Summary of Ph.D. Thesis

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

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1. Introduction

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).

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). 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). The school-age population (11.5-17.5 y.o.) has been regularly surveyed since 1985 by the WHO at an 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 Child Depression Questionnaire (CDI) short version, indicating the presence of depressive symptoms (Aszmann, 2003). Data from a survey of school-age children (15 years and older) in Hungary in 1988 and 1995 (Hungarostudy) showed that the prevalence of the major depressive disorder in the 1995 survey, especially among those requiring treatment, showed a significant increase compared to the 1988 survey. (Kopp et al. 1997).

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, 2001, Kapornai and Vetró, 2008). 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). 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). The impaired ability to reduce sadness and dysphoria is a key problem for depressed and depressed-prone individuals (Kovacs and Yaroslavsky, 2014). 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). 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). 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). 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 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).

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). 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).

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.

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 the 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 was conducted in two parts (Study 1. and Study 2.) 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).

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).

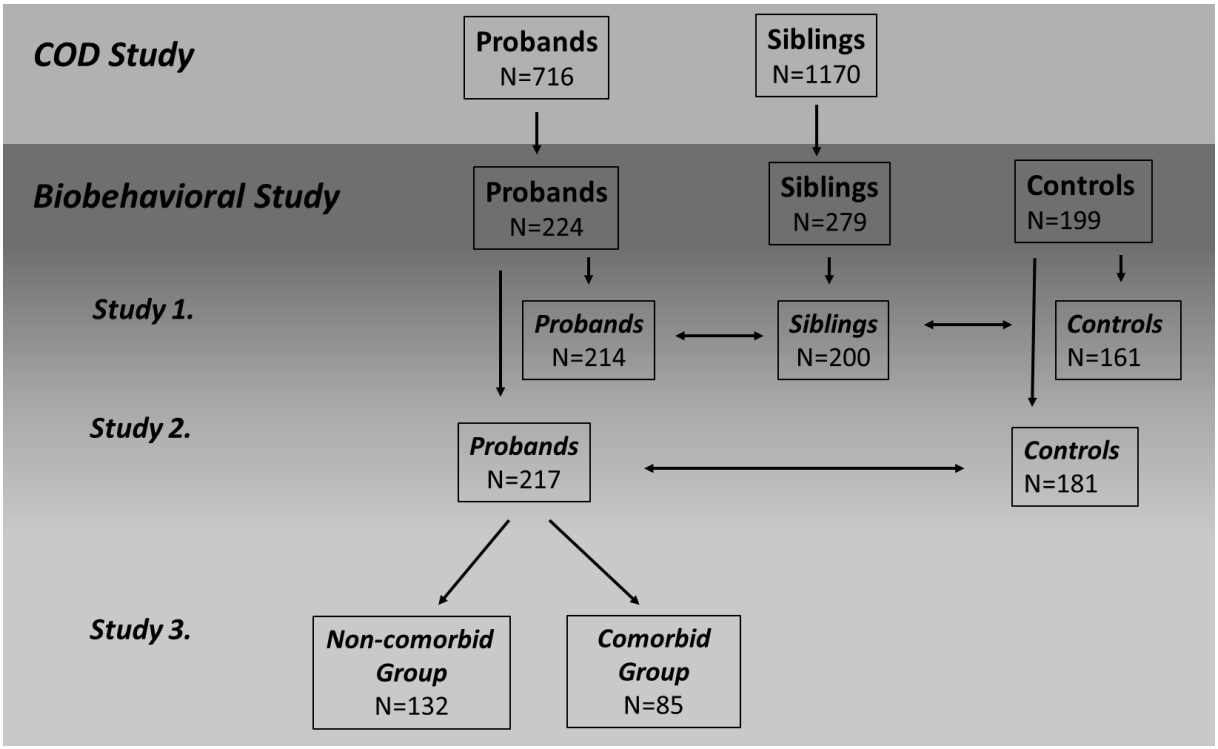

Fig. 1. Study samples COD Study, Biobehavioral Study, Study1. and Study 2.

Measurements

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

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) (Sherrill 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 in the Biobehavioral Study. 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

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. 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). In order to control for depressive symptoms, the Child Depression Inventory (CDI) was administered (Kovacs, 1992).

Sample

As presented in Fig 1, our proband subjects originated from a large sample recruited for the COD study. For the COD study children were recruited through 23 child psychiatric facilities (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. 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. 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. 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. 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.).

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. 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). During the Biobehavioral Study, the enrollment of the control subjects was continuous. 181 healthy controls were enrolled at the time point of Study 2. (Fig.1).

3. Results

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 1, *p*s<.01). Probands reported lower Adaptive and higher Maladaptive FAM-C scores relative to controls across all mood repair response domains (*p*s<.001). 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 (Bylsma et al, 2015).

Study 2

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.) We repeated the comparison of FAM-C scores between probands and controls. FAM-C scores showed similar results as in our findings in Study 1. (Table 1.)

Table 1. 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

We further examined the different FAM-C scores in males and females. 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 2).

Regarding the Maladaptive FAM-C scores female probands' sores were the highest of all analyzed groups through all Maladaptive domains. (Table 2).

Table 2. 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

Further, we compared the FAM-C scores of the proband group as a function of depressive status. 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 3).

Table 3. 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

Study 3.

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

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 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 4). 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 4).

Table 4. 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**

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 5). 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). 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).

Table 5. 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

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

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 6)

Table 6. FAM-C scores in the Non-Comorbid group and Comorbid group as a function of sex and the 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				

4. Discussion

The main aim of my research work was to investigate the ER of youths with major depression and comorbid depression and anxiety disorder to gain a broader understanding of the importance of the ER 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.

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.

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. 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. We found that anxiety comorbidity in youngsters with lifetime depression was associated with dysfunctional ER, since probands with comorbidity used maladaptive ER strategies more frequently than non-comorbid peers. To extend the previous findings in the field, we examined different aspects of ER 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. 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. 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 (Fig 2., Fig 3.)

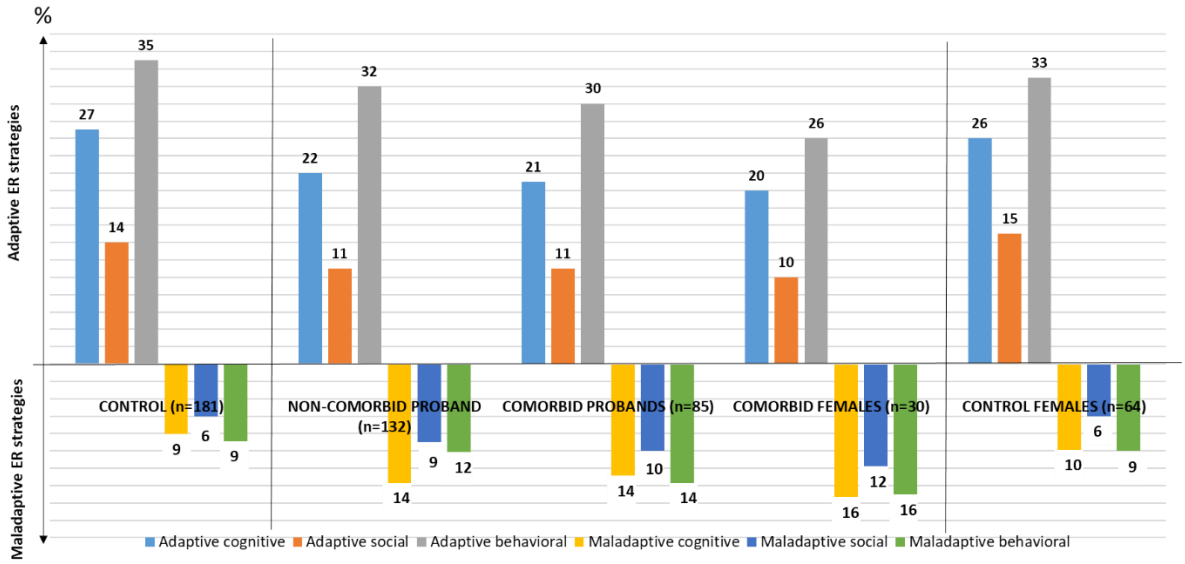

Fig 2. ER profile of study groups as a function of internalizing psychopathology and sex

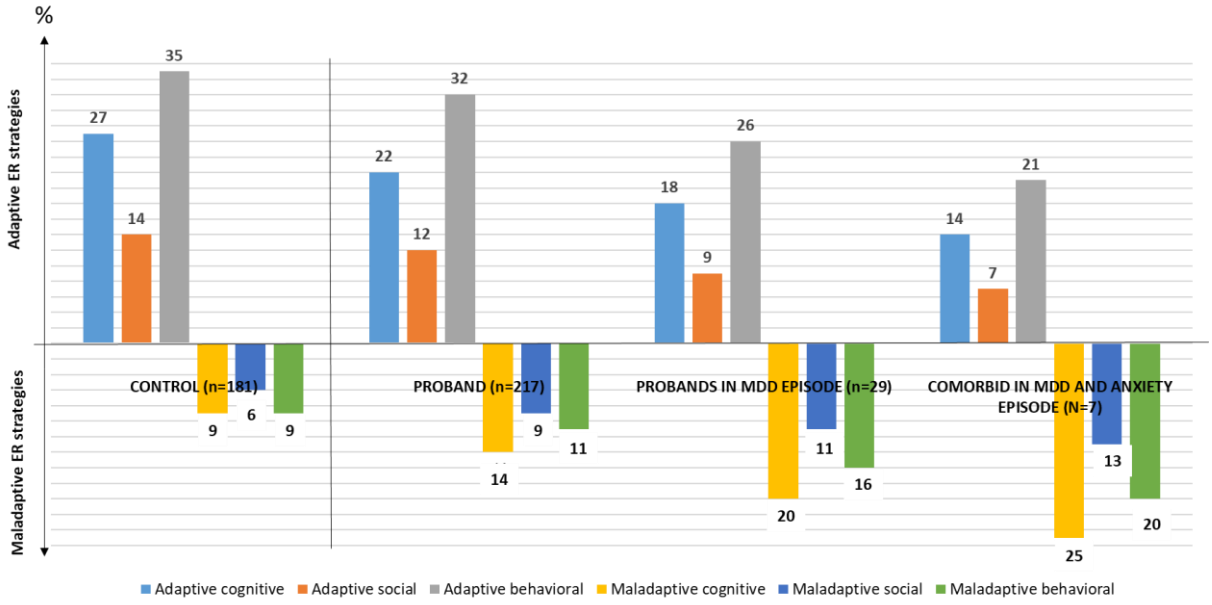

Fig 3. ER profile of study groups as a function of MDD and anxiety episode status (lifetime episode vs. currents episode)

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.

We can conclude that 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 (Fig. 2. 3).

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

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1. Kapornai K, Baji I, Benák I, **Dochnal R**, Dósa E, Kiss E, Merkely B, Prohászka Z, Szabados E, Varga A, Vetró Á, Kovács M. A gyermekkori depresszió rizikótényezői – múlt, jelen, jövő. Psychiátria Hungarica. "Friss kutatási eredmények az idegrendszer fejlődése és pszichés zavarok területén" *Psychiat Hung* 2020, 35(1):46-57

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