.78**	**Control < Sibling < Proband**
Maladaptive Cognitive	4.07 (3.58)	3.88 (3.11)	2.89 (2.49)	8.14	Control < Sibling, Proband
Maladaptive Social	2.72 (2.14)	2.47 (1.93)	1.85 (1.72)	11.07	Control < Sibling < Proband
Maladaptive Behavioral	3.31 (2.76)	3.51 (2.29)	2.78 (2.08)	10.01	Control, Sibling < Proband

Important findings were that females had higher Adaptive and Maladaptive scores than males. For example, females' Total Adaptive score was 23.88±9.11on average while males' was 20.58±8.6. The highest Total Adaptive was in control females, the highest Total Maladaptive was in proband females. Indeed, sex was a significant predictor of the FAM-C score in the analysis, as seen in Study 1 thus these results were further investigated in Study 2 and 3.

Furthermore, depressed status had an effect only on the maladaptive scores. Currently depressed probands' scores were significantly higher compared with probands in remission (Total Maladaptive 17.89, SD:7.6 vs. 8.59, SD:5.86, Maladaptive Cognitive: 7.86, SD: 4.12 vs.

3.22, SD:2,8, Maladaptive Social: 4.07, SD: 2.59 vs.2.21.SD:2.59 vs. 2.21, SD: 1.88, Maladaptive Behavioral: 5.96, SD:2.71 vs. 3.16, SD: 2.4).

3.2. Study 2.

3.2.1. Comparison of FAM-C scores in Probands, and Controls

During the Biobehavioral Study, the enrollment of control subjects continued, so in the second part of my research the size of our samples increased slightly (Study 2, 3) We repeated the comparison of FAM-C scores between probands and controls. (Table 4.)

Table 4. FAM-C scores in Probands and Controls

FAM-C Sores	Group Mean (SE)		Tukey Post Hoc *p<0.05
	Probands (N=217)	**Controls (N=181)**	
Total Adaptive	19.3 (0.58)	24.15 (0.63)	*Control>Proband
Adaptive Cognitive	6.63 (0.23)	8.68 (0.24)	*Control> Proband
Adaptive Social	3.34 (0.17)	4.37 (0.23)	*Control> Proband
Adaptive Behavioral/Physical	9.34 (0.31)	11.11 (0.31)	*Control> Proband
Total Maladaptive	10.68 (0.48)	7.47 (0.37)	* Proband >Control
Maladaptive Cognitive	4.07 (0.24)	2.88 (0.19)	* Proband >Control
Maladaptive Social	2.75 (0.14)	1.85 (0.12)	* Proband >Control
Maladaptive Behavioral/Physical	3.88 (2.76)	2.74 (2.03)	* Proband >Control

FAM-C scores showed similar results as in our findings in Study 1. Probands differed significantly on all FAM-C scores compared to controls. The Total Adaptive FAM-C scores were significantly lower in probands compared to controls (19.3, SD:0.58 vs. 24.15, SD:0.63). The largest difference between the two groups was in the Cognitive subdomain (8.68, SD:0.24vs. 6.63, SD:0.23). Probands scored significantly higher on the Total Maladaptive scale than controls (10.68, SD:0.48 vs. 7.47, SD:0.37). Similarly, all maladaptive subdomains were

significantly higher in probands compared to controls, the Cognitive subdomain showing the largest difference (4.07, SD:0.24 vs. 2.88, SD:0.19). (Table 4)

3.2.2 Assessment of sex differences of FAM-C scores in Proband and Control groups

We further examined the different FAM-C scores in males and females (Table 5)

Table 5. FAM-C scores in Probands and Controls as a function of sex

FAM-C Scores	**Group Mean (SE)**				**Tukey Post Hoc** ***p<0.05**
	Proband Females (PF) (n=78)	**Proband Males (PM) (n=139)**	**Control Females (CF) (n=65)**	**Control Males (CM) (n=116)**	
Total Adaptive	21.21 (1)	18.36 (0.69)	**27.09 (1.11)**	22.49 (0.72)	*CF>CM, PM, PF
Adaptive Cognitive	7.12 (0.39)	6.36 (0.28)	**9.57 (0.42)**	8.17 (0.28)	*CF>CM, PM, PF
Adaptive Social	4.06 (0.3)	3 (0.2)	**5.63 (0.39)**	3.66 (2.7)	*CF>CM, PM, PF
Adaptive Behavioral	9.99 (0.5)	8.98 (0.38)	**11.89 (0.53)**	10.66 (4)	*CF>PM
Total Maladaptive	**13.44 (0.84)**	9.13 (0.55)	9.32 (0.7)	6.4 (0.39)	*PF>CM, PF, PM **CF vs. CM
Maladaptive Cognitive	**4.7 (0.42)**	3.7 (0.29)	3.6 (0.34)	2.48 (0.21)	*PF>CM
Maladaptive Social	**3.72 (0.24)**	2.2 (0.16)	2.25 (0.23)	1.63 (0.14)	*PF>CM, PF, PM
Maladaptive Behavioral	**4.97 (0.35)**	3.26 (0.2)	3.48 (0.31)	2.32 (0.14)	*PF>CM, PF, PM **CF vs. CM

According to our analysis, Adaptive FAM-C scores were significantly higher in control females compared with all other groups. The most outstanding difference was seen between control females and proband males, as proband males had the lowest scores from all groups on all Adaptive FAM-C domains. (Table 5).

Regarding the Maladaptive FAM-C scores female probands' sores were the highest of all analyzed groups through all Maladaptive domains. The lowest Maladaptive scores were observed in control male subjects (6.4, SE:0.39, 2.48, SE:0.21, 1.63, SE:0.14, 2.32, SE:0.14). The Maladaptive Behavioral/Physical FAM-C subdomain showed the most significant difference between proband female and control male groups (4.97, SE:0.35 vs. 2.32, SE:0.14). The Total Maladaptive and Maladaptive Behavioral/Physical FAM-C scores were significantly higher in control females compared to control males (9.32, SE:0.7 vs. 6.4, SE:0.39, 3.48, SE:0.31 vs. 2.32, SE:0.14). (Table 5)

3.2.3 Assessment of FAM-C scores in the Proband group by current MDD status

Further, we compared the FAM-C scores of the proband group as a function of depressive status (Table 6).

Table 6. FAM-C scores in function of actual depressive status in probands

FAM-C Sores	Group Mean (SE)		Tukey Post Hoc *p<0.05
	Probands (no MDD episode) (N=188)	**Probands in MDD episode (N=29)**	
Total Adaptive	19.53 (0.6)	18.46 (1.88)	
Adaptive Cognitive	6.7 (0.24)	6.18 (0.77)	
Adaptive Social	3.43 (0.18)	3.17 (0.53)	
Adaptive Behavioral/Physical	9.38 (0.32)	9.07 (1.06)	
Total Maladaptive	9.7 (0.47)	**16.68 (1.4)**	* Probands >Probands in MDD episode
Maladaptive Cognitive	3.59 (0.23)	**7.14 (0.78)**	* Probands > Probands in MDD episode
Maladaptive Social	2.57 (0.14)	**3.9 (0.49)**	* Probands > Probands in MDD episode
Maladaptive Behavioral/Physical	3.6 (0.19)	**5.56 (0.49)**	* Probands > Probands in MDD episode

In our proband group, the actual depressive status had statistically significant effect on the Maladaptive FAM-C scores. Specifically, those youths who were in MDD episode at the time of the interview scored significantly higher on all Maladaptive scales (16.68, SE:1.4, 7.14, SE:0.78, 3.9, SE:0.49, 5.56, SE:0.49). The Cognitive Maladaptive subdomain showed the largest difference (7.14, SE:0.78 vs. 3.59, SE:0.23). The adaptive values were not statistically different between the two groups (Table 6).

3.3 Study 3.

3.3.1 Comparison of FAM-C scores in the Non-Comorbid vs. Comorbid groups

Our further goal was the assessment of ER patterns in youths with histories of childhood-onset depression with and without comorbid anxiety.

From our proband group, n=85 (39.17%) youths had at least one comorbid (lifetime or current) anxiety disorder. The most frequent anxiety disorders in the comorbid group were: phobia (33 subjects, 38.82%), generalized anxiety disorder (GAD) (28 subjects, 32.94%), and separation anxiety disorder (25 subjects, 29.41%). Other comorbidities were: anxiety not otherwise specified (NOS) (14 subjects, 16.47%), obsessive-compulsive disorder (7 subjects, 8.23%), panic disorder (4 subjects, 4.7%), and post-traumatic stress disorder (4 subjects, 4.7%). Of the 85 comorbid patients, 50 subjects had one comorbid anxiety disorder and 35 subjects had two or more comorbid anxiety disorders.

As mentioned before (Method 2.4.2) the depressive status, age of onset of first mood disorder, and the number of MDD episodes showed statistically significant differences in the two groups. Therefore, we used these variables as covariates in our group analyses.

Table 7. FAM-C scores in the Non-Comorbid group vs. Comorbid group

FAM-C Scores	Group Estimated Mean (SE)		Tukey Post Hoc *p<0.05
	Non-Comorbid (N=132)	**Comorbid (N=85)**	
Total Adaptive	18.9 (0.76)	20.1 (0.94)	*0.313*
Adaptive Cognitive	6.4 (0.31)	6.8 (0.38)	*0.422*
Adaptive Social	3.3 (0.23)	3.5 (0.28)	*0.593*
Adaptive Behavioral/Physical	9.2 (0.41)	9.7 (0.51)	*0.404*
Total Maladaptive	10 (0.5)	**11.9 (0.62)**	*0.023**
Maladaptive Cognitive	3.9 (0.27)	4.4 (0.33)	*0.306*
Maladaptive Social	2.5 (0.17)	**3.2 (0.21)**	*0.019**
Maladaptive Behavioral/Physical	3.5 (0.22)	**4.4 (0.27)**	*0.016**

The Total Adaptive score of the FAM-C did not show statistically significant difference between the groups, while the Total Maladaptive score was significantly higher in the comorbid compared to non-comorbid subjects (11.9, SE:0.62 vs. 10, SE: 0.5). (Table 7)

We found that none of the Adaptive subscales was significantly different between the groups, however, Maladaptive Social (3.2, SE: 0.21) and Maladaptive Behavioral/Physical (4.4, SE:0.27) subscales were significantly higher in comorbid children. (Table 7).

When we looked at specific items of the above-mentioned maladaptive subscales, the item reflecting social withdrawal in the Social subscale and the item reflecting self-harm in the Behavioral/Physical subscale were more frequently used by comorbid youth (data not shown). The maladaptive Cognitive subscale was not significantly different across groups. However, one of the cognitive items similar to rumination was significantly more frequently endorsed by the patients in the comorbid group *("think of being sad")*.

3.3.2 Assessment of sex differences of FAM-C scores in Comorbid and Non-Comorbid groups

We compared the FAM-C scores of depressed males and depressed females with and without comorbid anxiety disorder (non-comorbid males, comorbid males, non-comorbid females, comorbid females). (Table 8)

The Total Adaptive scores were significantly higher in non-comorbid females (21.64, SE:1.3) compared with non-comorbid males (17.3, SE:0.8). Among the Adaptive Subscales only the Adaptive Social subscale showed statistically significant difference between non-comorbid females and males (4.25, SE. 0.3 vs. 2.81, SE:0.2). However, non-comorbid females did not differ significantly from ether comorbid groups.

The Maladaptive FAM-C scores were highest in comorbid females through all maladaptive domains (Total Maladaptive: 1 5.86, SE:1.3, Maladaptive Cognitive: 5.73, SE:0.7, Maladaptive Social: 4.4, SE:0.43, Maladaptive Behavioral/Physical: 5.73, SE:0.58). The analysis revealed statistically significant differences between non-comorbid and comorbid males in the Total Maladaptive scale (15.86, SE:1.3 vs. 8.2, SE: 0.6, 10.4, SE: 0.89) and in the Maladaptive Social subscale (4.4, SE:0.43 vs. 1.99, SE: 0.19, 2.53, SE: 0.29). The Behavioral/Physical subscale was significantly higher in comorbid males versus non-comorbid males (5.73, SE: 0.58 vs. 2.86 SE:0.24). Interestingly, non-comorbid females' scores were significantly higher compared to that of non-comorbid males in the Maladaptive Social (3.29, SE:0.27 vs. 1.99, SE:0.19) and Maladaptive Behavioral/Physical subdomains (4.5, SE:0.43 vs. 2.86, SE:0.24) (Table 8).

Table 8. FAM-C scores in the Non-Comorbid and Comorbid groups as a function of sex

FAM-C Scores	**Group Mean (SE)**				**Tukey post Hoc *p<0.05**
	Non-Comorbid Females (n=48)	**Non-Comorbid Males (n=84)**	**Comorbid Females (n=30)**	**Comorbid Males (n=55)**	
Total Adaptive	**21.64 (1.3)**	17.3 (0.8)	20.52 (1.44)	19.9 (1.1)	*Non-Comorbid Females>Non-Comorbid Males
Adaptive Cognitive	7.17 (0.5)	6.07 (0.3)	7.03 (0.6)	6.8 (0.46)	
Adaptive Social	**4.25 (0.3)**	2.81 (0.2)	3.77 (0.58)	3.35 (0.36)	* Non-Comorbid Females>Non-Comorbid Males
Adaptive Behavioral/ Physical	10.23 (0.79)	8.43 (0.4)	9.59 (0.63)	9.8 (0.65)	
Total Maladaptive	11.92 (1)	8.2 (0.6)	**15.86 (1.3)**	10.4 (0.89)	*Comorbid Females>Comorbid Males, Non-Comorbid Males
Maladaptive Cognitive	4.11 (0.5)	3.43 (0.36)	**5.73 (0.7)**	4.09 (0.46)	* Comorbid Females > Non-Comorbid Males
Maladaptive Social	3.29 (0.27)	1.99 (0.19)	**4.4 (0.43)**	2.53 (0.29)	* Comorbid Females > Non-Comorbid Males, Comorbid males **Non-Comorbid Females> Non-Comorbid Males
Maladaptive Behavioral/ Physical	4.5 (0.43)	2.86 (0.24)	**5.73 (0.58)**	3.87 (0.33)	* Comorbid Females > Non-Comorbid Males, Comorbid Males *Non-Comorbid Females> Non-Comorbid Males

3.3.3 Assessment of FAM-C scores in Comorbid and Non-Comorbid groups by current MDD and/or anxiety status

The exact pattern of past and current MDD and anxiety episodes in our sample is shown in Figure 2. 82.4% of the proband sample were in total remission (54.8% from the non-comorbid group, 27.6% from the comorbid group). 3.2% had current both MDD and anxiety episodes, 4.1% had current MDD and remitted anxiety, and 4.1% had current anxiety and depression in remission. (Fig 2)

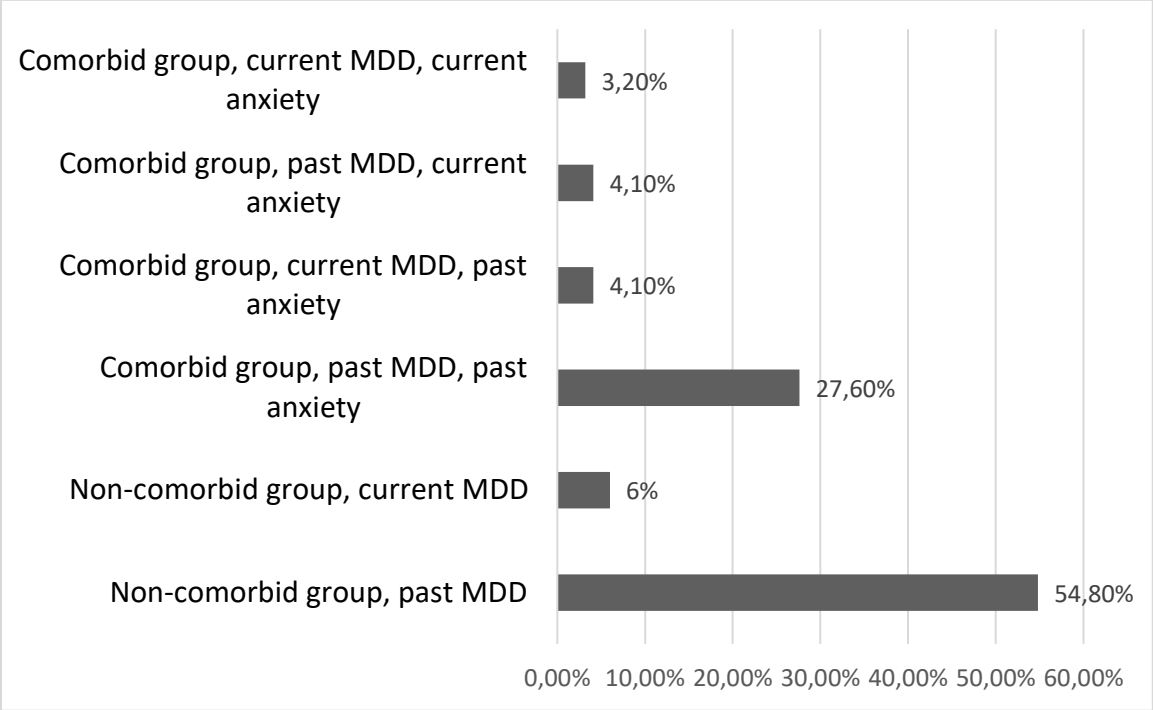

Figure 2. Percent of current MDD and/or anxiety in Comorbid and Non-Comorbid subjects

The Adaptive FAM-C scores did not differ between groups.

The Maladaptive FAM-C scores were the highest in the comorbid group actually in MDD and in anxiety episodes (Total Maladaptive: 17.35, SE:2.39, Maladaptive Cognitive: 7.5, SE:1.26, Maladaptive Social: 3.9, SE:0.74, Maladaptive Behavioral/Physical: 6, SE:0.95) and in non-comorbid group actually in MDD episode (Total Maladaptive: 17.11, SE:1.77, Maladaptive Cognitive: 7.35, SE:0.93, Maladaptive Social: 3.9, SE:0.55, Maladaptive Behavioral/Physical: 5.8, SE:0.7). Total Maladaptive and Maladaptive Cognitive scores were significantly higher in these two groups compared with the scores of non-comorbid subjects in remission (Total Maladaptive: 17.35, SE:2.39 and 17.11, SE:1.77 vs. 8.7, SE:0.57, Maladaptive

Cognitive: 7.5, SE:1.26 and 7.35, SE: 0.93 vs. 3.2, SE:0.3). The Maladaptive Behavioral/Physical subscale showed statistically significant difference between non-comorbid patients in MDD episode and non-comorbid patients in remission (5.8, SE:0.7 vs. 3.1, SE: 0.23). (Table 9)

Table 9. FAM-C scores in the Non-Comorbid group and Comorbid group as a function of sex and internalizing disorder

FAM-C scores	**Group Estimated Mean (SE)**					
	non-comorbid, no episode (n=119)	**non-comorbid**, MDD episode (n=13)	**comorbid**, no episode (n=60)	**comorbid**, MDD episode (n=9)	**comorbid**, anxiety episode (n=9)	**comorbid**, MDD and anxiety episode (n=7)
Adaptive Scores						
Total	18.7 (0.76)	20.4 (2.35)	21.8 (1.07)	19.8 (2.8)	14.9 (2.8)	12.8 (3.1)
Cognitive	6.3 (0.3)	7.5 (0.94)	7.6 (0.43)	6 (1.19)	4.5 (1.12)	4.4 (1.27)
Social	3.3 (0.23)	3.1 (0.72)	3.6 (0.33)	4.1 (0.86)	2.7 (0.86)	2 (0.97)
Behavioral/ Physical	9 (0.41)	9.7 (1.27)	10.4 (0.59)	9.4 (1.56)	7.5 (1.52)	6.3 (1.72)
Maladaptive Scores						
Total	8.7 (0.57)	**17.11 (1.77)**	11 (0.81)	15 (2.11)	14.6 (2.12)	17.5 (2.39)
	p=0.000		*p=0.007*			
Cognitive	3.2 (0.3)	**7.35 (0.93)**	3.9 (0.43)	6.2 (1.11)	5.6 (1.11)	7.5 (1.26)
	p=0.001		*p=0.019*			
Social	2.2 (0.18)	3.9 (0.55)	3 (0.25)	3.7 (0.65)	3.6 (0.65)	3.9 (0.74)
Behavioral/ Physical	3.1 (0.23)	**5.8 (0.7)**	4.1 (0.32)	5 (0.84)	5.4 (0.84)	6 (0.95)
	p=0.008					

3 Discussion

The main aim of my research work was to investigate the emotion regulation of youths with major depression and comorbid depression and anxiety disorder to gain a broader understanding of the importance of the emotion regulation profile in childhood-onset internalizing psychopathology. We were particularly interested in whether comorbid anxiety worsens the use of impaired ER repertoire of depression-prone youths.

Studies on clinical depression have long emphasized that the failure to properly regulate emotions contributes to the risk of major depressive disorder. People at risk of clinical depression do not differ in their initial experience of dysphoria, but rather in how they respond to dysphoric mood. They tend to think and behave in ways that reinforce or possibly cause the symptoms of MDD or the onset and recurrence of major depression (Kovacs et al, 2009). It is already been proved that the onset and recurrence of MDD are related to maladaptive ER strategies, however, the literature mainly focused on impairment in cognitive strategies, and relatively little is known about the broader ER repertoire of depressed individuals (Garnefski et al, 2006, Kovacs, et al., 2009; Kovacs & Lopez-Duran, 2010). Thus, we extended our investigation toward social and behavioral/physical response domains of ER as well. The questionnaire we used (FAM-C, Kovacs et. al, 2000) was specifically designed for children and adolescents, and sheds light on several aspects of ER. It is important to note that the FAM-C questionnaire examines adaptive and maladaptive emotion regulation, and within these, it also examines the sub-dimensions (Cognitive, Social, Behavioral/Physical) of both aspects. Better knowledge about the emotion regulation profile of depressed youths can provide deeper insight into the pathophysiology of MDD and allow us to design and use more effective and targeted therapeutic approaches.

In the first part of our study, we analyzed the ER strategies of youths with history of MDD compared to healthy, never depressed controls. Consistent with previous reports on ER difficulties among depressed and high-risk individuals and corresponding to our first hypothesis, we found that our probands with depression histories reported higher rates of maladaptive and lower rates of adaptive ER responses compared to controls across all ER response domains (Total, Cognitive, Social, Physical/Behavioral). Interestingly, never depressed, high-risk siblings (of probands with depression histories) showed impaired ER strategies as well. We can therefore assume that greater use of maladaptive ER strategies and reduced use of adaptive ones may contribute to the risk for major depression. Importantly, in

line with the literature, the Cognitive subscale showed the largest difference between the proband and control groups in both Adaptive and Maladaptive ER subscales. Cognitive emotion regulation strategies involve attention focusing and conscious thinking. Adaptive cognitive strategies, such as considering the good aspects of the situation or putting what is happening into a broader interpretive framework (eg. *"think about being relaxed, calm", "think about what to do to feel better", "think about projects or things to do"*) help the individual to adapt to the situation and thus regulate emotions properly. However, maladaptive cognitive strategies, such as blaming oneself or others (eg. *"think about everything being my fault"*), magnifying loss or danger (catastrophizing) (eg. *"think about things being bad forever*"), or ruminating on negative thoughts and feelings (rumination) (eg.*"think about why I am sad")* play role in the development and maintenance of pathological emotional reactions. Cognitive emotion regulation strategies are cognitive factors that can be modified by psychotherapeutic means, and their study may therefore be of particular importance in the prevention and treatment of major depression.

In addition to the cognitive ER strategies, we analyzed the ER regulation strategies in the social domain as well. Social, interpersonal ER refers to the process through which a person initiates social contact to regulate his or her emotional experience (Grecucci, 2015). Our results showed the use of maladaptive strategies in the social domain more frequently (eg. " *I argue with people", "go off to be alone")* and adaptive ones less frequently (eg. *"I try to call or see a friend", "talk to my family about it")* in the depressed group compared with healthy controls. Verbal sharing and exploration of emotions greatly reduce dysphoria, especially when the environment responds with supportive and empathic behavior. More positive and less negative interaction with others is associated with healthy regulation of emotions. In depression, distraction from negative emotions is an adaptive strategy that can be facilitated by supportive social interactions. The social supporter may simply encourage a complete distraction from the emotional situation, or redirection of the stimulus to other, more positive features. Due to attentional and motivational difficulties that are characteristics of depression, social interaction with others can be stressful for the patient. The attention is mostly oriented towards negative content and therefore it is recommended to communicate mainly positive content during social interactions in order to achieve an adaptive effect in depressive patients (Grecucci 2015, Hofmann, 2014, Marrouquin, 2011).

Our analysis also revealed significant impairment in the behavioral domain of ER profile. Probands used maladaptive behavioral strategies (eg. *"throw, kick or hit objects", "pick my skin, pull my hear, or bite my fingers")* more frequently than adaptive behavioral/physical

ones (eg. *"go outside to run or walk", "try to sing or dance*") than controls. Maladaptive behavioral strategies mentioned above are behavioral ER strategies that are predisposing to self-harm (Andover and Morris, 2014). Literature suggests that ER disruption plays an important role in non-suicidal self-injury (NSSI). Patients often implement NSSI as a maladaptive ER strategy, as it reduces the experience of negative emotions (e.g., tension, fear, and sadness) (Andover and Morris, 2014). A deeper understanding of the behavioral ER strategies could help in the development of integrated cognitive and behavioral interventions in the prevention and treatment of depression. Moreover, knowing the increasing prevalence of NSSI and its impact on the dissipation of dysphoric feelings in depression, targeted treatment of maladaptive behavioral ER strategies underlying NSSI would increase the effectiveness of the treatment (Sorgi et al., 2021).

Further analyzing our data by sex, we found that girls with depression history more frequently use maladaptive strategies that may contribute to the development or maintenance of depression. They are more likely to choose activities that maintain sadness and dysphoria (eg. withdrawing, listening to sad music) and are more likely to do self-harm like, sensory-seeking behavior.

Additionally, probands currently in depressive episode do not differ from the probands in remission regarding the adaptive ER strategies but, at the same time, they are characterized by higher rates of maladaptive ER responses than probands in remission.

Our study included a large, carefully diagnosed clinical sample of Hungarian children and adolescents with depressive history, of whom about 39% had lifetime comorbid anxiety disorder as well and our aim was to answer our first research question by examining whether anxiety disorder as a comorbid condition worsens the impaired ER in youngsters with histories of depression. Poor regulation of emotions appears to be a risk factor common to anxiety and major depression in adults. Research by Burklund et al (2015) in adults revealed altered ER in patients with comorbid social phobia and depression. Aldao and Nolen-Hoeksema (2010) also concluded, that maladaptive ER strategies (e.g. rumination, avoidance) had strong associations with psychopathology including depression and anxiety in adults. However, the ER profile of comorbid children and adolescent patients has not been fully characterized. In fact, there is scant information about how anxiety as a comorbid condition affects the habitual use of different ER strategies in depressed youngsters. Queen et al. (2014) found that adolescents with anxiety and depression had poorer emotional awareness, greater emotional suppression, greater reluctance to express negative emotions, and greater inhibition of sadness compared with patients with only anxiety disorder. Similarly, we found that anxiety comorbidity in youngsters

with lifetime depression was associated with dysfunctional emotion regulation, since probands with comorbidity used maladaptive ER strategies more frequently than non-comorbid peers. Our results are in line with other findings that showed frequent use of maladaptive ER strategies in youths with comorbid depression and anxiety symptoms (Garnefski et al., 2016, Klemanski et al., 2017, McLaughin et al., 2011, Queen et al., 2014, Schafer et al., 2016). It is particularly important that the treatment of depression is more difficult in the presence of anxiety, as comorbidity lengthens the duration of treatment and decreases the response to interventions (Brent et al., 1998; Brown et al., 1996). Our results may suggest one possible explanation regarding treatment resistance, that depressed youngsters with anxiety comorbidity use maladaptive ER responses to sadness even more frequently than their non-comorbid peers, which is likely to worsen their dysphoria.

To extend the previous findings in the field, we examined different aspects of emotion regulation in childhood-onset internalizing psychopathology.

It is important to point out that anxiety comorbidity worsened ER skills mainly in social and in behavioral/physical domains, especially in girls depressed probands with comorbid anxiety showed a different repertoire of various ER domains compared to youngsters with only major depression (Fig.3). Specifically, while maladaptive cognitive strategies were used to the same extent, the social and behavioral maladaptive ER strategies were used more often in the comorbid group and even more by comorbid females. Social withdrawal (*when I am sad or down, I frequently "go off to be alone" and "hide from people"*) within the Social domain can be considered as a social avoidant strategy consistent with the nature of anxiety. As reported by Schafer et al. (2016), avoidant behavior was associated with depressive and anxiety symptoms. While avoiding social situations to cope with sadness might reduce negative emotion in the short term, however, it also prevents patients from using social support to attenuate sadness.

Regarding the behavioral/physical domain, self-harm or autoagression (e.g. *when I am sad or down, I frequently "pick my skin, pull my hair, or bite my fingers" and "stomp my feet, bang my head, hit myself*") can be interpreted as negative somatic sensitivity response/tendency to self-harm. The utilization of these negative, emotion-driven somatic, sensory-focused responses may indicate a lack of more sophisticated regulatory strategies which can be potentially harmful, and might be a predisposing factor to NSSI. It is also possible that anxiety, as one of the earliest forms of childhood psychopathology, might itself predispose individuals

to more somatically based and sensory-oriented ER responses. This might be the subject of further research.

Interestingly, the presence or absence of anxiety comorbidity in patients with depression histories made no significant difference in the use of ER responses in the adaptive domain. Our results are in line with that of Aldao et al. (2010), whose meta-analysis found that adaptive ER strategies were less associated with psychopathology, including depression or anxiety, than maladaptive ones. Indeed, patients with comorbidity may not derive benefits from expanding their repertoires of adaptive ER responses, rather they should be trained to recognize and replace the maladaptive behavior reaction with adaptive ones from their repertoire. Our finding also suggests that depressed-prone females with anxiety retain their adaptive ER skills, but they are more likely to choose maladaptive strategies in case of dysphoria.

Finally, being in MDD and/or anxiety episode at the time of the assessment did not make any difference between the groups regarding the use of adaptive ER strategies. However, in the non-comorbid group patients with current MDD episode were likely to use maladaptive cognitive and behavioral/physical strategies. Further, probands with co-occurring MDD and anxiety episodes in the comorbid group tended to use maladaptive cognitive strategies, thus showing the most impaired ER profile. It is important to note that these findings should be interpreted with caution because of the low sample size of patients in current episodes.

The main aim of our work was to explore and better understand the emotional regulation of children and adolescents with depression and with comorbid depression and anxiety. In order to better describe the ER repertoire of different groups in our study, we calculated the proportion of every strategy (3 adaptive and 3 maladaptive) within the total ER profile. (Fig 3, 4). We present the characteristic emotion regulation profile of our control and probands samples by their comorbid status and by sex (Figure 3.) and also by their current vs. lifetime MDD episode status (Figure 4.).

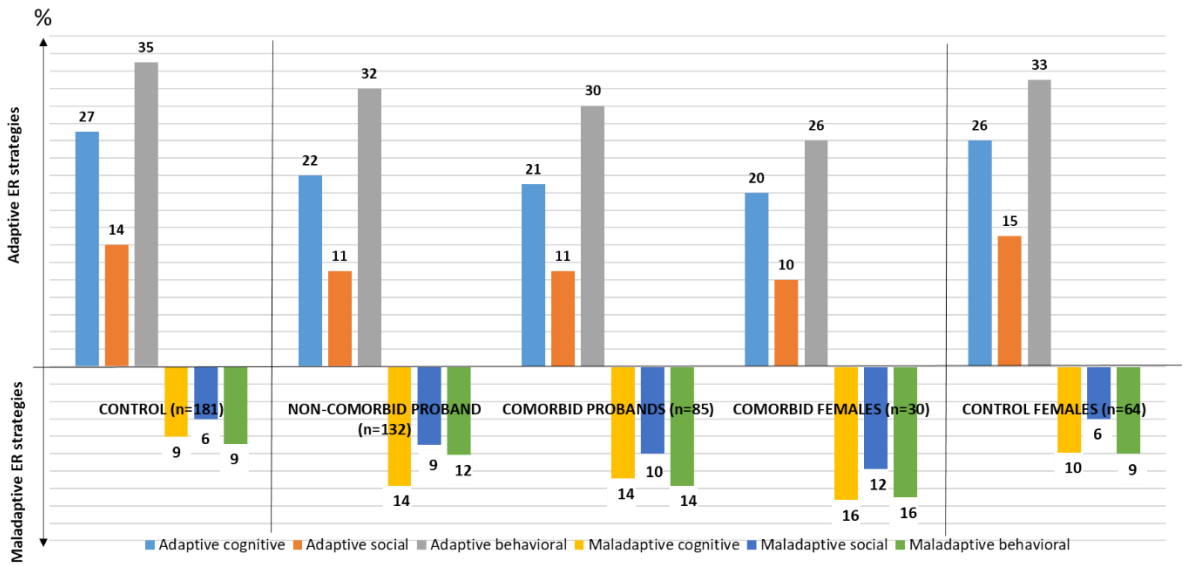

Fig 3. ER profile of study groups as a function of internalizing psychopathology and sex

CONTROL=control group, PROBAND= proband group (proband with MDD histories), COMORBID PROBANDS=comorbid group (probands with MDD and anxiety histories), COMORBID FEMALES= comorbid female group (female probands with MDD and anxiety histories), CONTROL FEMALES=control female group

Fig. 3 shows that comorbid females showed the most impaired profile as they were using maladaptive behavioral/physical strategies more often than any other youngsters even among the depressed population. Based on the profile of the groups as a function of the presence of current episode (MDD and/or anxiety) (Fig 4.) the tendency to use maladaptive cognitive and maladaptive behavioral/physical strategies in patients with co-occurring MDD and anxiety is clinically significant.

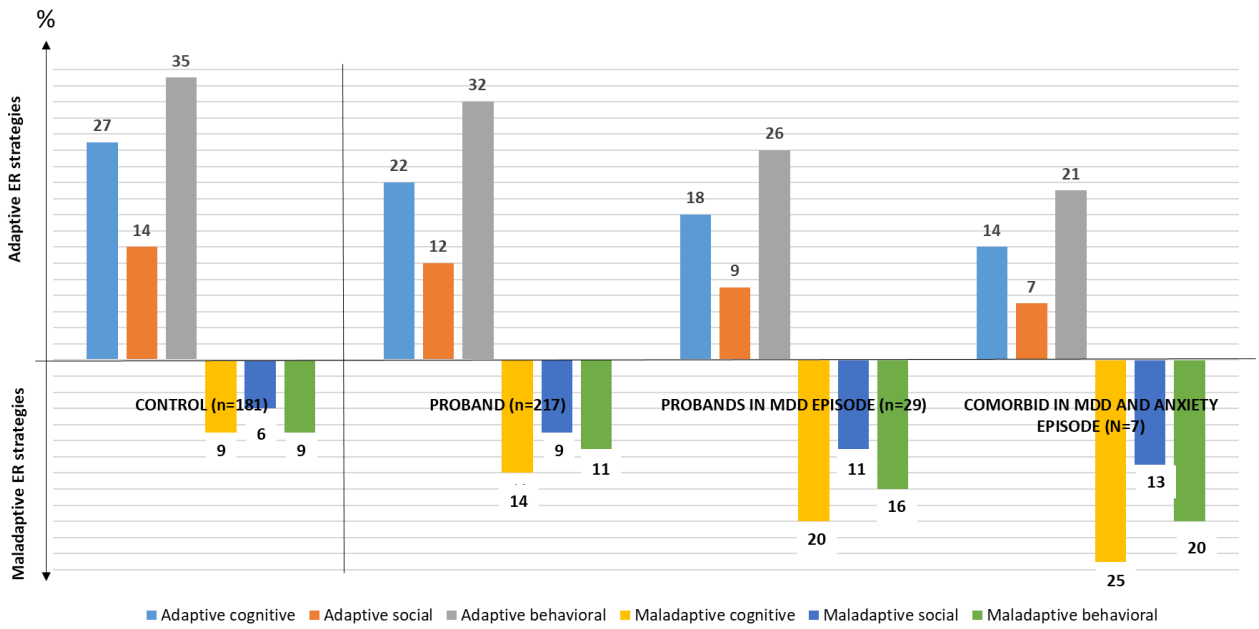

Fig 4. ER profile of study groups as a function of MDD and anxiety episode status (lifetime episode vs. currents episode)

CONTROL=control group, PROBAND= proband group (proband with MDD histories), PROBANDS IN MDD EPISODE= proband group (proband with MDD histories) actually in MDD episode, COMORBID IN MDD AND ANXIETY EPISODE= comorbid group (probands with MDD and anxiety histories) actually in MDD and anxiety episode

In summary, the results of our current study extended previous findings in several ways: 1) we examined adaptive and maladaptive ER strategies in multiple domains; 2) we used a large clinical sample of youngsters with childhood-onset depression, and our sample was carefully diagnosed with childhood-onset depression by trained psychiatrists and psychologists. The ability to use adaptive cognitive strategies to regulate emotion in case of dysphoria may play a role in the development of childhood-onset depression. Anxiety comorbidity leads to more impaired profile in the social and behavioral/physical emotional regulation domains. Our research also shows that the ER repertoire is influenced not only by the underlying psychopathology but also by sex and the presence of a current internalizing disorder.

Understanding the ER of children and adolescents with depression and comorbid depressive and anxiety disorders is of paramount importance for improving the effectiveness of existing treatments and developing new interventions. Facilitating the development of adaptive ER is a central component of most evidence-based psychotherapies, although different modalities emphasize different skills. Cognitive behavioral therapy (CBT), emphasizes cognitive restructuring and promotes the use of reappraisal, while the 'third wave'

psychotherapies (e.g. mindfulness-based cognitive therapy, dialectical behavioral therapy) focus on acceptance and decentering (Hayes et al, 2017, Linehan, 1993).

Importantly our research suggests that patients with comorbid depression and anxiety may benefit from psychotherapeutic methods that aim to replace maladaptive ER responses with adaptive ones (Adrian et al, 2019, Mehlum et al, 2019, Hawton et al, 2015). One effective psychotherapy is dialectical behavioral therapy (DBT), which aims to improve ER by teaching several ER skills (e.g., emotion identification, increasing positive emotional events, taking opposite action, and distress tolerance techniques) (Linehan et al, 1993). Promising results have been reported regarding the development and effectiveness of transdiagnostic-behavioral therapy for children and adolescents with comorbid depression and anxiety (symptoms or disorder) (Ehrenreich-May et al, 2012, Essau et al, 2019, Garcia-Escalera et al, 2016, Norton and Paulus, 2016,). In light of our results, the module of modifying maladaptive emotion-driven behaviors of transdiagnostic behavioral therapy could be especially beneficial for depressed children and adolescents with anxiety comorbidity (Chu et al, 2016).

Few therapeutic interventions target positive emotion regulation. Examples include Positive Affect Treatment (PAT), which is specifically designed to treat anhedonia in adults. It promotes the identification and the experience of positive emotions through a variety of behavioral, cognitive, and experiential exercises (Craske et al, 2106). Future research is needed to adapt similar interventions for adolescents as well.

Because most therapeutic approaches involve multiple elements, it can be difficult to identify the truly effective components of treatments. Newer therapeutic methods (Cognitive Bias Modification) aim to separately analyze the effects of specific treatment components. These are mainly shorter computer-based training sessions focusing on changing attention or cognitive biases (Attention Bias Modification, Interpretation Bias Modification) (Hertel and Mathews, 2011).

Being aware of the fact that anxiety-depression comorbid children tend to respond more poorly to cognitive behavioral therapy (CBT), our results may have important implications for treatment. Findings from this study underline important, individually tailored treatment procedures, and they suggest that comorbid patients may require more social skill improvement and behavioral training. We would like to highly emphasize the tendency for self-injury in comorbid patients. This type of maladaptive ER, and the association between anxiety and depression comorbidity and self-injury requires further research.

Limitations

Limitations of this research should also have to be mentioned. Since our study was cross-sectional, it was not possible to examine the causal relationship between internalizing disorders and ER. Also, using self-rating questionnaire may have led to some bias in measuring ER profile. The use of self-administered questionnaires to investigate emotion regulation is a widely used method, however to obtain information through more objective interview techniques and behavior observation would be necessary. We did not have enough subjects in current MDD and anxiety episodes in order to stratify our groups according to present or past diagnoses. Finally, it is important to note that our proband sample is originally from a Research Project is investigating risk factors - including molecular genetic factors – in the development of childhood onset depression and to have at least one biological sibling of depressed proband was among the inclusion criteria, therefore, the generalizability of the results might be limited.

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