THE BIOLOGICAL CORRELATES OF EMOTION DYSREGULATION IN ADOLESCENTS

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TITLE: The biological correlates of emotion dysregulation in adolescents

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LAY ABSTRACT

Emotion dysregulation (ED) is a transdiagnostic feature of psychopathology that presents as elevations in comorbid internalizing and externalizing symptoms and/or disorders; however, it is unknown whether ED may manifest more prominently from externalizing versus internalizing brain process. A neural measure of ED would help differentiate between these processes. Thus, the first study in this thesis synthesized the available literature on biological correlates of ED and found evidence for differences in neural correlates involved in mood versus behavioural disorders. The second study explored correlations between frontal and parietal electroencephalographic asymmetry and ED in a transdiagnostic sample of youth and compared youth with major depressive disorder (MDD) only to youth with MDD comorbid with oppositional defiant disorder (ODD) or disruptive mood dysregulation disorder (DMDD) and controls. Findings of this thesis suggest differences in neural processes underlying ED in different disorder categories, which has important implications for the measurement and treatment of ED.

ABSTRACT

Background: Emotion regulation is the ability to modulate behavioural responses to emotion-inducing stimuli in a goal directed manner. When emotion regulation processes become maladaptive, it results in emotion dysregulation (ED). ED is present in 25-45% of children with psychiatric disorders and strongly predicts poor clinical outcomes. ED presents as elevations in comorbid internalizing and externalizing symptoms. The relative contributions of these heterotypic comorbidities to ED in a particular patient is unclear. Clinicians must prioritize treatment of either domain of symptoms without empirical evidence. Objective measures of ED would assist in guiding treatment decisions. This thesis aimed to explore the biological correlates of ED with a focus on associations between ED and electroencephalographic (EEG) asymmetry. A secondary aim was to explore whether these relationships differed in populations with mood versus behavioural disorders.

Methods: A systematic review was conducted to qualitatively evaluate present literature on ED and its biological correlates. The relationship between frontal and parietal EEG asymmetry and ED, measured by the child behaviour checklist – dysregulation profile, was assessed in a secondary analysis of the D-Psypher dataset with a transdiagnostic sample of 88 adolescents with varying severity of psychopathology and risk for ED. Relationships were assessed in the whole sample, and according to the following groups: depression only, depression comorbid with a behavioural disorder, and controls.

Results: The systematic review included 12 studies and found ED-related differences in neural, cardiac, and genetic measures. The second study found associations between right parietal EEG asymmetry and ED in the whole sample and in youth with depression only. In youth with comorbid depression, ED was associated with left frontal asymmetry.

Conclusion: This thesis outlines several findings related to the biological correlates of ED in adolescents. Understanding how these correlates differ in various disorder categories has important implications for the measurement and treatment of ED.

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Finally, I would like to thank my family for their endless amounts of love and support. Most importantly, I would like to extend my utmost gratitude to my husband for always believing in my potential and supporting and encouraging all my dreams, no matter how big – this would not have been possible without you.

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LIST OF ALL ABBREVIATIONS AND SYMBOLS

ED → emotion dysregulation
RSA → respiratory sinus arrhythmia
EEG → electroencephalographic
LPP → late positive potentials
BPD → bipolar disorder
ADHD → attention deficit hyperactivity disorder
RSA → respiratory sinus arrhythmia
WM → white matter
FC → functional connectivity
ODD → opposition defiant disorder
DMDD → disruptive mood dysregulation disorder
MDD → major depressive disorder
RdoC → research domain criteria
MeSH → medical search heading
LAMS → Longitudinal Assessments of Manic Symptoms
K-SADS-MRS → Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale
K-SADS-DRS → Depression Rating Scale
PGBI-10M → Parent General Behaviour Inventory-10 Item Mania Scale
DSM-5 → Diagnostic and Statistical Manual of Mental Disorders – fifth edition
DBD → disruptive behaviour disorders
GFA → generalized fractional anisotropy
CBCL-DP → Child Behaviour Checklist – Dysregulation Profile
fMRI → functional magnetic resonance imaging
EFNBACK → emotional-n-back
PFC → prefrontal cortex
dlPFC → dorsolateral prefrontal cortex
vlPFC → ventrolateral prefrontal cortex
dACC → dorsal anterior cingulate cortex
MDCT → mindfulness-based cognitive therapy
ERC → Emotion Regulation Checklist
CDRS-R → Children's Depression Rating Scale- Revised
YMRS → Young Mania Rating Scale
FPN → frontoparietal network
CON → cingulo-opercular network
DMN → default mode network
ACC → anterior cingulate cortex
ERN → error-related negativity
DERS → Difficulties in Emotion Regulation Scale
ERP → event-related potentials
HUF → Hungarian Forints

MIDT → monetary incentive delay task
RewP → reward positivity
SPN → stimulus preceding negativity
RST-PQ BIS → personality questionnaire behavioural inhibition scale
ECG → electrocardiogram
BRIEF → Behaviour Rating Inventory of Executive Function
ASD → autism spectrum disorder
HP → heart period
MDE → major depressive episode
NE → negative emotionality
PANAS -C → Positive Affect and Negative Affect Schedule for Children
$ETCO_2$ → continuous end-tidal CO_2
RR → respiratory rate
ANOVA → analysis of variance
MFQ → Mood and Feelings Questionnaire
YSR → Youth Self Report
CBC → Child Behaviour Checklist
ASEBA → Achenbach System of Empirically Based Assessment
ODD → oppositional defiant disorder
mPFC → medial prefrontal cortex

DECALARATION OF ACADEMIC ACHIEVEMENT

I am the primary author of each study featured in this thesis. For each study I developed the research question and study protocol. I planned and performed all statistical analyses and wrote each manuscript. Detailed explanations of all authors' contributions are described below.

This sandwich thesis consists of four chapters. Chapter 1 provides an overview of background information relevant to the two studies presented in this thesis. Chapter two presents a literature review on emotion dysregulation and its biological correlates in adolescents. This paper is currently under review for publication. Chapter 3 presents a primary research manuscript on the relationship between electroencephalographic asymmetries and emotion dysregulation in adolescents. Chapter 4 concludes the thesis with a general discussion of the concepts discussed across both studies presented in this thesis.

BG is the sole author for chapters 1 and 4 of this thesis. For chapter 2, BG and KB jointly conceived the paper. BG was the primary author of the manuscript and developed the methodology and data extraction form. KB approved the study design and BG and NS screened and extracted data from the available literature. BG primarily wrote the manuscript with assistance from KB and NS in drafting early versions of the manuscript. Authors KB, LM, and IB assisted in critically revising the manuscript. All authors (BG, NS, LM, IB, KB) reviewed several versions of the manuscript and read and approved the final manuscript.

For chapter 3, the research protocol was created by KB and LS. Participant recruitment, data, collection, and data recording/processing was done by KB, LS, LD, VS, and DH. For this manuscript, BG was the primary author. BG devised the research question and methodology based on the pre-collected data and performed all statistical analyses and wrote the manuscript. KB supervised and assisted in the development of the research question and data analysis, and critically reviewed and approved the manuscript. LS also assisted in guiding the research question and data analysis. This study was funded by the Ontario Mental Health Foundation Grant.

CHAPTER 1. GENERAL INTRODUCTION

1.1 Emotion Regulation

Emotions refer to momentary changes in behaviour, subjective experience, and peripheral nervous system physiology that unfold overtime. According to the modal model of emotion, emotional responses follow a linear path, where a psychologically relevant situation grasps the attention of the subject, followed by cognitive appraisal of the situation, and finally an emotional response to said situation (Gross, 1998). Depending on the context, these emotional responses can either be helpful or harmful. Helpful emotional responses involve appropriate attention allocation towards key contextual cues that allow an individual to engage in appropriate contextual appraisal and resultantly an appropriate emotional and behavioural response. This includes emotions of fear that may prevent an individual from engaging in a potentially harmful activity. Emotions may also be harmful if they are experienced at a maladaptive frequency, intensity, or duration, or if the type of emotion is inappropriate for the context. For example, feelings of extreme sadness that interfere with one's daily functioning.

Emotion regulation refers to attempts in controlling the type, frequency, intensity, and duration or emotions (Gross, 1998). Successful regulation of emotion can occur at any stage of the modal model. In the first stage, an individual can select situations to engage in according to prospective emotional responses, or the selected situation can be modified to alter its emotional impact. Moreover, attention can be directed to aspects of the situation that promote an emotional response in line with the individual's goals. During

cognitive appraisal, cognitive change can be used to select one of several potential emotions that may be elicited in response to the situation. In the final stage, emotion can be regulated by modifying responses to the emotional stimulus once emotion has been elicited. This includes up or downregulation in response tendencies to the emotional stimulus.

Attentional deployment is a strategy that develops in infancy and continues being used into old age. This strategy generally involves using a distractor to disengage attention from a negative stimulus. This may occur spontaneously or effortfully. Electroencephalographic (EEG) studies demonstrate that these processes occur early on in the emotion generation process and help downregulate late positive potentials (LPP) associated with both negative and positive arousal (Hajcak et al., 2009; Thiruchselvam et al., 2011). Functional neuroimaging studies demonstrate the role of distraction in downregulating activation in subcortical regions involved in emotion generation, like the amygdala (Ferri et al., 2013; McRae et al., 2010).

1.2 Emotion Dysregulation

Emotion dysregulation (ED) manifests as ineffective emotion regulation and the phenotype is most certainly variable. Theoretically, ED results from deficits in some facet or several facets of the emotion regulation process. Given the centrality of emotion regulation capacity to normative mental functioning, ED confers vulnerability to several neuropsychiatric disorders in children and adolescents and indeed is evident in the clinical phenotype of affected individuals. This is consistent with definitions in adults whereby anger and impulsivity are core features of illnesses in which ED is a core feature (i.e.,

bipolar disorder (BPD)). Clinically, this presents as extreme and transient increases in emotional intensity and lability, often alongside angry or impulsive behaviours (Theodore P. Beauchaine 2015). However, theoretically, any clinical syndrome where a set of symptoms implies difficulties in effectively modulating behaviour in a goal directed manner may qualify as ED (Hilt, Hanson, and Pollak 2011; D'Agostino et al. 2017).

In the thesis, I adhere to the conceptualization that ED would necessarily imply that the affected individual experiences emotional problems in both internalizing and externalizing domains of functioning. Given this organizing construct of ED – albeit one used by many other experts in the field - one important consideration is the variation in internalizing and externalizing symptoms. That is, the extent to which internalizing or externalizing symptoms contribute to the phenotypic presentation of ED does vary greatly within patient groups. To date, no standardized phenotypic description for ED exists, however, it is standardly referred to as a pattern of emotional expression that interferes with appropriate, goal-directed behaviour (Beauchaine 2015).

Clinically, the most typical way ED is measured clinically is by the presence of co-occurring relative elevations in the patient's externalizing and internalizing symptoms (Brinke et al., 2020). Such broadband measures of ED likely identify a heterogeneous construct that is determined by different biological pathways to the same outcome. This is a significant problem for management or therapeutic interventions for ED or determining subtypes of ED that may have different etiologies. However, at this time in history, other measures of ED have yet to be adequately developed. As such, we use the internalizing and externalizing composite and examine its biological correlates.

Given this conceptualization, measuring ED in depressed youth and exploring its physiological correlates is likely to be important to guide specificity in formulation and treatment options for depression as a broader syndrome. For purposes of the thesis, ED is not thought to be a separate disorder but also is not a subtype of any disorder. It is measured as a dimensional construct whereby some people have more or less of it, and it occurs alongside any disorder or syndrome of interest.

1.3 Using Electroencephalography to Study Emotion Dysregulation

Emotional states were once considered to be subjective, unquantifiable, and unnameable in scientific research (T. P. Beauchaine & Zalewski, 2016). We now understand that the prefrontal cortex is central to the mediation of emotional processes (Gray, 1990). Today, Davidson's approach/withdrawal model of frontal alpha EEG asymmetry has been widely explored and validated as a neurobiological correlate of multiple psychopathologies and emotional and motivational tendencies (Coan & Allen, 2003; R. J. Davidson, 1984; Richard J. Davidson, 1994). EEG asymmetry refers to the relative difference in cortical activation between the right and left hemispheres. It is calculated by subtracting the natural log-transformed power scores from the right hemisphere minus the left hemisphere while using the central Cz electrode as a reference electrode (Coan & Allen, 2004). For example, frontal asymmetry values are calculated by subtracting the natural log-transformed power scores from site F4 minus F3. Parietal asymmetry values are calculated by subtracting scores from site P4 minus P3. Power scores are inversely related

to activity, meaning that higher scores on this asymmetry metric reflect greater relative left frontal activity and lower scores reflect greater relative right activity.

Davidson's frontal activation-emotion model posits that approach-related tendencies are identifiable by patterns of greater relative left frontal activation compared to right frontal activation (herein referred to as left frontal asymmetry), and withdrawal-related tendencies are identifiable by greater relative right frontal activation compared to left (herein referred to as right frontal asymmetry) (Coan & Allen, 2004). Withdrawal related behaviours have been found to be associated with internalizing symptoms and increased sensitivity to threatening stimuli. Meanwhile, approach related behaviours are associated with externalizing symptoms and increased sensitivity to reward-related cues (Grimshaw & Carmel, 2014). As such, right frontal EEG asymmetry theoretically reflects the presence of greater internalizing symptoms, while left frontal EEG asymmetry reflects greater externalizing symptoms in a particular patient (Theodore P. Beauchaine, 2015; Bunford et al., 2015; Coan & Allen, 2003; R. J. Davidson, 1984; Grimshaw & Carmel, 2014; Palmiero & Piccardi, 2017). As a reminder, ED can be measured by increases in externalizing and internalizing symptoms, making frontal EEG asymmetry a plausible point of investigation in relation to ED. Keeping in mind the differential contributions of externalizing versus internalizing symptoms in the manifestation of psychopathology mediated by ED, further exploration surrounding the applicability of the EEG asymmetries that characterize approach and withdrawal related affect to ED is needed.

The impetus for exploring the role of parietal EEG asymmetry in ED stems from research about ED in youth with attention deficit hyperactivity disorder (ADHD). There is a

significant overlap in the clinical presentation of ED and ADHD, including shared deficits in inhibition, temporal discounting, delay aversion, and difficulties in regulation – during periods of over- or under-activation (Bunford et al., 2015). Youth with ADHD are more likely to experience intensified emotions and appear to have a lack of control over these emotions. They also engage in impulsive behaviour, hyper-talkativeness, and intense emotions. These symptoms appear to be a result of a lack of control from the prefrontal cortex to the amygdala, presenting similar to a dysregulated profile (Hale et al., 2010; Shaw et al., 2016). The prefrontal cortex plays a central role in regulatory and control processes and samples of youth with ED and youth with ADHD both demonstrate deficiencies in prefrontal maturation, suggesting that ADHD and ED may arise from abnormalities in shared neurobiological pathways (Theodore P. Beauchaine, 2015; Shaw et al., 2016). Existing literature suggests that adult patients with ADHD demonstrate right-sided EEG asymmetry in inferior parietal regions as compared to healthy controls (Hale et al., 2014). Further, in both ADHD and ED, literature implicates the role of deficient top-down control of the amygdala from the prefrontal cortex (Beauchaine, 2015). Thus, existing literature provides the basis for exploring parietal and frontal EEG patterns in individuals exhibiting a dysregulation profile.

1.4 Thesis Objectives

This thesis is comprised of two studies. Chapter two describes the first study, which is a systematic review exploring the scope of currently studied, objective, biological markers of ED in the adolescent population. Chapter three focuses on the second study, which

delves further into exploring potential associations between EEG asymmetry and ED in adolescents with MDD.

The primary aim of the systematic review was to identify the breadth of currently explored biological correlates of ED in the adolescent population. The adolescent period is an important developmental period for consideration in the study of ED. The neural underpinnings of ED begin maturing in early childhood and continue developing into the early 20s. During the adolescent period, youth are also expected to engage in social experiences that promote the use of emotion regulation skills to maintain interpersonal relationships. Since emotion regulation is less heritable and mainly socialized, these experiences are vital for the developing adolescent brain. Failure to develop this capacity for emotion regulation confers risk for multiple psychopathologies in youth and adulthood. As such, early detection of ED is imperative, and given the aforementioned difficulties in defining and measuring ED, exploring biological measures associated with ED is essential in aiding this early detection. This review summarizes findings from studies that look at the associations between ED and the following biological measures: respiratory sinus arrhythmia (RSA), white matter (WM) integrity, functional connectivity (FC), neural electrical activity, and genetic polymorphisms in the serotonin-transporter-linked promoter region gene.

Given the diversity in diagnostic categories that participants were assigned to across the studies included in the review, our secondary aim was to assess how ED varied between clinical groups, and between clinical groups and healthy controls, and whether the underlying biological correlates of ED also varied between these groups. This objective

played a central role in informing the research aims for the second study highlighted in this thesis. In the systematic review, we found that the brain-based biological correlates associated with ED (i.e., white matter microstructural integrity) may vary between behavioural versus ED disorders. Although ED is a transdiagnostic phenomenon, our results suggested that biologically, it may manifest differently in different disordered populations. This provided the basis for exploring how the relationship between ED and its biological correlates varies between youth from different disorder categories.

As such, the primary aim of the second study is to explore the relationship between ED and frontal and parietal asymmetry in a transdiagnostic sample of care-seeking youth and youth from the community with no psychiatric disorder. Our secondary aim is to assess for any differences in EEG asymmetry related to ED in youth with an emotional disorder only, compared to youth with comorbid emotional and behavioural disorders, and healthy controls. The mood disorder present within our sample is MDD, and the behavioural comorbidities included are opposition defiant disorder (ODD) and disruptive mood dysregulation disorder (DMDD).

We were interested in exploring these associations in youth with MDD due to the high degree of overlap between MDD and ED, and the large degree of heterogeneity within MDD. The onset of MDD peaks between the ages of 15 and 29, and earlier onset is associated with a chronic course of symptoms across a patient's lifetime. Moreover, child or adolescent-onset depression is associated with higher levels of negative patient-reported outcomes compared to patients with adult-onset MDD or healthy populations. Currently, 256 different symptom clusters exist that can qualify an individual for a

diagnosis of MDD. This introduces a high degree of phenotypic heterogeneity within MDD. For example, some symptoms of MDD produce contrasting effects, such as sleeping too much versus sleeping too little. Moreover, individuals with MDD are also likely to have another comorbid mental or physical disorder, like obesity or anxiety, which also contributes to heterogeneity in clinical presentation. ED is a transdiagnostic feature of many psychopathologies, including depression, that may contribute to the heterogeneity that we see in depression.

With these two studies in mind, the overarching theme of this thesis is to establish greater measurement specificity for the construct of ED. ED is a priority target for treatment in mood and behavioural disorders. It confers a higher risk of poor treatment outcomes, like suicidality, making it important for clinicians to consider how the phenomenon may differ phenotypically and neurobiologically between patients. The possibility of using an objective, measurable construct, like EEG asymmetry, to measure ED has the potential to clearly and efficiently identify patients that may benefit from interventions that target ED. By exploring how these objective measures may differ in their relationship with ED across different patient subgroups, we can also develop measures and treatments that are more specific to treating ED in particular patient populations.

CHAPTER 2. Biological Correlates of Emotion Dysregulation in Adolescents: A Systematic Review

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This paper is currently under review for publication.

2.1 ABSTRACT

Background: Emotional dysregulation is a complex disorder that is highly prevalent in adolescents. ED manifests with impairment in cognitive, biological, social, behavioural, and/or attentional processes. The multi-system deficits observed with ED make diagnosis challenging and the course of illness often difficult to predict. Herein, this present review will investigate the neural correlates of ED that may guide treatment approaches.

Methods: Studies that evaluated the association between ED and separate neural correlates in adolescent populations were searched in ProQuest, OVID, EBSCO, and PsycINFO between database inception and September 22, 2021. Four independent reviewers evaluated the studies in accordance with the inclusion/exclusion criteria. A separate search was conducted in the reference list of articles that were selected for a full-text review.

Results: Twelve studies met the inclusion criteria following the literature search. Four studies assessed the association between ED and RSA. Greater RSA withdrawal was associated with greater ED. Two studies compared neural measures of WM microstructural integrity to scale-based measures of ED. Neural correlates associated with ED included associations between ED and ERN, as well as ED and ERP.

Conclusion: The most commonly assessed biological correlates were RSA and there was association between changes in RSA and ED development. Neural correlates, like ERPs and ERN, appear to be associated with ED-related changes in activation, connectivity, or structure. However, transdiagnostic samples are needed to accurately assess the generalizability of these results in a diverse patient population like adolescents with ED.

2.2 Introduction

Emotion dysregulation (ED) is a highly impairing and complex emotional and behavioural manifestation in adolescents. It is common in clinical settings and not rare in community samples, and there is extant variation in how it is defined across clinical and research settings. Clinically, it is defined as patterns of emotional experience/expression that interfere with appropriate goal directed behaviour, and typically presents as extreme, in the moment, emotional intensity and lability, and is often associated with angry or impulsive behaviours (Beauchaine, 2015). Theoretically, cognitive, biological, social, behavioural, and attentional processes work together to modulate behaviour, and ED is defined as the failure to effectively learn or apply any one or more of these processes (Hilt et al., 2011). Due to variation in definitions and measurement, some outpatient settings report rates of dysregulation amongst pediatric clinical populations to be as low as 7%, while others report numbers as high as 45% (Althoff & Ametti, 2021). Data from adult literature confers that this number is likely closer to 25-45% of patients in clinical settings (Shaw et al., 2016). It is associated with comorbidity, clinical complexity and is a stronger risk factor for suicide and poor clinical outcomes than other symptom clusters (D'Agostino et al., 2017). Being able to identify and treat ED requires understanding of the processes contributing to ED, and how it may be different from other psychiatric syndromes.

A potential problem for the field of measurement is that there are many behavioural or checklist measures of ED currently in use (Althoff & Ametti, 2021). This is due to the variation in defining ED, and as a result of this variation, most measures only assess one

particular aspect of emotion regulation to infer ED. Meanwhile some measures assess broad challenges with self-regulation using extreme elevations in symptoms of co-occurring internalizing and externalizing disorders (Brinke et al., 2020). Internalizing disorders are characterized by avoidance-related behaviours, such as depression and anxiety. Meanwhile, externalizing disorders are characterized by approach-related behaviours, like impulsivity and aggression (Beauchaine, 2015). However, the extent to which internalizing versus externalizing symptoms contribute to ED may vary, where for some youth, ED is more likely to result from externalizing processes, as opposed to internalizing (Beauchaine, 2015). Some measures are empirically derived including self-report or observer report indicators relating to the intense experience of all negative emotions, associated impulses, urges, or associated behaviours (i.e., self-harm, yelling). Other scales use measures of emotion regulation to index ED, and typically involve inferring successful regulation of emotions through positive behavioural responses to negative or challenging emotional stimuli (Beauchaine, 2015). While many of these measures are associated with clinical impairment that is extreme, and in many cases distinct from other clinical disorders such as major depressive disorder (MDD), more work is needed to establish discriminant validity for ED.

Using behavioural measures to index psychopathology are generally less reliable than biological measures when the latter are available. The Research Domain Criteria (RDoC) emphasizes that the validity of psychiatric syndromes should not rest solely on behavioural measures (Insel, 2014). Behavioural symptoms generally result from multiple possible etiological pathways, as such, the best choice for treatment cannot be determined

by assessing levels of externalizing versus internalizing symptoms alone (Beauchaine & Hinshaw, 2020). Thus, it is imperative that we find an objective biological measure of ED to assist in guiding clinical decision making.

This systematic review has two aims: First, to identify the breadth of currently studied objective correlates of ED. Based on the existing literature, we expect to identify studies involving respiratory sinus arrhythmia (RSA), neuroimaging and electroencephalography. Based on the correlates that are identified, we will describe what these measures currently inform us about the biological processes involved in ED in adolescents. The second aim is to consider whether ED in clinical groups differs from healthy controls, and possibly other, non-dysregulated clinical groups to demonstrate the content validity of the construct of ED in adolescents.

2.3 Methods

2.3.1 Literature Search and Study Selection

We operationalized ED as any pattern of emotional experience and/or expression that interferes with an individual's ability to modulate behaviour in an appropriate and goal-directed manner (Beauchaine, 2015). The literature was assessed for studies that evaluated associations between ED and biological factors in pediatric populations. A search was conducted on S for English-language articles published between database inception to September 22nd, 2021 using the following medical search heading (MeSH) terms and search strings: emotion* dysregulation AND adolescen* AND (biological OR

biomarker OR correlate OR predictor). An additional search was performed in the reference list of identified articles.

2.3.2 Eligibility Criteria

Inclusion Criteria:

Our inclusion criteria are as follows:

1. Participant age ranging from 10 to 19 years old.
2. Recorded biological correlates of ED.
3. Recorded validated measure of ED.
    a. (observational, or self-report or objective)

Exclusion Criteria:

Our exclusion criteria are as follows:

1. Unpublished data sets, case studies, conference reports, non-refereed abstracts, or observational studies.
2. Multiple reports from the same data set.
3. No recorded biological measures of ED.
4. No recorded validated measures of ED.
5. Animal studies.

2.3.3 Data Extraction

Four independent reviewers systematically screened all titles and abstracts for eligibility. Authors B.G. and N.S. reviewed the full-text of all articles that met inclusion criteria. Data was extracted using a standard data extraction form for: study ID or DOI, title, author, year, specific aims, study design, population description (clinical/non-clinical,

primary diagnosis/symptoms), sample size, gender distribution, age of participants, validated measure for ED, and biological correlate of ED.

2.4 Results

2.4.1 Search Results and Study Characteristics

Our initial search revealed 666 studies. After the removal of 50 duplicates, we reviewed the titles and abstracts of 616 unique articles. The full texts of 38 articles were screened for eligibility, and 26 articles were excluded. The reasons for exclusion are as follows: ten articles were excluded for having participants that did not meet our specified age range, seven studies were excluded for not recording a validated measure of ED, seven studies were excluded for not recording a biological correlate of ED, and two studies were excluded for reporting results from already included datasets. A complete summary of the search results is reported in **figure 1**. Findings from a total of twelve studies were systematically reviewed. A summary of the study characteristics is displayed in **table 1**.

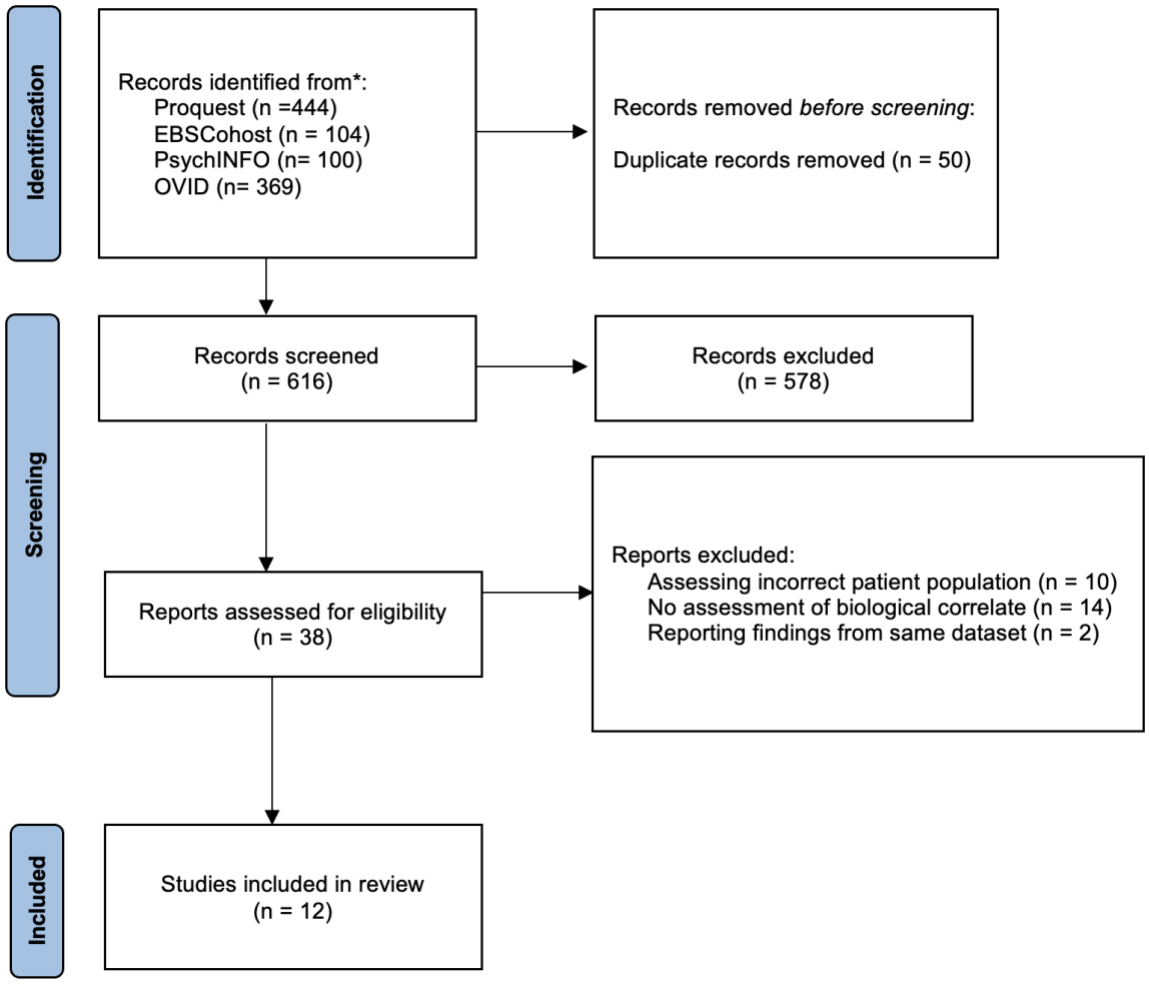

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) study selection flow diagram.

2.4.2 Neural Correlates of Emotion Dysregulation

2.4.2.1 White Matter Structural Integrity

Two studies explored the association between ED and white matter (WM) microstructural integrity using diffusion imaging tractography (Tsai et al., 2021; Versace et al., 2015). Versace et al. (2015) studied a mixed clinical/control sample of 121 youth recruited from the Longitudinal Assessments of Manic Symptoms (LAMS) study. The clinical groups included youth with behavioural and/or emotional dysregulation disorders, including, attention deficit hyperactivity disorder (ADHD), bipolar spectrum disorder, depressive or anxiety disorders, and disruptive behaviour disorder. They compared dimensional measures of ED (hypomanic/manic and depressive symptoms on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale [K-SADS-MRS], and Depression Rating Scale [K-SADS-DRS], and the Parent General Behaviour Inventory-10 Item Mania Scale [PGBI-10M]) and categorical measures of ED (clinician determined diagnoses using K-SADS) with WM structural integrity (gauged by fractional anisotropy and radial diffusivity) in the cingulum, uncinate fasciculus, and forceps minor. The axial diffusivity, radial diffusivity, and volume of each WM tract of interest was also extracted for each participant. These brain regions have been consistently found to play a role in a number of emotional psychiatric disorders (ex: MDD) in youth, and to a lesser extent in behavioural psychiatric disorders (ex: ADHD). This includes the role of the forceps minor in supporting interhemispheric associations of emotions, and the role of the uncinate fasciculus in emotion reappraisal strategies, warranting further exploration (Versace et al., 2015).

Researchers found a main effect of diagnostic group on WM integrity in the forceps minor ($P = .042$) and the uncinate fasciculus ($P = .009$), and a main effect of manic symptoms on WM integrity in the cingulum ($P = .043$). Post-hoc analyses revealed that participants with ED disorders only demonstrated significantly lower fractional anisotropy in the forceps minor compared to typically developing controls ($P = .006$), and to those with both behavioural and ED disorders ($P = .015$), or with behavioural dysregulation disorders only ($P = .025$). Similar trends were seen in fractional anisotropy in the uncinate fasciculus, where participants with ED disorders demonstrated lower fractional anisotropy compared to both other diagnostic categories (both $P = .004$), and controls ($P = .005$). Researchers also found lower axial diffusivity in the forceps minor and uncinate fasciculus of youth with ED disorders compared to control youth or youth from the other two diagnostic categories (all $P < .004$). Furthermore, a significant main effect of mania scores on fractional anisotropy ($P = .043$) and axial diffusivity ($P = .05$) in the cingulum was observed. There was a significant positive association between mania scores and fractional anisotropy in the cingulum across both control and clinical samples ($P = .048$). However, this association did not remain significant for scores of 14 or more in clinically diagnosed youth, or scores of less than 14 in control youth. Exploratory analyses using conventional Diagnostic and Statistical Manual of Mental Disorders – fifth edition (DSM-5) diagnoses revealed higher fractional anisotropy in the uncinate fasciculus in youth with pure or comorbid ADHD compared to youth without ADHD ($P = .038$), and youth with pure or comorbid disruptive behaviour disorders (DBD) compared to youth without DBD ($P = .026$). Compared to typically developing controls, youth with

DBD demonstrated lower fractional anisotropy in the uncinate fasciculus (P = .079) (Versace et al., 2015).

Tsai et al. (2021) assessed the association between ED and WM integrity (gauged using the generalized fractional anisotropy value [GFA]) in 91 youth with a DSM-IV-TR diagnosis of ADHD, compared to 122 typically developing controls. The GFA corresponds to the fractional anisotropy value featured in the study by Versace et al. (2015). However, it is superior to fractional anisotropy in characterizing diffusion in environments of complex tissue and heterogenous fiber configurations. Tsai et al. (2021) used a whole-brain tract-brain approach, where major WM tracts across the brain were analyzed and mean GFA values from 76 tracts were derived from each participant. GFA values correspond to WM integrity, where higher GFA values indicate better WM microstructural integrity. The GFA values of 19 of the 76 tracts were found to positively correlate with severity of ED, measured by elevated scores on the Child Behaviour Checklist – Dysregulation Profile (CBCL-DP). The 19 tracts of interest have been found to play an integral role in connecting cortical regions associated with sensory and affective processing, emotion regulation, and cognitive control. In particular, the WM integrity of the mid- and posterior-corpus collosum was found to covary with ED, suggesting dysfunction in the interhemispheric integration of affective information. Interestingly, the direction of the relationship differed between youth with ADHD versus typically developing controls, wherein youth with ADHD demonstrated a negative correlation between ED severity and GFA values of the 19 tracts, and the control group exhibited a positive correlation. As such, in youth with ADHD, lower ED severity was

associated with better WM integrity, while in typically developing controls, better WM integrity was associated with greater ED severity. Additionally, the presence of ADHD and ADHD symptom severity was found to be negatively associated with GFA values, while intelligence (measured by the full-scale intelligence quotient) was positively associated with GFA values (Tsai et al., 2021).

2.4.2.2 Functional Connectivity and Neural Activity

Two studies used functional magnetic resonance imaging (fMRI) to examine changes in functional activity and connectivity in adolescents with dysregulated mood (Bertocci et al., 2014; Qin et al., 2021). Bertocci et al. (2014) assessed task-based neural activity during the emotional-n-back (EFNBACK) task. They divided a subsample of youth from the LAMS study into two trajectories of ED, based on biannually collected scores across five years on the PGBI-10M: 1) youth with initially high ED that continued to decrease (HighD), and 2) youth with initially low ED that continued to decrease (LowD). Data collected from these two groups was compared to 24 healthy controls to determine functional abnormalities in neural circuitry associated with trajectories of ED by measuring recruitment of prefrontal cortical systems during the EFNBACK task, where emotionally salient stimuli are presented during a working memory task.

Results indicated that compared to healthy controls, LowD demonstrated greater activation in the bilateral dorsolateral prefrontal cortex (dlPFC), but this group showed only laterally greater activation in the left dlPFC when while compared to HighD (both P = .001). Interestingly, participants from the HighD group also performed poorly on the

EFNBACK task compared to both the LowD and healthy control groups (P = .003), suggesting that greater activation in the dlPFC may be involved in compensating for mild decreases in task performance due to emotional and behavioural dysregulation. Analysis of functional connectivity (FC) between the amygdala and regions of the bilateral prefrontal-anterior cingulate cortex that are associated with ED found that compared to LowD, HighD had reduced positive FC between bilateral amygdala and the left ventrolateral PFC (vlPFC) ($p<.001$). Similarly, compared to LowD, HighD also had reduced FC between bilateral amygdala and two clusters in the left dorsal anterior cingulate cortex (dACC) (P = .001). Functional connectivity between amygdala and dACC/vlPFC of healthy controls did not differ significantly from LowD and HighD. Healthy controls were recruited on the basis of having no psychiatric diagnoses themselves, along with no first-degree relatives with any mood disorders and psychosis, and any second-degree relatives with bipolar spectrum disorder and psychosis. It is unclear whether these parameters were determined on the basis of current or lifetime diagnoses, and no clinical measures were collected for healthy controls to substantiate their categorization in the control group. Including clinical measures for these individuals may assist in further explaining this finding (Bertocci et al., 2014).

Qin et al. (2021) studied the impact of a 12-week mindfulness-based cognitive therapy (MBCT-C) intervention on network-level neurofunction at rest, specifically network efficiency and characteristic path length, in ten adolescents with ED and a familial history of bipolar disorder. Dysregulation was determined by meeting any one of the following cut-offs: a score <27 on the Emotion Regulation Checklist (ERC), a score >28 on the

Children's Depression Rating Scale- Revised (CDRS-R), or a score >12 on the Young Mania Rating Scale (YMRS). No significant changes in clinical measures of depression (P = .474), global functioning (P = .059), mania (P = .553) or emotion regulation (P = .102) were seen following the MBCT-C protocol. Participants underwent fMRI scanning before and after the intervention. The frontoparietal network (FPN), cingulo-opercular network (CON), and the default mode network (DMN) were the major networks of interest due to their previously demonstrated involvement in mindfulness-based interventions. Following MBCT-C, the FPN and the CON demonstrated lower characteristic path length (FPN p=.017, CON p=.023) and higher network efficiency (FPN p=.014, CON p=.020). No such differences were seen in the DMN. Notably, the reduction in characteristic path length of the CON was significantly associated with a change in scores on the ERC (P = .005). Moreover, increased functional connectivity was seen in a region of the CON comprised of 14 nodes and 19 connections (involved mainly in the anterior cingulate cortex [ACC], dlPFC, basal ganglia, insula, and thalamus), as well as three nodes and two connections within the right fusiform and bilateral superior frontal gyrus of the DMN following MBCT-C. Associations between neuronal function at the aforementioned regions of interest and scores on the ERC at baseline was not assessed (Qin et al., 2021).

2.4.2.3 aElectroencephalographic Measures

Heffer and Willoughby (2021) assessed error-related negativity (ERN) in a subsample of 424 youth using EEG during the go/no-go task. Latent class analysis further subdivided the subsample into four groups according to impulsivity measured by participant ratings

to four statements related to impulsive behaviours, and ED measured by three items of the Difficulties in Emotion Regulation Scale (DERS): High Dysregulation/High Threat Sensitivity/Low-Moderate Impulsivity (group one), Moderate Dysregulation/Moderate Threat Sensitivity/High Impulsivity (group two), Low-Moderate Dysregulation/Moderate Threat Sensitivity/Low-Moderate Impulsivity (group three), and Low Dysregulation/Low Threat Sensitivity/Low Impulsivity (group four). With a 95% bootstrapped confidence interval, group one (i.e., the high dysregulation/high threat sensitivity/low-moderate impulsivity group) demonstrated the largest ERN during the task and group two demonstrated the lowest. Groups three and four did not demonstrate any significant differences (Heffer & Willoughby, 2021).

Zubovics et al. (2021) assessed the role of neural responsivity during reward processing tasks in predicting ED and dispositional affectivity using Event-related potentials (ERP). The Doors task is a measure of reward sensitivity, where participants were briefly presented with 120 sets of two doors and were asked to select either the left or right one. After each trial, they were presented with either an arrow facing up to indicate a gain of 100 100 Hungarian Forints (HUF), or an arrow facing down to indicate a loss of 50 HUF. The Monetary Incentive Delay (MID) task was used as a measure of reward sensitivity and anticipation. Participants underwent 192 trials where they were presented with a series of cues in the form of full circles, full squares, and empty circles or squares to indicate the gain, loss, or neutral nature of each trial, respectively. Following a brief anticipatory period, participants were presented with a target stimulus and were required to press a button to gain or avoid losing money. They were informed of their success and

failures, along with the total cumulative monetary award they earned on the screen. Participants were informed that any virtual money earned from either task would be redeemable for snacks and fruits.

The following five subscales of the DERS were used to assess ED: nonacceptance of emotional response, difficulty engaging in goal directed behaviour, impulse control difficulites, lack of emotional awareness, and limited access to emotion regulation strategies. Event-related potentials of interest included: reward positivity (RewP), Cue P3, Target P3, and stimulus preceding negativity (SPN). Regression analyses revealed that during gain trials of the Doors task, RewP was negatively associated with the DERS awareness subscale ($P = .046$), and during loss trials, RewP was negatively associated with scores on the DERS strategies subscale ($P = .046$). During both the gain and loss trials, there was a negative correlation between Cue P3 and scores on the DERS strategies subscale (both $P = .046$). Meanwhile, SPN during loss anticipation on the MID task was negatively associated with scores on the DERS impulse subscale ($P = .046$). Results from multiple regression analyses revealed that 10.9% of the variance in DERS strategies scores is related to the Cue P3 gain trials of the Doors task, while self-reported scores on the reinforcement sensitivity theory – personality questionnaire behavioural inhibition scale (RST-PQ BIS) described 29.8% of the variance in scores on the DERS strategies subscale ($P < .001$). Furthermore, 9.8% of the variance in DERS impulse scores was related to SPN during loss trials of the MID, and an additional 18.2% of the variance was related to RST-PQ-BIS scores ($P = .008$).

2.4.3 Cardiac and Respiratory Correlates of Emotion Dysregulation

2.4.3.1 Respiratory Sinus Arrhythmia

Four studies used electrocardiogram (ECG) to examine the association between RSA and ED in various clinical samples of youth. All four studies assessed the association between ED and baseline RSA, along with one or more related cardiac measure (Byrd et al., 2020; Guy et al., 2014; Kovacs et al., 2016; Van Beveren et al., 2019). Three studies found no relation between baseline RSA and ED (Guy et al., 2014; Kovacs et al., 2016; Van Beveren et al., 2019). Meanwhile, one study found that in 162 youth receiving psychiatric treatment for any emotional or behavioural problem, baseline RSA measured during three two-minute periods of mundane tasks interacted with RSA reactivity (RSA-R) during an eight-minute parent-child conflict task to predict dysregulation of complex emotions (shame, guilt, loneliness, and emptiness) in response to parent-child conflict ($P = .016$). Moreover, higher RSA withdrawal was associated with greater dysregulation of basic emotions (sadness, anger, nervousness, and stress) ($P = .013$). It is of note that participants were oversampled for high emotional reactivity according to the Affective Instability subscale of the Personality Assessment Inventory-Adolescent version. Emotion dysregulation was assessed during a four-day ecological momentary assessment protocol, where participants reported subjective feelings of various emotions on a four-point Likert scale at ten timepoints (Byrd et al., 2020).

A separate study investigated how scores on the Emotional Control subscale of the Behaviour Rating Inventory of Executive Function (BRIEF) related to baseline and task-based RSA and heart period (HP) in 19 youth diagnosed with autism spectrum disorder

(ASD) compared to a typically developing sample of 22 controls. Task-based RSA and HP were measured during two, five to six minute long socially and cognitively challenging tasks (the social conversation task from the Autism Diagnostic Observation Schedule and the Matrices subtest of the Differential Abilities Scale – Second Edition). Baseline RSA and HP measures were collected before and after the administration of these tasks. Researchers found that participants with ASD demonstrated significantly greater levels of ED compared to controls ($P < .001$). Furthermore, a positive association between ED and HP across both groups was observed ($P < .05$), and no significant relationship between RSA and ED was found (Guy et al., 2014).

Kovacs et al. (2016) studied the association between ED indexed by parent- and self-reports of latent mood repair, and baseline RSA and RSA-R. The sample consisted of 178 youth in remission with a history of recurrent major depressive episodes (MDEs). At visit one, baseline RSA was measured during a 180 second period of paced breathing, and RSA was also measured while youth watched a 164-second clip from a film used to induce sadness. RSA-R was calculated as the difference in baseline RSA and RSA during the film clip. As such, RSA withdrawal was indicated by positive RSA-R values, while augmented RSA was indexed by negative RSA-R values. Normative patterns of RSA were defined by baseline RSA values higher than the sample mean combined with RSA withdrawal. All other combinations of RSA and RSA-R were defined as atypical. While baseline RSA and RSA-R were not individually associated with ED, RSA patterns were correlated with ED, where atypical patterns were correlated with higher ED and normative patterns were related to lower ED ($P < .05$) (Kovacs et al., 2016).

Van Beveren et al. (2019) studied the relationship between ED and change in RSA (ΔRSA) from baseline in a sample of 55 adolescents at the extreme ends of the negative emotionality (NE) spectrum. Participants were selected from a sample of youth who participated in a larger study. They were screened based on their scores on the negative (PANAS-NE) and positive (PANAS-PE) emotionality scales of the Positive Affect and Negative Affect Schedule for Children (PANAS-C). Participants with a score ≥38 on the PANAS-NE and ≤43 on the PANAS-PE were assigned to the higher end of the NE spectrum. Meanwhile, they were assigned to the lower end of the NE spectrum if they scored ≤28 on the PANAS-NE and ≥50 on the PANAS-PE. Emotion dysregulation was inferred from maladaptive versus adaptive emotion regulation strategies, measured using the total adaptive, total maladaptive, and external emotion regulation subscales of the FEEL-KJ. Five baseline epochs for resting RSA were measured while adolescents watched an eight minute film clip that was confirmed to evoke neutral mood ($P < .001$). Baseline RSA measures for each epoch did not differ significantly from one another. As such, an average baseline RSA value was computed for each participant. Respiratory sinus arrythmia was also measured during the reward (four epochs) and frustration (four epochs) conditions of the affective Posner paradigm. Four ΔRSA scores per condition were calculated for each participant by subtracting the average baseline RSA from the RSA scores measured during each condition of the Posner paradigm. Researchers found that ΔRSA decreased across epochs in both Posner conditions. In the frustration condition of the paradigm, the slope of the ΔRSA was associated with both self- ($P = .012$) and parent- ($P = .018$) reported maladaptive emotion regulation strategy usage. Youth with

higher self-reported usage of maladaptive emotion regulation strategies also demonstrated greater reductions in ΔRSA from baseline to epoch one in the frustration condition, along with slower decreases in ΔRSA across epochs in the frustration condition. There was no association between ΔRSA and adaptive or external emotion regulation in either condition (all $P \geq .053$) (Van Beveren et al., 2019).

2.4.3.2 Hyperventilation

One study explored the relationship between hyperventilation and ED. Henje Blom et al. (2014) compared 66 age-matched healthy controls against 79 female adolescent psychiatric patients with a validated diagnosis of MDD and/or an anxiety disorder. Hyperventilation was recorded using an oxycapnograph to measure continuous end-tidal CO_2 ($ETCO_2$) and respiratory rate (RR), where low $ETCO_2$ and high RR indicated hyperventilation. As expected, significantly higher levels of ED were found in the clinical group compared to the control group ($P < .001$). Whole-sample analyses demonstrated that higher ED was correlated with a higher RR ($P < .01$) and lower ETCO2 ($P < .001$), suggesting that ED is associated with hyperventilation. Notably, these correlations were not significant when the clinical and control groups were analyzed separately (Henje Blom et al., 2014).

2.4.3.3 Genetic Correlates of Emotion Dysregulation

Our search of the available literature identified one study that assessed genetic correlates of ED in youth (Zimmermann & Spangler, 2016). This study explored the interaction between the short (ls/ss) versus long (ll) allelic variations of the serotonin-transporter-linked promoter region (5-HTTLPR) gene, and maternal attachment style on adolescent

observed emotion regulation during a standardized, emotion eliciting computer game. Results from a gene x attachment analysis of variance (ANOVA), with the frequency of effective emotion regulation strategies engaged in by youth as the dependent variable, and maternal intrusiveness and task duration as covariates, showed no significant main effect of 5-HTTLPR polymorphisms on emotion regulation. The same ANOVA performed with the frequency of ineffective emotion regulation as the dependent variable also demonstrated no significant effects. However, post hoc analyses using t-tests found that heterozygous or homozygous carriers of the short allele with a secure attachment style demonstrated significantly fewer instances of ineffective emotion regulation strategies, compared to short allele carriers with an insecure attachment style ($P = .04$). Interestingly, participants that were homozygous for the long allele of the 5-HTTLPR gene were significantly faster at completing the computer game than ls or ss carriers ($P = .024$). This may indirectly reflect better regulation of emotion in individuals homozygous for the long allele. Notably, participants homozygous for the long allele with insecure attachment styles also demonstrated fewer instances of ineffective emotion regulation compared to carriers of either one or two short allelic variations ($P = .023$). Apart from this, no significant effect of attachment on ineffective emotion regulation in individuals homozygous for the long allele was seen. The effects of allelic variations on emotion dysregulation without the effects of maternal intrusiveness were not assessed. Gender effects were discussed briefly, where the frequency ($P = 0.014$) and duration ($P = 0.012$) of negative emotions was higher in females compared to males (Zimmermann & Spangler, 2016).

2.5 Discussion

This systematic review explored the association between several biological measures and the clinical phenomenon of ED in adolescents. Twelve studies met the inclusion criteria for our review, and each study found differences in neural, cardiac, or genetic measures related to ED (Bertocci et al., 2014; Byrd et al., 2020; Guy et al., 2014; Heffer & Willoughby, 2021; Henje Blom et al., 2014; Kovacs et al., 2016; Qin et al., 2021; Tsai et al., 2021; Van Beveren et al., 2019; Versace et al., 2015; Zimmermann & Spangler, 2016; Zubovics et al., 2021). The most prevalent biological correlate assessed across four studies was RSA (Byrd et al., 2020; Guy et al., 2014; Kovacs et al., 2016; Van Beveren et al., 2019). With regards to neural measures, two studies compared WM microstructural integrity to scale-based measures of ED (Tsai et al., 2021; Versace et al., 2015). Meanwhile, two separate studies assessed changes in FC associated with ED (Bertocci et al., 2014; Qin et al., 2021). Neural-based studies also found associations between ED and ERN (Heffer & Willoughby, 2021), and ED and ERP (Zubovics et al., 2021). Finally, one study assessed differences in ED according to genetic polymorphisms of the 5-HTTLPR gene and its interaction with maternal attachment (Zimmermann & Spangler, 2016).

2.5.1 Respiratory Sinus Arrythmia

In the available literature, RSA was the most prevalent biological measure assessed in relation to ED. At baseline, RSA was not found to correlate with ED (Guy et al., 2014; Kovacs et al., 2016; Van Beveren et al., 2019). However, RSA-R and the interaction between RSA and RSA-R was found to be associated with ED across three studies (Byrd et al., 2020; Kovacs et al., 2016; Van Beveren et al., 2019). In a transdiagnostic sample of

youth with high emotional reactivity, greater RSA withdrawal was associated with higher ED (Byrd et al., 2020). In youth in remission from recurrent major depressive episodes, typical patterns of RSA (baseline RSA levels higher than sample mean combined with RSA withdrawal during emotion inducing stimulus) was associated with lower ED, while any other patterns of RSA were associated with higher ED (Kovacs et al., 2016). In youth with extreme negative emotions, higher RSA-R was associated with parent- and self-reported usage of maladaptive emotion regulation strategies (Van Beveren et al., 2019). Literature supports the role of RSA as a marker of cardiac vagal tone, and higher RSA-R (driven by higher RSA withdrawal) reflects higher arousal following exposure to emotional stimuli (DiPietro et al., 1992; Fortunato et al., 2013; Grossman & Taylor, 2007). This increased arousal (or increased RSA withdrawal) is generally associated with greater attention allocation to the emotion-inducing stimulus coupled with lower regulatory control over one's affective response, signifying difficulties in inhibitory processes that would allow for the optimal use of psychological resources (Fortunato et al., 2013; Kovacs et al., 2016). As such, our results may suggest that altered parasympathetic tone in youth with ED may subserve maladaptive attentional control strategies that contribute to poor affective regulation. However, these aberrant attention allocation strategies are also well documented in MDD literature and given the high prevalence of depressive symptoms in the samples of these studies, it may be that these findings are reflective of other symptoms related to depression, and not ED. This suggests the possibility of either intense affect, or difficulties with regulation that may subserve ED and its associated parasympathetic correlates. Empirical studies that parse between

ED and emotional intensity are needed to explain the role of increased RSA-R in these samples of youth.

2.5.2 Functional Neuroimaging

Functional neuroimaging studies demonstrated changes in regions of the FPN and CON in participants with ED, with the most robust changes being observed in the dlPFC (Bertocci et al., 2014; Qin et al., 2021). During the EFNBACK task, the lateralization of these changes varied according to the level of dysfunction demonstrated by participants, where participants with low ED demonstrated a bilateral increase in dlPFC activity, and individuals with higher levels of ED demonstrated a left-sided increase only. Coupled with findings that reflect lower task performance on the EFNBACK by individuals with high ED, this suggests that individuals with low ED can effectively upregulate dlPFC activity to aid in task performance. Meanwhile, those with high ED are unable to sufficiently compensate for poorer task performance. Similarly, reduced FC between the bilateral amygdala and the left vlPFC, and the bilateral amygdala and the left dACC was also observed in highly dysregulated individuals (Bertocci et al., 2014). Additionally, following intervention with MBCT-C, participants with ED plus a familial history of bipolar disorder demonstrated improved functional integration in the CON (which includes the dACC, insula, and thalamus), and these changes were also associated with improvements in regulating affect (Qin et al. 2021).

2.5.3 White Matter Microstructural Integrity

Neuroimaging studies measuring WM microstructural integrity demonstrated a loss in connectivity between regions involved in the interhemispheric integration of affective

information, the regulation and processing of affect, and cognitive control in youth with ED and behavioural or emotional psychopathology. Namely, in youth recruited from the LAMS study, ED was associated with loss in WM integrity in the mid- and posterior-corpus collosum, the forceps minor, and the uncinate fasciculus (Bertocci et al., 2014; Versace et al., 2015). Interestingly, in youth with ADHD, higher ED severity was associated with improved WM integrity in regions related to cognitive control and affective processing and regulation, including the limbic system, cortico-limbic circuitry, and sensory-emotional feed-forward circuitry. Meanwhile, in typically developing controls, higher severity of ED was associated with reduced WM integrity in the same regions. This altered directionality of the relationship between ED and WM integrity in youth with ADHD may reflect the role of distinct neural correlates underlying behaviours associated with ED in youth with ADHD, and these differential neural underpinnings may be associated with unique emotion regulation strategies in ADHD (Tsai et al., 2021).

2.5.4 Neural Electrical Activity

Task-based EEG studies demonstrated ED-related differences in ERP and ERN (Heffer and Willoughby 2021; Zubovics et al. 2021). As a reminder, ERP measures neural activations related to cognitive, motor, and sensory processing, and ERN is a type of ERP that appears following an incorrect response during tasks that require the correct classification of any particular stimulus (Hallion et al., 2018; Sur & Sinha, 2009). During the go/no-go task, which measures response inhibition, typically developing youth exhibiting high ED (measured using the DERS), high threat sensitivity, and low to moderate impulsivity demonstrated the highest ERN, while youth with moderate ED,

moderate threat sensitivity, and high impulsivity demonstrated the lowest ERN (Heffer and Willoughby 2021). This suggests that ERN potency – an indicator of self-monitoring – is not only logically associated with threat sensitivity as shown by others (Weinberg et al., 2015), but also ED. Whether this process occurs for all youth with ED remains to be studied.

During the Doors task, significant differences related to difficulties in regulating emotion according to the DERS self-report were found in RewP (measure of reward processing), SPN (measure of reward anticipation and cognition), and CueP3 (measure of attentional orienting) (Zubovics et al., 2021). Neural activations consistent with poor reward processing (gauged by RewP) in gain trials were associated with scores that reflected difficulties in remaining aware of one's own affective state. Meanwhile, during loss trials, patterns of RewP that reflected poor reward processing were associated with scores that demonstrated difficulties in improving mood. Participants with difficulties in improving mood also demonstrated ERPs consistent with difficulties in appropriately orienting attention in a goal-directed manner (gauged by CueP3). Finally, during the MID task, a measure of reward sensitivity and anticipation, participants with scores suggesting difficulties in regulating behaviour when in distress demonstrated patterns of ERPs consistent with poor loss processing (SPN) (Zubovics et al., 2021). As such, these results suggest that difficulties in reward processing and attention allocation may underlie ED.

2.5.5 Biological Correlates of ED in Behavioural versus Emotional Dysregulation Disorders

The findings of this review suggest that the biological correlates associated with ED may vary between behavioural and ED disorders. Versace et al. (2015) studied a transdiagnostic sample that included participants with behavioural dysregulation disorders (operationalized as ADHD and DBDs), and ED disorders (operationalized as depressive and bipolar spectrum disorders). Youth with ED disorders only demonstrated significantly lower WM integrity in the forceps minor and uncinate fasciculus compared to youth with behavioural plus ED disorders, youth with behavioural disorders only, and controls. The latter three groups demonstrated levels of WM integrity that were similar to one another. An exploratory analysis using conventional DSM-5 diagnoses demonstrated that youth with pure behavioural dysregulation disorders, or youth with comorbid emotional and behavioural dysregulation disorders had higher levels of WM integrity in the uncinate fasciculus compared to youth without behavioural disorders. All of the groups also demonstrated significant positive correlations between symptoms of mania and WM integrity in the cingulum for K-SADS-MRS scores >14 in the clinical samples and <14 in the control group (Versace et al., 2015). Similarly, Tsai et al. (2021) also found a negative correlation between WM integrity and ED in youth with ADHD, however, the directionality of this association differed for healthy controls, where higher ED were positively correlated with WM integrity in the control group (Tsai et al., 2021). Including a transdiagnostic sample in this study would help delineate whether this change in directionality is specific to ADHD, or if these differences are a result of differential

neural correlates subserving behavioural disorders, compared to ED disorders or healthy controls. These differences between youth from different diagnostic categories also warrant further exploration of scale-based or biological measures that are specific to detecting ED in particular disordered populations.

2.6 Limitations and Future Directions

Psychiatric illnesses are complex and involve multiple, interdependent biological processes contributing to their clinical symptomatology. Measurement error decreases when using psychiatric symptoms to physiological or anatomical measures, as well as from categorical to dimensional measures (Beauchaine & Hinshaw, 2020). According to the RDoC, the role of neural systems should be given increased focus in research about mental illness, and, in addition, DSM-5-based disorder categories may not be the optimal starting points for RDoC informed research (Beauchaine & Hinshaw, 2020).

Of particular importance to measurement in this review, ED was measured clinically using several different scales, which may index different aspects of ED. To this point, reports of the prevalence of ED in clinical samples of youth is quite variable (7-45%), depending on the measure or sample used (Althoff & Ametti, 2021; Holtmann et al., 2008). A recent review of the literature recommended using the combination of a broadband measure of ED (ex: the CBCL-DP) along with a measure of chronic issues with mood regulation (ex: the affective reactivity index), plus a measure that retrospectively characterizes emotional outbursts to index ED most accurately in children and adolescents (Althoff & Ametti, 2021). Moreover, ED is an index of difficulties in regulation and functional impairment, making a measure of social dysfunction a critical

component for the measurement of ED (Silverman et al., 2022). These components of measurement are important in ensuring that the construct measured is indeed ED, and not severe psychopathology.

Only four of the 12 studies in this review used more than one measure to gauge ED (Byrd et al., 2020; Qin et al., 2021; Van Beveren et al., 2019; Versace et al., 2015). In fact, one study did not use any scale-based measures at all, rather inferred ED using clinician observation (Zimmermann & Spangler, 2016), while another study used the presence of ED disorders and mood symptoms to infer ED (Versace et al., 2015). As the concept of ED disorders has not yet been established, nor has the distinctiveness of ED from behavioural symptoms consistent with depression in youth, this approach introduces confusion as to whether ED is the outcome or a covariate in the research study. Future studies should aim to measure ED clinically using multiple measures.

The sampling approach used may be as critical as selecting the measure of ED. In theory, ED, as its biological correlates has transdiagnostic properties. At the same time, it may manifest differently in participants depending on their phenotypic composition, and this is a critical research question. Thus, it behooves researchers to consider both issues simultaneously, when comparing independent study findings OR ideally in the context of systematic review and meta-analysis. The key question remains: in what aspects is the physiology of ED similar across different clinical groups AND is in what ways is it different? This may be hypothesis driven research, depending on whether the research question implies a more top-down or bottom-up framework, or the extent to which participant abilities to regulate affect or behaviour are considered in the model. Ability to

regulate may be an important covariate in predicting different brain pathways that are independent of clinical phenotype. The take home point is that we know that ED and biological processes are transdiagnostic and not disorder-specific and therefore should not be treated as such (Aldao, 2012; Fernandez et al., 2016), and at the same time, recruitment typically occurs while classifying participants into groupings that are theoretically guided. A disorder-specific approach to assessing the utility of these biological measures in indexing ED across disorders is insufficient and at times necessary and future research will benefit from integrating findings across studies with similar measures or population composition, with the most heterogenous samples offering the most informative results. Future studies should aim to recruit transdiagnostic samples to better highlight correlates specific to ED. Furthermore, considering the equifinality of ED, whole-brain analyses are important in gaining an accurate representation of the neural correlates underlying ED.

The importance of considering multiple related measures is emphasized by findings from Guy et al. (2014). This study examined RSA differences in youth with ASD and found that although the patterns of HRV, RSA and RR in the ASD sample reflected what is seen in populations with deficits in emotion regulation, there was no statistically significant relationship between baseline RSA and ED. The authors speculate that this may be due to the limited capabilities of their choice of scale-based measure of ED, the emotional control subscale of the BRIEF (Guy et al., 2014). However, the remaining RSA-related studies in this review found differences in RSA-R, or the interaction between RSA and RSA-R to be associated with ED; this study did not evaluate these relationships (Byrd et

al., 2020; Guy et al., 2014; Kovacs et al., 2016; Van Beveren et al., 2019). Additional analyses exploring associations between RSA-R would help clarify these results.

2.7 Conclusion

In conclusion, ED is a construct that underlies several psychiatric illnesses in youth and adulthood and is a strong predictor of negative clinical outcomes and suicidality. Current clinical guidelines require clinicians to infer the presence of ED using indirect measures, which often leads to a significant degree of impreciseness. Objective measures are needed, and this review summarizes the current literature exploring objective, biological correlates of ED. The most widely explored correlate is RSA, and RSA-R demonstrates significant correlations with ED across clinical groups. Neural correlates, like ERPs, functional connectivity, and WM integrity are becoming increasingly more prevalent in ED research, and our review found some consistency in brain regions that demonstrated ED-related changes in activation, connectivity, or structure. Future studies should aim to use transdiagnostic samples to assess the accuracy and generalizability of these results to diverse patient populations, and the genetic correlates of ED should also be further assessed.

Table 1: Study Characteristics

Study	Sample size	Gender (No. %)	Mean Age (SD)	Biological Measure	Validated Scale-based or Observational Measure	Clinical Diagnoses Present in the Sample	Main Findings
Bertocci et al., 2014	85	F: 44%; M: 56%	HC: 14.11 (1.93); LAMS: 13.41 (2.21)	Task-based changes in FC	PGBI-10M (parent-report), collected biannually for five years.	Transdiagnostic sample including: ADHD, BPSD, DBD, depressive or anxiety disorders	Youth that started off with low ED scores that continued to decrease demonstrated higher ED-associated activation in the bilateral dlPFC compared to HC, and youth that started off with high ED scores that continued to decrease demonstrated higher activation in the left dlPFC only. Youth with initially high ED also demonstrated reduced positive FC between the bilateral amygdala and left vlPFC, and the bilateral amygdala and the dACC, compared to youth with initially low ED.
Byrd et al., 2020	162	F: 47%; M: 53%	12.03 (0.92)	RSA	Clinician rating plus variability in self-reported feelings of negativity across a four-day ecological momentary assessment	Transdiagnostic sample including: ADHD, ODD, BPD, MDD, GAD, SAD, CD, DMDD, social phobia, PTSD, PD	Interaction between baseline RSA and RSA-R is predictive of ED.
Guy et al., 2014	36	F: 0%; M: 100%	HC: 13.12 (3.04); ASD: 12.27 (2.97)	RSA	Emotional Control subscale of the BRIEF (self-report)	ASD	High prevalence of ED in ASD group. No association between RSA and ED in either control or clinical group. Positive association between HP and ED across both groups.
Heffer & Willoughby, 2021	424	F: 49%; M: 51%	11.45 (1.78)	ERN	DERS (self-report)	N/A	Highest ERN observed in youth with high dysregulation plus high threat sensitivity, and low-to-moderate impulsivity.
Henje Blom et al., 2014	145	F: 100%; M: 0%	Clinical: 16.8; HC:16.5. No SDs provided.	HRV, $ETCO_2$, and RR	SDQ-em (self-report)	MDD and/or any anxiety disorder	Whole sample analyses revealed significant associations between ED and hyperventilation. Correlations insignificant when analyzed by group.
Kovacs et al., 2016	178	F: 37%; M: 63%	17.14 (1.38)	RSA	FAM (both parent- and self-report versions)	Remission from recurrent major depressive episodes	Interaction between baseline RSA and RSA-R is related to ED, where atypical patterns are associated with higher ED.
Qin et al., 2021a	10	F: 60%; M: 40%	14.6 (1.8)	Change in resting FC post-MBCT-C	ERC (parent-report), CDRS-R (self-report), YMRS (self-report)	Dysregulated mood plus familial risk for BPSD	Reduced characteristic path length of the CON (mainly localized to the ACC, dlPFC, basal ganglia, insula, and thalamus) post-MBCT-C was associated with changes in ER scores.

Tsai et al., 2021a	91	F: 26%; M: 74%	ADHD: 11.63 (2.43); HC: 12.19 (2.85)	WM structural integrity	CBCL-DP (parent-report)	ADHD	WM integrity in the mid- and posterior-corpus collosum covaried with ED. The directionality of the relationship differed between youth with ADHD and HC. In youth with ADHD, lower levels of ED were associated with better WM integrity. In HC, higher levels of ED were associated with better WM integrity.
Van Beveren, Mueller, & Braet, 2019	55	F: 60%; M: 40%	13.69 (1.61)	RSA	FEEL-KJ total adaptive, maladaptive, & external ER subscales (self- and parent-report)	Youth at extreme end of negative emotionality, determined using the PANAS-NE and PANAS-PE	Change in RSA was correlated with parent and youth reported ED. Youth higher in ED demonstrated greater decreases in RSA.
Versace et al., 2015	91	F: 36%; M: 55%	13.8 (2.1)	WM structural integrity	Categorical measurement: clinician determined diagnoses using parent- and child-reports on the K-SADS. Dimensional measurement: K-SADS-MRS, K-SADS-DRS (both parent-and youth-reports), PGBI-10M (parent-report)	Transdiagnostic sample including: ADHD, BPSD, DBD, depressive or anxiety disorders	Lower WM integrity (indexed by FA) in forceps minor and uncinate fasciculus of youth with ED-disorders compared to healthy controls, those with behavioural and emotional dysregulation disorders, or behavioural disorders only. Lower WM integrity in cingulum was associated with greater manic symptoms. Exploratory analyses using DSM-5 diagnoses demonstrated higher WM integrity in uncinate fasciculus of youth with pure or comorbid ADHD or DBD, compared to youth without ADHD or DBD.
Zimmerman & Spangler, 2016	88	F: 51%; M: 49%	12 (0)	Genetic polymorphisms of the 5-HTTLPR gene	Clinician-ratings during observation of participants playing an emotion-eliciting computer game with their mothers	N/A	No significant main effect of 5-HTTLPR gene polymorphism on ER (gauged by frequency of effective ER) or ED (frequency of ineffective ER), with maternal intrusiveness and task duration as covariates. Post-hoc t-tests demonstrated that individuals hetero/homozygous carriers of the short allele plus a secure attachment style demonstrated fewer instances of ineffective ER compared to short allele carriers with an insecure attachment style. Those homozygous for the long allele also demonstrate better ER through faster task completion. Effects independent of attachment style were not assessed.
Zubovics et al., 2020	43	F: 67.4%, M: 32.6%	15.67 (1.01)	Task-based changes in ERP during the MID and Doors tasks	DERS (self-report)	N/A	**MID task** *Loss trials:* negative correlation between SPN and DERS impulse scores. **Doors task** *Gain trials:* negative correlation between RewP and DERS awareness scores. *Loss trials:* negative correlation between RewP and DERS strategies scores. *Both gain and loss trials:* negative correlation between Cue P3 and DERS strategies scores.

Abbreviations: SD=standard deviation, F=female, M=male, HC=healthy controls, LAMS=Longitudinal Assessment of Manic Symptoms Study, FC=functional connectivity, PGBI-10M= Parent General Behaviour Inventory-10 Item Mania Scale, ADHD=attention deficit hyperactivity disorder, BPSD=bipolar spectrum disorder, WM=white matter, DBD=disruptive behaviour disorder, dlPFC, dorsolateral prefrontal cortex, vlPFC=ventrolateral prefrontal cortex, dACC=dorsolateral anterior cingulate cortex, RSA=respiratory sinus arrhythmia, ODD=oppositional defiant disorder, BPD=borderline personality disorder, MDD=major depressive disorder, GAD=generalized anxiety disorder, SAD=separation anxiety disorder, CD=conduct disorder, DMDD=disruptive mood dysregulation disorder, PTSD=post-traumatic stress disorder, PD=panic disorder, RSA-R=respiratory sinus arrhythmia reactivity, ED=emotion dysregulation, BRIEF=Behavior Rating Inventory of Executive Function, ASD=autism spectrum disorder, HP=heart period, ERN=error related negativity, DERS=Difficulties in Emotion Regulation Scale, HRV=heart rate variability, $ETCO_2$=end-tidal carbon dioxide, RR=respiratory rate, SDQ-em= Strengths and Difficulties Questionnaire – Emotional Symptoms Subscale, FAM= Feelings and My Child, and Feelings and Me, MBCT-C=mindfulness based cognitive therapy for children, ERC= Emotion Regulation Checklist, CDRS-R= Children's Depression Rating Scale-Revised, CON=cingulo-opercular network, ACC=anterior cingulate cortex, YMRS= Young Mania Rating Scale, ER=emotion regulation, CBCL-DP=Child Behavior Checklist-Dysregulation Profile, PANAS-NE= Positive Affect and Negative Affect Schedule for Children-Negative Emotionality Scale, PANAS-PE= Positive Affect and Negative Affect Schedule for Children-Positive Emotionality Scale, FA-fractional anisotropy, DSM-5=Diagnostics and Statistical Manual of Mental Disorders – Fifth Edition, K-SADS= Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, K-SADS-MRS=K-SADS Mania Rating Scale, K-SADS-DRS=K-SADS Depression Rating Scale, 5-HTTLPR= serotonin-transporter-linked promoter region, ERP=event related potentials, MID=Monetary Incentive Delay, SPN=stimulus preceding negativity.

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CHAPTER 3. The Association Between Frontal and Parietal EEG Asymmetry and Emotion Dysregulation in a Transdiagnostic Sample of Adolescents

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3.1 ABSTRACT

Background: Major depressive disorder is a leading cause of global morbidity and a risk factor for early mortality. Adolescent-onset MDD is associated with a worse course of illness and increased symptom severity. Emotional dysregulation and dysregulated affective response are core features of MDD psychopathology. Emotion dysregulation is a transdiagnostic feature of psychopathology with several overlapping etiological correlates with MDD. Herein, the present study explores the association between frontal and parietal asymmetry and ED in a mixed clinical/control sample of care-seeking youth with MDD, oppositional defiant disorder (ODD), dysregulated mood disorder (DMDD), and healthy controls.

Methods: We completed a post-hoc analysis of the D-Psypher dataset. The study was approval by the Hamilton Health Sciences Research Ethics Board. A mixed clinical/control sample of 88 adolescents were included (61.4% female). Participants completed two study visits. The first visit included self-report assessments for mood and behaviour followed by a six-minute resting state EEG scan. The EEG scan was repeated at the second visit. Correlational and linear regression analyses were used to explore associations between frontal/parietal EEG asymmetry and ED scores in the whole sample, and in youth with MDD-only compared to MDD comorbid with ODD or DMDD and controls.

Results: In the whole sample, parietal asymmetry was significantly associated with ED scores (β = -0.28, p = 0.03). When separated by diagnostic category, parietal asymmetry was significantly associated with ED (β = -0.47, p =0.02) and significantly predicted ED

in youth with MDD-only (R^2 = .33, $F_{(3,16)}$ = 4.11, p = 0.02). In youth with MDD-comorbid, ED was significantly associated with frontal asymmetry (β = 0.41, p =0.04).

Conclusion: This study demonstrates that ED in a mixed community clinical sample of youth, and in youth with MDD only is associated with right parietal asymmetry. In youth with MDD comorbid with ODD or DMDD is associated with left frontal asymmetry. It appears that the neurobiological mechanisms of ED differ between youth with mood disorders only, compared to youth with comorbid mood and behavioural disorders.

3.2 Introduction

Major depressive disorder (MDD) is a leading cause of morbidity and disability in both youth and adult populations. The onset of MDD peaks between the ages of 15 and 29 and earlier onset is associated with a chronic course of symptoms across a patient's lifetime. Extant literature indicates that child or adolescent-onset MDD is associated with higher levels of negative patient-reported outcomes compared to patients with adult-onset MDD or healthy populations (Blazer et al., 1994; Lewinsohn et al., 1999). This includes higher rates of both mental and physical comorbidities, greater psychosocial impairment, and a greater risk of suicidality (Hammen et al., 2008; Lewinsohn et al., 1999; Marmorstein et al., 2014; Rohde et al., 2013).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) identifies five broadband categories of depression, with MDD alone accounting for 256 possible unique symptom clusters that warrant a diagnosis. Moreover, approximately three quarters of individuals with MDD experience one or more neuropsychiatric comorbidities. This variability in possible symptom clusters combined with high rates of comorbidity confers a high level of heterogeneity in clinical presentation, and resultantly diagnosis and treatment, between patients, as well as between depressive episodes in the same patient. It also suggests the presence of variable biological processes that may underlie psychopathology between patients. Despite this heterogeneity, transdiagnostic features of MDD exist across patients, with emotion dysregulation (ED) being a frequently cited feature of psychopathology in youth.

Dysregulated affective responses are a hallmark feature of depression. Depression is also associated with more frequent uses of maladaptive emotion regulation strategies, and reduced use of adaptive emotion regulation strategies (McLaughlin et al., 2011). These are all features of ED, demonstrating a high degree of overlap between MDD and ED, which suggests that the neurobiology of ED is fundamental to understanding MDD. Dysregulated emotion refers to a pattern of emotional expression that interferes with appropriate, goal-directed behaviour. In clinical settings, it is typically measured using co-occurring elevations in internalizing and externalizing symptoms (Beauchaine, 2015). However, the relative contribution of these heterotypic comorbidities in the manifestation of ED may vary across patients, and this variation may subserve the variation in underlying neurobiology, symptoms, and clinical presentation of patients with MDD. Although comorbid psychiatric disorders generally belong to the same family of disorder (i.e., internalizing, or externalizing disorders), this may not always be the case (Caspi et al., 2020). For example, oppositional defiant disorder (ODD), an externalizing disorder, demonstrates high rates of comorbidity with internalizing disorders, like anxiety and MDD (Boylan et al., 2007).

Internalizing and externalizing symptoms are generally characterized by withdrawal and approach-related behaviours, respectively. Withdrawal and approach-related behaviours are identifiable by patterns of frontal cortical EEG asymmetries, where leftward frontal alpha asymmetry is associated with approach related behaviours and rightward with withdrawal-related behaviours. As such, the underlying neural mechanisms involved in internalizing disorders are different from what is involved in externalizing disorders. As

such, although ED is a transdiagnostic contract underlying both internalizing and externalizing forms of psychopathology, its biological underpinnings likely vary based on the type of disorder or based on the extent to which internalizing versus externalizing symptoms contribute to psychopathology in a particular patient. Thus, further exploration of how neural correlates of ED vary according to disorder categories is imperative.

For the purposes of this study, the adolescent period is a key developmental stage of interest. It is a period that confers a high risk for the onset of MDD and a critical period for the development of adaptive emotion regulation skills (McLaughlin et al., 2011; Steinberg et al., 2015). During adolescence and early adulthood, the limbic system, a key component of the emotion regulation neurocircuitry, continues to mature to allow for more sophisticated forms of cognitive emotion regulation with lessened reliance on adult caregivers to assist in regulating emotion (Gross, 2015). Due to this evolving neurocircuitry in the adolescent brain, particularly the development of neural connections underlying inhibition/self-reflection, this is a key period for intervention and treatment (Beauchaine, 2015). Despite this, the average time elapsed between the onset of depressive symptomatology and the start of treatment is 11 years (Wang et al., 2004). This heterogeneity in clinical presentation of depression may be related to variability in underlying neural mechanisms.

3.2.1 The Neurobiology of Emotion Dysregulation

Emotion regulation is a complex phenomenon that involves several related, yet unique processes (i.e., cognitive, social, behavioural). It is thought that understanding the neurobiological underpinnings of emotional regulation will help elucidate the onset and

progression of ED. The psychopathology of ED calls for a transdiagnostic approach that will be effective in predicting disease progression across psychiatric illness (i.e., mood disorders, behavioural disorders). The fronto-limbic system has emerged as an important treatment target for populations affected by ED due to its role in emotion regulation and processing.

The limbic system consists of cortical (i.e., fornix), subcortical (i.e., hippocampus, amygdala) and diencephalic structures (i.e., hypothalamus). Projections from the limbic sites to frontal and prefrontal areas are heavily implicated in emotion processing, as well as many other important executive functions (i.e., memory consolidation). Unsurprisingly, alterations at the fronto-limbic sites are correlated with a number of psychopathologies (i.e., cognitive impairment, ED, anhedonia) that are common diagnostic features of mood and behavioural disorders.

While ED is a transdiagnostic feature of psychopathology, it remains a challenging target for treatment. For example, adolescence, a period characterized by significant biological changes, is associated with significant social and emotional challenges. It has been hypothesized that changes in brain structures combined with novel social experiences during this period makes it particularly difficult for some youth to regulate emotions, elevating the risk of adolescent mood and behavioural disorders (Powers & Casey, 2015). Notably, remodeling of the frontal-limbic connections during times of extreme social pressures (i.e., adolescence) causes the emotional development to follow a non-linear trajectory. Indeed, the variability in neural development can alter functioning at the level of the frontal-limbic pathway leading to intra-individual variability at these

neurobiological sites. In particular, the development of emotions can be seen in developmental increases of both top-down and bottom-up processes. Bottom-up regulatory processes are centered around the amygdala, ventral striatum, and the orbitofrontal cortex and their main purpose is to detect salient stimuli and signal that regulatory control is needed (Shaw et al., 2016). Meanwhile, top-down regulatory processes involve the medial prefrontal cortex (mPFC) and dlPFC, which are involved in attenuating attention allocation to emotional stimuli (Shaw et al., 2016). Any alteration in these structures during these developmental stages can greatly affect the top-down and bottom-up activity for emotion regulation.

3.2.2 Using Electroencephalography to Study Emotion Dysregulation

Currently, there is an increased focus on neurobiological correlates in the study of psychopathology due to their higher specificity and lower rates of measurement error compared to behavioural measures (Beauchaine & Hinshaw, 2020; Burt et al., 2016). In particular, frontal EEG asymmetry is a promising neural measure in the study of emotion-based disorders (Burt et al., 2016; Coan & Allen, 2004; Smith et al., 2017). The previously described role of externalizing and internalizing symptoms in defining and measuring ED combined with the approach and withdrawal nature of externalizing and internalizing symptoms, respectively, allows for the use of EEG to measure the relative contribution of these heterotypic comorbidities to the psychopathology experienced by a particular patient. As such, according to Davidson's frontal alpha EEG asymmetry model, greater relative left frontal EEG activation compared to right suggests greater externalizing symptoms, while greater relative right frontal EEG activation suggests

greater internalizing symptoms (Coan & Allen, 2003, 2004; R. J. Davidson, 1984; Richard J. Davidson, 1994; Palmiero & Piccardi, 2017).

The potential role of frontal alpha oscillations in measuring ED is further substantiated by research on cortical and subcortical neural structures and how they relate to EEG activation. Subcortically, frontal asymmetry has been shown to be a reliable indicator of functional connectivity between the amygdala and the frontal lobe, an important part of the emotional response (X. Deng et al., 2021). Furthermore, dorsolateral prefrontal cortical activation is associated with emotion regulation via cognitive reappraisal (Cole & Schneider, 2007; Horato et al., 2022). In particular, ED is associated with left dlPFC activity in highly dysregulated individuals, and studies demonstrate that participants with left dlPFC injury exhibit frontal EEG patterns that are similar to participants with MDD, where both groups exhibit greater leftward activation compared to right (Horato et al., 2022). Anatomically, electrode placements at site F3 and F4 correspond to the dorsolateral prefrontal cortex (Chai et al., 2019). As such, frontal EEG asymmetry is an important consideration in the study of ED.

As previously discussed, ED is a multi-faceted phenomenon with a variable phenotype and presumably variable biological signature. As such, this study will also explore the role of parietal EEG asymmetry in ED. The parietal lobe plays an important role in mediating attentional control to negative stimuli, thereby regulating emotion via attentional deployment, and electrodes P3 and P4 correspond to dorsal attentional processes (Lei & Liao, 2017; Shomstein, 2012). This relationship between parietal lobe activation and ED is further strengthened by the overlap between ED and attention deficit

hyperactivity disorder (ADHD), where ED is commonly found amongst patients with ADHD. In both ADHD and ED, patients experience intensified emotional experiences combined with a lack of control over their emotional responses (Bunford et al., 2015; Hale et al., 2014; Shaw et al., 2016). It is possible that the biological underpinnings of ED and ADHD overlap, where symptoms of both ED and ADHD arise from abnormalities in shared neurobiological pathways that involve a lack of top-down control from the prefrontal cortex of the amygdala.

3.2.3 Aims and Objectives

The primary aim of this study is to explore the association between frontal and parietal asymmetry and ED in a mixed clinical/control sample of care-seeking youth with MDD, oppositional defiant disorder (ODD), dysregulated mood disorder (DMDD), and healthy controls. To date, no empirical studies have assessed the relationship between ED and EEG asymmetry in a transdiagnostic sample of youth (Cai et al., 2021). Due to the transdiagnostic nature of ED, it is important to explore the neural correlates of ED in sample that spans atypical and normative development in youth.

As a secondary aim, this study will also explore whether these associations between frontal and parietal asymmetry and ED differ in youth with MDD only, compared to youth with MDD comorbid with ODD or DMDD. This is because youth with MDD that is comorbid with DMDD or ODD typically exhibit more severe symptoms and a higher likelihood of negative outcomes like suicidality, compared to youth with MDD only (Holtmann et al., 2011). As such, it was of interest to this study to explore whether

differences in the association between EEG asymmetry and ED differed in youth with MDD only compared to youth with MDD comorbid with ODD or DMDD.

We hypothesize that higher levels of ED in the whole sample will be associated with rightward parietal asymmetry due to youth with higher levels of ED having greater difficulties mediating attentional control towards emotional stimuli. We also hypothesize that compared to youth with MDD only, youth with comorbid MDD and ODD or DMDD will demonstrate greater levels of frontal leftward asymmetry, due to the externalizing nature of ODD and DMDD.

3.3 Methods

3.3.1 Participants

The present study is a secondary analysis of the D-Psypher dataset. A mixed clinical sample of adolescent participants (N = 88, age range = 10-18, mean age = 14.59, and 61.4% female) with varying degree of psychopathology and risk for ED were recruited. Four participants who were assigned female sex at birth identified as male. 86.4% of participants identified as Caucasian, 4.5% identified as multi-ethnic, 3.4% identified as Hispanic, 1.1% identified as Indigenous, 1.1% identified as Asian, 1.1% identified as African-Canadian/West Indian, and 2.3% identified as other. Clinical participants were recruited from the McMaster Children's Hospital mental health clinic, while healthy controls (n= 19) were recruited from the McMaster Department of Psychology register.

3.3.2 Eligibility Criteria

Inclusion Criteria:

Participants were recruited according to the following inclusion criteria:

1. Participant age ranging from 10-18 years old.
2. A diagnosis of MDD with no history of behavioural disorders for participants assigned pure-MDD clinical group.
3. A diagnosis of MDD comorbid with ODD or DMDD for participants assigned to the mixed-MDD group.
4. No current or past diagnoses of mood, behaviour, or anxiety disorders for participants assigned to the control group.

Exclusion Criteria:

Participants were recruited according to the following exclusion criteria:

1. A minimum score equivalent to the grade six level on the Slosson Oral Reading Test.
2. History of head injury, autism spectrum disorder, or psychotic or bipolar spectrum disorder.

3.3.3 Procedures

The study received approval from the Hamilton Health Sciences Research Ethics Board. Adolescents and their caregivers provided informed consent to participate in the study and were briefed regarding the study procedures prior to their participation. Participants underwent two separate study visits. At visit one, youth were administered a series of diagnostic and baseline assessments and questionnaires. This included the Mood and Feelings Questionnaire (MFQ) Child Self-Report Version to measure symptoms of depression, and the Child Behaviour Checklist (CBCL/6-18) and Youth Self Report (YSR/11-18) to assess ED. At the first visit, participants underwent a six-minute resting state EEG scan using a stretchable cap, with three minutes of eyes open data and three

minutes of eyes closed data. The scans were repeated at visit two to ensure stability. Participants were compensated with a $20 gift card per visit for their participation.

3.3.4 Clinical Measures

3.3.4.1 Child Behaviour Checklist/Youth Self-Report

Parents/guardians of participants were administered the CBCL/6-18, while participants were administered the youth self-report YSR/11-18 versions of the Achenbach System of Empirically Based Assessment (ASEBA). Both scales are validated, dimensional measures of psychopathology in youth. The CBCL/6-18 consists of 112 problem behaviour items and 20 adaptive behaviour items, while the YSR/11-18 consists of 105 problem behaviour items and 14 adaptive behaviour items. Parents and youth were administered either scale by two independent research assistants, and were required to rate each item from 0 (not true) to 2 (very true). For the purposes of this study, the Anxious/depressed, Aggressive behaviour, and Attention problems subscales of the CBCL and YSR were extracted to form the Child Behaviour Checklist-Dysregulation Profile (CBCL-DP). The t-scores from each subscale were summed to form a youth self-report ED score and a parental-report ED score. Dysregulation was measured continuously, and participants with a score greater than two standard deviations above the mean were considered dysregulated (Achenbach & Rescorla, 2001).

3.3.4.2 Mood and Feelings Questionnaire

Recent depressive symptomology was assessed using the youth self-report version of the MFQ. The MFQ is a 33-item scale that retrospectively assesses participants' mood in the

last two weeks. Participants were required to rate each item from 0 (not true) to 2 (true). For our study, a cut-off score of 24 on the MFQ identified participants as depressed (Angold et al., 1987). Complete MFQ scores were available for 76 participants.

3.3.4.3 EEG Data Collection and Processing

Participants were instructed to remain seated and stare straight ahead with their feet flat on the floor, hands in their lap for the duration of the EEG recording. Six minutes (three minutes eyes open, three minutes eyes closed) of continuous, resting state EEG data were collected using a high-density 128 electrode Hydrocel stretchable cap (manufactured by Electrical Geodesics Incorporated [Eugene, Oregon]). Participants kept their eyes open for the first three minutes of the scan. After three minutes, a research assistant informed participants to close their eyes and the scan continued for an additional three minutes. Data in the delta, theta, alpha, and beta frequency bands from both the left and right anterior (i.e., mid-frontal, F3, F4) and posterior regions (i.e., parietal, P3, P4) were collected. Electrodes followed the international 10/20 system and were referenced to the central (Cz) scalp site. Data were sampled at 250 Hz (.1 Hz high pass, 100 Hz low pass), and a high impedance amplifier was used to improve signal-to-noise ratio.

Data were preprocessed offline through a 0.1 Hz first order high-pass filter, and a 50 Hz low-pass filter using Net Station. Brain Vision Analyzer (BVA; Brain Products GmbH, Gilching, Germany) was used to visually score and edit the data. Relevant channels were isolated for processing and continuous EEG data were segmented into eyes-open and eyes-closed data. Segmented data between the end of the eyes-open period and the start of the eyes-closed period was removed from analyses. Independent component analysis

(ICA) was used to remove eye blinks and data was segmented into 100 millisecond epochs with 50 milliseconds overlap. A Hamming Window was used to extract artifact-free epochs. Fast Fourier Transform was used to extract EEG features and compute spectral power density (μV2/Hz) in the alpha band (eight to 13 Hz).

3.3.4.4 Statistical Analyses

All analyses were completed using SPSS Statistics for iOS, version 28.0.1.0 (IBM Corp., Armonk, N.Y., USA). The distribution of the EEG data was normalized, and all power density values were transformed using the natural logarithm. Due to a high degree of correlation between data collected during eyes-open and eyes-closed trials (r= 80-.86), composite EEG scores were calculated by taking the average activation across eyes-open and eyes-closed trials. To ensure accuracy and minimize error due to differing head shapes and sizes, cluster scores were used by taking the average activation of the key electrodes of interest (i.e., F3, F4, P3 and P4), and the four surrounding electrodes. Asymmetry scores were calculated as the difference between the natural log-transformed scores (ln[right]-ln[left]). Asymmetry scores were based on the following homologous pairs: F4-F3 and P4-P3. Due to the inverse relation between EEG power and activation, higher asymmetry scores translate to greater relative left frontal/posterior activation while lower scores translate to greater relative right frontal/posterior activation.

Two main statistical tools were used to achieve our primary and secondary objectives. Bivariate correlation analyses were used to assess for any correlations between ED scores and the following variables in the whole sample: age, MFQ scores, frontal, and parietal

EEG asymmetry scores. Three separate stepwise linear regression analyses were conducted to further delineate the effects of EEG asymmetry on ED scores. In each regression analysis, ED scores were entered as the dependent variable. Although age and ED scores were not significantly correlated with one another in the bivariate correlational analysis, it was still added to the regression model as a predictor due to the effects of age on brain maturation (Arain et al., 2013). Sex was also included as a predictor in the regression models due to sex differences in the prevalence and symptoms of MDD (Hilt & Nolen-Hoeksema, 2009). Sex was coded as 1 = male, 2 = female. An exploratory interaction term between sex and EEG asymmetry was also included as a predictor due the sex differences in resting frontal alpha EEG asymmetry (Cave & Barry, 2021). As such, the following variables were added to the regression model as predictors in the following order: sex (step 1), age (step 2), asymmetry (step 3), the interaction between asymmetry scores (step 4). Three separate models were used to assess the following: 1) the effects of parietal asymmetry on ED in the whole sample (model 1), the effects of frontal asymmetry on ED according to diagnostic category (model 2), and the effects of parietal asymmetry on ED according to diagnostic category (model 3). An alpha level of 0.05 was used for all statistical analyses.

There are five assumptions that must be met for a successful regression analysis: linearity of data, multivariate normality, no or little multicollinearity, no autocorrelation, and homoscedasticity. The current study's data met four out of five of these assumptions. The assumption of multicollinearity was not met since the interaction term is a product of two already included predictors in the regression analyses (i.e., asymmetry measure and sex).

As such, a high degree of correlation can be expected between these independent variables. Since this multicollinearity is a result of the addition of the exploratory interaction term, and does not remain after this term is removed, this assumption can be safely ignored for the purposes of this study.

3.3.4.5 Missing Data

Three participants were excluded due to missing diagnostic data, eight participants were excluded for having no diagnosis of MDD, and 11 participants were excluded due to missing EEG data. The final sample consisted of 66 participants (n=44 female; M age= 14.80, SD =1.64). There was no significant difference between the final sample and excluded participants with regards to age, CBCL scores, MFQ scores, or EEG asymmetry scores. The final sample was disproportionately female (66.7% female), and this was considered in the analyses by including sex as a predictor in the regression analyses. From the final sample, youth were distributed into the following diagnostic categories for analyses pertaining to the secondary objective of this paper: 19 youth were assigned to the control group, 20 to the depression only group, and 27 to the mixed depression group.

3.4 Results

3.4.1 Descriptive Statistics

The following tables summarize the descriptive statistics and correlations for the whole sample and at the group level.

Table 1: Descriptive statistics for variables of interest.

	Whole Sample (n=66)	Control (n=19)	MDD-only (n=20)	MDD-comorbid (n=27)
Sex	M: 33.3% F: 66.7%	M: 31.6% F: 68.4%	M: 20.0% F: 80.0%	M: 44.4% F: 55.6%
Mean age (SD)	14.80 (1.64)	14.68 (1.80)	15.20 (1.32)	14.59 (1.74)
Mean youth-reported CBCL-DP scores (SD)	186.83 (29.38)	163.95 (13.66)	197.60 (26.39)	194.96 (31.30)
Mean Anxious/ Depressed Subscale T-Scores (SD)	66.45 (13.62)	58.63 (9.45)	73.25 (12.99)	66.93 (14.08)
Mean Attention Problems Subscale T-Score (SD)	62.97 (12.69)	53.16 (4.45)	67.40 (13.10)	66.59 (12.82)
Mean Aggressive Behaviour Subscale T-Score (SD)	57.41 (8.55)	52.16 (4.10)	56.95 (7.93)	61.44 (9.38)
Mean MFQ scores (SD)	21.89 (17.22)	6.44 (5.79)	33.29 (12.68)	23.30 (17.62)
Mean Frontal Asymmetry Scores (SD)	0.06 (1.26)	0.09 (0.70)	0.04 (0.60)	-0.01 (0.62)
Mean Parietal Asymmetry Scores (SD)	0.39 (.80)	0.41 (0.85)	0.34 (0.91)	0.40 (0.69)

Note. Frontal and Parietal Asymmetry Scores are in units of (ln)μV2

Table 2: Correlations of independent and dependent variables of interest in the whole sample.

Variable	1	2	3	4	5	6
1. Sex	-					
2. Age	-.066	-				
3. CBCL-DP Scores	.166	.075	-			
4. MFQ Scores	.209	.070	.674**	-		
5. Frontal Asymmetry Scores	.097	-.095	.175	-.093	-	
6. Parietal Asymmetry Scores	-.172	.061	-.293*	-.085	-.423**	-

*$p < .05$. **$p < .01$.

Table 3: Correlations of independent and dependent variables of interest in the control group.

Variable	1	2	3	4	5	6
1. Sex	-					
2. Age	-.317	-				
3. CBCL-DP Scores	.014	.022	-			
4. MFQ Scores	-.112	-.118	.461	-		
5. Frontal Asymmetry Scores	.180	-.334	-.015	.147	-	
6. Parietal Asymmetry Scores	-.388	.133	-.106	-.113	-.788**	-

*$p < .05$. **$p < .01$.

Table 4: Correlations of independent and dependent variables of interest in the MDD-only group.

Variable	1	2	3	4	5	6
1. Sex	-					
2. Age	-.213	-				
3. CBCL-DP Scores	.352	.218	-			
4. MFQ Scores	.512*	-.137	.606**	-		
5. Frontal Asymmetry Scores	-.167	-.030	.093	-.069	-	
6. Parietal Asymmetry Scores	-.028	-.066	-.501*	-.376	-.119	-

**p< .05. **p< .01.*

Table 5: Correlations of independent and dependent variables of interest in the MDD-comorbid group.

Variable	1	2	3	4	5	6
1. Sex	-					
2. Age	.092	-				
3. CBCL-DP Scores	.193	-.008	-			
4. MFQ Scores	.153	.045	.528**	-		
5. Frontal Asymmetry Scores	.174	.053	.431*	-.176	-	
6. Parietal Asymmetry Scores	-.113	.116	-.312	.184	-.370	-

**p< .05. **p< .01.*

3.4.2 Predicting ED Using Parietal Asymmetry in a Mixed Clinical/Control Sample of Youth

Table 6 summarizes the first regression analysis predicting ED using parietal asymmetry scores in the whole sample. In model 1, sex and age were entered as independent variables. This model described 0% of the variance in ED scores (R^2 = .00, $F_{(2,63)}$ = 1.14, p = 0.33). Neither sex (β = 0.17, p = 0.17) nor age (β = 0.09, p = 0.49) significantly predicted ED scores. In model 2, parietal asymmetry scores were added to the model. This model explained an additional 7% of the variance in ED scores (R^2 = .07, $F_{(3,62)}$ = 2.54, p = 0.06) compared to model 1. The effects of sex (β = 0.13, p = 0.31) and age (β = 0.10, p = 0.41) remained insignificant in this model, while parietal asymmetry (β = -0.28, p = 0.03) was significantly correlated with ED scores. In the final model, the interaction term between sex and parietal asymmetry was added. This model explained 2% less variance in ED compared to model 2 and did not significantly predict ED scores (R^2 = .05, $F_{(4,61)}$ = 1.88, p = 0.13). The effects of sex (β = 0.13, p = 0.39) and age (β = 0.10, p = 0.41) remained insignificant in this model. The effects of parietal asymmetry (β = -0.25, p = 0.62) were no longer significant, and the effect of the interaction term between sex and parietal asymmetry (β = -0.03, p = 0.95) was also insignificant.

Table 6: Whole sample Hierarchical Regression Analysis Using Parietal Asymmetry Scores to predict ED.

	Model 1			Model 2			Model 3		
Variable	B	SE B	β	B	SE B	β	B	SE B	β
Sex	10.60	7.67	.17	7.71	7.54	.13	8.01	9.23	.13
Age	1.54	2.23	.09	1.79	2.16	.10	1.80	2.18	.10
Parietal Asymmetry				-10.23	4.49	-.28*	-9.20	18.59	-.25
Sex x Parietal Asymmetry							-.59	10.35	-.03
Adjusted R^2		.00			.07			.05	
F for change in R^2		1.14			2.54			1.88	

**p<0.05. **p<0.01.*

3.4.3 Differences in Predicting ED Using Frontal Asymmetry According to Diagnostic Group

Table 7 summarizes the first regression analysis predicting ED using frontal asymmetry scores in each diagnostic group using a stepwise linear regression analysis. In model 1, sex and age were entered as independent variables. This model described 0% of the variance in ED scores (R^2 = .00, $F_{(2,16)}$ = 0.08, p = 0.99). Neither sex (β = 0.02, p = 0.93) nor age (β = 0.03, p = 0.91) significantly predicted ED scores. In model 2, frontal asymmetry scores were added to the model. Similarly, this model did not account for the variance in ED scores (R^2 = .00, $F_{(3,15)}$ = 0.05, p = 0.99). The effects of sex (β = 0.03, p =0.93) and age (β = 0.03, p = 0.93) remained insignificant in this model and the effects of frontal asymmetry were also insignificant (β = -0.01, p =0.97). In model 3, the interaction term between sex and frontal asymmetry was added. Similar to models 1 and 2, this model also did not predict variance in ED (R^2 = .00, $F_{(4,14)}$ = 0.05, p = 1.00). The effects of sex (β = 0.02, p = 0.94), age (β = 0.03, p = 0.93) and frontal asymmetry (β = 0.13, p = 0.95) remained insignificant in this model. The effect of the interaction term between sex and frontal asymmetry (β = -0.14, p = 0.95) was also insignificant. Therefore, neither model using frontal EEG asymmetry scores significantly predicted ED scores in the control group.

For the MDD-only group, the first model included sex and age as independent variables. This model described 12% of the variance in ED scores (R^2 = .12, $F_{(2,17)}$ = 2.31, p = 0.13). Neither sex (β = 0.42, p = 0.08) nor age (β = 0.31, p = 0.18) significantly predicted ED

scores. In model 2, frontal asymmetry scores were added to the model. This model accounted for 2% less variance in ED scores compared to model 1 (R^2 = .10, $F_{(3,16)}$ = 1.73, p = 0.20). The effects of sex (β = 0.45, p =0.06) and age (β = 0.32, p = 0.17) remained insignificant in this model and the effects of frontal asymmetry were also insignificant (β = 0.18, p =0.43). In the model 3, the interaction term between sex and frontal asymmetry was added. This model only accounted for 6% less variance in ED compared to model 2 (R^2 = .04, $F_{(4,15)}$ = 1.22, p = 0.35). The effects of sex (β = 0.45, p = 0.13), age (β = 0.32, p = 0.19) and frontal asymmetry (β = 0.16, p = 0.94) remained insignificant in this model. The effect of the interaction term between sex and frontal asymmetry (β = 0.02, p = 0.99) was also insignificant. Therefore, neither model significantly predicted ED scores in the MDD-only group.

For the MDD comorbid group, the first model included sex and age as independent variables. This model did not account for any of the variance in ED scores (R^2 = .00, $F_{(2,24)}$ = 0.47, p = 0.63). Neither sex (β = 0.20, p = 0.34) nor age (β = -0.03, p = 0.90) significantly predicted ED scores. In model 2, frontal asymmetry scores were added to the model. This model accounted for an additional 10% of the variance in ED scores (R^2 = .10, $F_{(3,23)}$ = 1.94, p = 0.15). The effects of sex (β = 0.13, p =0.52) and age (β = -0.04, p = 0.83) remained insignificant in this model while the effects of frontal asymmetry reached statistical significance (β = 0.41, p =0.04). In the model 3, the interaction term between sex and frontal asymmetry was added. This model accounted for an additional 1% of the variance in ED (R^2 = .11, $F_{(4,22)}$ = 1.84, p = 0.16). The effects of sex (β = 0.09, p = 0.65) and age (β = -0.06, p = 0.77) remained insignificant. Notably, the effects of frontal

asymmetry did not remain significant either (β = 1.43, p = 0.12). The effect of the interaction term between sex and frontal asymmetry (β = -1.03, p = 0.25) was also insignificant.

Table 7: Group level Hierarchical Regression Analysis Using Frontal Asymmetry Scores to predict ED

		Model 1			Model 2			Model 3		
Group	Variable	B	SE B	β	B	SE B	β	B	SE B	β
Control	Sex	.677	7.534	.024	.701	7.808	.025	.601	8.226	.021
	Age	.224	2.003	.029	.200	2.166	.026	.211	2.248	.028
	Frontal Asymmetry				-.198	5.336	-.010	2.587	42.997	.133
	Sex x Frontal Asymmetry							-1.432	21.936	-.143
	Adjusted R^2		-0.12			-0.20			-0.28	
	F for change in R^2		.008			.005			.005	
MDD-Only	Sex	26.842	14.153	.417	28.930	14.533	.450	28.828	18.026	.448
	Age	6.134	4.394	.307	6.380	4.450	.320	6.375	4.630	.319
	Frontal Asymmetry				7.847	9.723	.178	6.981	85.606	.159
	Sex x Frontal Asymmetry							.445	43.701	.020
	Adjusted R^2		0.12			0.10			0.04	
	F for change in R^2		2.313			1.728			1.215	
MDD-Comorbid	Sex	12.082	12.427	.195	7.748	11.732	.125	5.366	11.795	.087
	Age	-.470	3.621	-.026	-.750	3.371	-.042	-.986	3.346	-.055
	Frontal Asymmetry				20.805	9.566	.412*	72.056	43.957	1.426
	Sex x Frontal Asymmetry							-28.43	23.808	-1.031
	Adjusted R^2		-0.04			0.10			0.11	
	F for change in R^2		.473			1.941			1.839	

**p<0.05. **p<0.01.*

3.4.3 Predicting ED Using Parietal Asymmetry According to Diagnostic Group

Table 8 summarizes the first regression analysis predicting ED using parietal asymmetry scores in the whole sample. In model 1, sex and age were entered as independent variables. This model described 0% of the variance in ED scores (R^2 = .00, $F_{(2,63)}$ = 1.14, p = 0.33). Neither sex (β = 0.17, p = 0.17) nor age (β = 0.09, p = 0.49) significantly predicted ED scores. In model 2, parietal asymmetry scores were added to the model. This model explained an additional 7% of the variance in ED scores (R^2 = .07, $F_{(3,62)}$ = 2.54, p = 0.06) compared to model 1. The effects of sex (β = 0.13, p = 31) and age (β = 0.10, p = 0.41) remained insignificant in this model, while parietal asymmetry (β = -0.28, p = 0.03) significantly predicted ED scores. In the final model, the interaction term between sex and parietal asymmetry was added. This model explained 2% less variance in ED compared to model 2 and did not significantly predict ED scores (R^2 = .05, $F_{(4,61)}$ = 1.88, p = 0.13). The effects of sex (β = 0.13, p = 0.39) and age (β = 0.10, p = 0.41) remained insignificant in this model. The effects of parietal asymmetry (β = -0.25, p = 0.62) were no longer significant, and the effect of the interaction term between sex and parietal asymmetry (β = -0.03, p = 0.95) was also insignificant.

For the MDD-only group, the first model included sex and age as predictors. This model described 12% of the variance in ED scores (R^2 = .12, $F_{(2,17)}$ = 2.31, p = 0.13). Neither sex (β = 0.42, p = 0.08) nor age (β = 0.31, p = 0.18) significantly predicted ED scores. In model 2, parietal asymmetry scores were added to the model. This model was significant and accounted for an additional 21% of the variance in ED scores (R^2 = .33, $F_{(3,16)}$ = 4.11, p = 0.02). The effects of sex (β = 0.40, p =0.06) and age (β = 0.27, p = 0.18) remained

insignificant while parietal asymmetry significantly affected ED scores in this model (β = -0.47, p =0.02). In the model 3, the interaction term between sex and parietal asymmetry was added. This model accounted for 3% less variance in ED than model 2 (R^2 = .30, $F_{(4,15)}$ = 2.99, p = 0.05). The effects of sex (β = 0.45, p = 0.07), age (β = 0.27, p = 0.22) and parietal asymmetry (β = 0.20, p = 0.90) remained insignificant in this model. The effect of the interaction term between sex and parietal asymmetry (β = -0.68, p = 0.66) was also insignificant.

For the MDD comorbid group, the first model included sex and age as predictors. This model did not account for any of the variance in ED scores (R^2 = .00, $F_{(2,24)}$ = 0.47, p = 0.63). Neither sex (β = 0.20, p = 0.34) nor age (β = -0.03, p = 0.90) significantly predicted ED scores. In model 2, parietal asymmetry scores were added to the model. This model accounted for 1% of the variance in ED scores (R^2 = .01, $F_{(3,23)}$ = 1.07, p = 0.38). The effects of sex (β = 0.16, p =0.43) and age (β = 0.11, p = 0.95) remained insignificant in this model. The effects of parietal asymmetry were also insignificant (β = -0.30, p =0.15). In the model 3, the interaction term between sex and parietal asymmetry was added. This model accounted for 1% less of the variance in ED (R^2 = -0.01, $F_{(4,22)}$ = 0.96, p = 0.45). The effects of sex (β = 0.26, p = 0.28), age (β = -0.06, p = 0.77), and parietal asymmetry remained insignificant (β = 0.20, p = 0.76). The effect of the interaction term between sex and parietal asymmetry was also insignificant (β = -0.53, p = 0.42).

Table 8: Group level Hierarchical Regression Analysis Using Parietal Asymmetry Scores to predict ED.

		Model 1			Model 2			Model 3		
Group	Variable	B	SE B	β	B	SE B	β	B	SE B	β
Control	Sex	.677	7.534	.024	-.634	8.319	-.022	-3.108	15.395	-.109
	Age	.224	2.003	.029	.233	2.056	.031	.278	2.137	.037
	Cluster Parietal Asymmetry				-1.907	4.456	-.119	-7.752	30.523	-.484
	Sex x Cluster Parietal Asymmetry							3.067	15.833	.345
	Adjusted R^2		-0.12			-0.18			-0.27	
	F for change in R^2		.008			.066			.056	
MDD-Only	Sex	26.842	14.153	.417	25.519	12.375	.397	29.130	14.927	.453
	Age	6.134	4.394	.307	5.426	3.849	.272	5.112	4.006	.256
	Cluster Parietal Asymmetry				-13.64	5.444	-.472*	5.690	42.417	.197
	Sex x Parietal Asymmetry							-10.04	21.847	-.667
	Adjusted R^2		0.12			0.33			.30	
	F for change in R^2		2.313			4.113*			2.985	
MDD-Comorbid	Sex	12.082	12.427	.195	9.812	12.218	.159	15.802	14.302	.256
	Age	-.470	3.621	-.026	.206	3.561	.011	1.441	3.889	.080
	Cluster Parietal Asymmetry				-13.42	9.003	-.295	9.091	28.858	.200
	Sex x Parietal Asymmetry							-16.34	19.887	-.533
	R^2		-0.04			0.01			-0.01	
	F for change in R^2		.473			1.072			.962	

**p< .05. **p< .01.*

3.5 Discussion

This study explored the association between ED and EEG asymmetry in a mixed clinical/control sample of adolescents. As a secondary aim, this study explored whether the association between ED and EEG asymmetry differed according to diagnostic category. That is, whether youth with comorbid emotional and behavioural disorders exhibited associations between EEG asymmetry and ED that were different from the associations exhibited by youth with emotional disorders only or controls. Participants in the clinical groups were care-seeking youth with MDD with or without comorbid behavioural disorders (i.e., ODD or DMDD). Participants assigned to the control group were recruited from the community. As a reminder, ED was measured using the youth self-report version of the CBCL-DP, which is made up of the following subscales of the CBCL: the anxious/depressed subscale, the attention problems subscale and the aggressive behaviour subscale.

This study found that right parietal asymmetry is a significant predictor of ED in a mixed community/clinical sample of youth. This is consistent with the hypothesized outcomes for the first objective, since youth with higher ED were expected to have greater difficulties in mediating attentional control towards emotional stimuli, which prior literature describes as being associated with right parietal asymmetry. When this effect is parsed according to diagnostic category, this study found that the predictive ability of right parietal asymmetry is strongest for youth with MDD only, and insignificant for typically developing controls and youth with comorbid MDD and ODD or DMDD. More specifically, in the whole sample, right parietal asymmetry was predictive of 7% of the

variance in ED scores. Meanwhile, in the MDD-only group, right parietal asymmetry explained 33% of the variance in ED scores.

With regards to group-level effects of frontal asymmetry on ED, this study found that left frontal asymmetry was significantly associated with ED in youth with MDD comorbid with DMDD or ODD. In particular, left frontal asymmetry significantly predicted 10% of the variance in ED scores in this group. This is consistent with the hypothesized outcome for this study's second objective, which anticipated greater left frontal asymmetry in the MDD-comorbid group due to the externalizing nature of ODD and DMDD, and Davidson's frontal EEG asymmetry model, which posits that left frontal asymmetry is characteristic of externalizing symptoms.

3.5.1 Maturation of the Adolescent Brain

The human brain experiences surges in development and maturation at three key stages of development: the prenatal/postnatal period, during puberty, and after puberty (Konrad et al., 2013). The development of vascular structures, axons, and synapses within the brain occurs during the prenatal and postnatal period, and glutamatergic neurotransmission also begins during this period. After the postnatal period, the next surge of neuronal development begins immediately before the start of puberty and continues till the age of 24. These changes include thickening of grey matter throughout the brain, dendritic pruning, and myelination (Vijayakumar et al., 2018). The most significant changes are observed in the limbic system, which is involved in governing emotional responses, decision making, risk taking, and self-control, and the frontal lobe, which experiences an

increase in myelin synthesis in areas related to cognition (Arain et al., 2013; Konrad et al., 2013).

Normative neurodevelopment in adolescence involves a general restructuring of the brain through synaptic pruning and myelination. Although the cerebral cortex reaches its maximum volume in infancy, synapses are concentrated towards the back of the brain, with regions like the primary sensorimotor cortex, inferior parietal gyrus, superior temporal gyrus, and dorsolateral prefrontal cortex developing first. Regions responsible for higher order cognitive functions and emotional responses, like the prefrontal cortex and limbic system, reach maturation later in adolescence. This reorganization is achieved by synaptic pruning and myelination. Grey matter formed in childhood decreases in an experience-dependent manner, where synapses that are used less often are eliminated via synaptic pruning. This is accompanied by a continuous increase in white matter through the myelination of axons (Konrad et al., 2013).

Gonadal hormones play an integral role in neural development by upregulating myelination and aiding in the organization and structural integration of neural connections (Arain et al., 2013). The development of regions related to emotions is particularly susceptible to changes in gonadal hormones. In particular, the hypothalamic pituitary adrenal (HPA) axis is particularly susceptible to gonadal hormones, and androgenic versus estrogenic hormones differentially affect HPA axis activation. Androgenic hormones downregulate the HPA axis through the inhibition of corticotropin-releasing hormone, while estradiol upregulates the HPA axis. This makes females more vulnerable to stress while being a protective factor for males (Naninck et al., 2011).

Gonadal hormones regulate dopaminergic and serotonergic signaling in the prefrontal cortex. These neurotransmitters, dopamine and serotonin, play an integral role in brain maturation. Dopaminergic neurotransmitters, primarily produced in the substantia nigra, ventral tegmental area, and hypothalamus, are implicated in pleasure, pain, movement and emotional responses. Downregulation or dysfunction in dopamine functioning by sex hormones, particularly in adolescence, may lead to difficulties in emotional regulation (Wahlstrom et al., 2010). Similarly, serotonin has profound effects on mood, anxiety and arousal. Serotonin is often downregulated in adolescence by gonadal hormones, which is linked to poor impulse control (Murrin et al., 2007). Notably, sex differences in dopamine and serotonin functioning are related to gonadal and stress hormones and pubertal hormone changes also contribute to cognitive and emotional changes in adolescence (Arain et al., 2013).

Neuroimaging studies have highlighted the sex differences that maybe implicated in emotional regulation development during adolescence. In particular, sex differences have been observed in the global grey and white matter volumes, as well as the amygdala-hippocampal complex. That is, the amygdala and hippocampal volume is higher in adolescent males and decreased in females. Delayed maturation of limbic system and PFC in boys compared to girls, this delay was also related to difficulties in emotion regulation (Satterthwaite et al., 2014). Interestingly, androgenic and estrogenic hormones differentially affect functional connectivity, where estradiol and progesterone improve both cortico-cortical and subcortical-cortical communication. Meanwhile, testosterone

may reduce subcortico-cortical connectivity while improving connectivity between subcortical regions (Peper et al., 2011).

Generally, females begin puberty and mature faster than males do. This may lead to a mismatch between the development of subcortical vs cortical brain structures. This mismatch makes females more susceptible to ED and ED related disorders. Meanwhile, the later development and maturation in males is protective and is related to greater positive personality traits (Graber, 2013). In normative development, the amygdala and hippocampus increase in volume throughout adolescence but at different trajectories for males versus females. However, if differences in maturation persist in adulthood, it leaves the individual susceptible to mood disorders. Patients with mood disorders have previously demonstrated reduced amygdala and hippocampal volumes compared to controls (Frere et al., 2020). As such, the development of mood disorders stemming from ED is related to poor hippocampal and amygdala development in adolescence. These differences in maturation in females compared to males is an important consideration for this study. The MDD-only group included a disproportionate number of female participants compared to male, where 80% of the sample was female. As such, future studies should aim to assess whether associations between ED and EEG asymmetry are different in males and females of the same age.

3.5.2 The Effects of Sex on the Association Between ED and EEG Asymmetry

Prior literature has established sex-related differences in emotion experience/expression and the prevalence of ED disorders. In childhood, female participants demonstrate a negativity bias, where they display greater emotional reactivity to negative stimuli

compared to males (Lithari et al. 2010). In adolescence and adulthood, this early negativity bias is theorized to either deplete cognitive resources for future emotion regulation processing (Williams et al. 2008), or it is thought to improve future emotion regulation processing by improving one's ability to appraise negative emotions (Moser, Most, and Simons 2010). Task-based functional neuroimaging studies exploring sex-based differences in reappraising negative emotional stimuli in adulthood demonstrate that amygdala and prefrontal cortical activation in response to negative stimuli is reduced in males compared to females, suggesting that females may have a greater capacity to regulate emotional responses towards negative stimuli (Whittle et al. 2011; McRae et al. 2008). However, due to poor temporal resolution in functional neuroimaging studies, it is difficult to discriminate between activation underlying emotion reactivity versus regulation (Domes et al., 2010; Gardener et al., 2013).

Compared to fMRI, EEG demonstrates superior temporal resolution (Burle et al., 2015). Due to previous literature highlighting the effects of sex on emotions, the effects of sex were an important consideration in this study. The sample in this study was also disproportionately female (66.7% females in the whole sample), and this was even more pronounced in the MDD-only group (80% females in the MDD-only group). In the stepwise linear regression models, the effects of sex and age were explored in step 1 of the model, the effects of the EEG metric of interest was explored in step 2, and the effects of the interaction between the EEG metric of interest and sex were considered in step 3. As a reminder, parietal asymmetry was associated with ED in the whole sample and in youth with MDD-only, and frontal asymmetry was associated with ED in youth with

MDD-comorbid. In the whole sample, parietal asymmetry explained 7% of the variance in ED scores. When the interaction term between asymmetry and sex was added, the model explained 2% less variance in ED scores. Similarly, in the MDD-only group, parietal asymmetry explained 33% of the variance in ED scores, while the addition of the interaction term between parietal asymmetry and sex explained 3% less variance. Interestingly, in the MDD-comorbid group, frontal asymmetry described 10% of the variance in ED scores and the interaction between frontal asymmetry and ED described an additional 1% of variance in ED scores.

Adjusted R-squared values were used to quantify the effects of the independent variables on ED. The adjusted R-squared term accounts for the number of variables included in the model and only increases when the addition of the new term increases the fit of the model by a value that is higher than chance. Meanwhile, the R-squared value does not decrease and only increases as new variables are added to the model. As such, the decreased adjusted R-squared values in our model assessing the effects of parietal asymmetry suggest that the addition of the interaction term between parietal asymmetry and sex does not significantly improve the fit of the model. This means that parietal asymmetry and sex do not interact to significantly affect ED scores in both the whole sample and in youth with MDD-only. Meanwhile, in youth assigned to the MDD-comorbid group, the addition of the interaction term between sex and frontal asymmetry improved the fit of the model and described an additional 1% of variance in ED scores compared to model 2 looking at the effects of frontal EEG asymmetry only. This is consistent with reports of sex differences in resting frontal alpha EEG asymmetry (Cave & Barry, 2021). As such, it

seems like the relationship between parietal asymmetry and ED is similar in both males and females, while frontal asymmetry differentially affects ED in males compared to females.

3.5.3 Differences in Depressive Symptom Severity Across Study Groups

Due to the comorbidities present in the MDD-comorbid group, it can be assumed that participants in this group exhibit a greater number of symptoms and clinically appear to be more impaired than the pure-depression group. The MFQ was used to assess MDD symptoms in the study sample. In clinical practice, a score of 27 or higher qualifies an individual for a diagnosis of MDD. In this study, the mean score on the MFQ for the MDD-comorbid group was 23, and for the MDD-only group, the mean MFQ score was 33, suggesting that the MDD-comorbid group demonstrated lower MDD severity. However, both clinical groups demonstrated ED scores on the CBCL-DP that were similar to one another (MDD-only group: mean score = 197.60, MDD-comorbid group: mean score = 194.96). Combined with findings that reflect differential patterns of neural electrical activity between the two groups (i.e., right parietal asymmetry associated with ED in the MDD-only group; left frontal asymmetry associated with ED in the MDD-comorbid group), it seems like ED in the MDD-only group is driven by processes that are different from the processes that subserve ED in the MDD-comorbid group.

One potential explanation for the differing aetiologies of ED between the two groups may be that lower severity of MDD in the MDD-comorbid group may contribute to higher left frontal activation, mitigating the effects of MDD that promote higher activation in right frontal regions instead of left. Meanwhile, the externalizing nature of the comorbidities

experienced by this group may contribute to greater left frontal activation. It may also be that greater left frontal activation may contribute to lower severity of MDD through increased use of adaptive emotion regulation strategies and impulse control, as evidenced in adult literature looking at frontal alpha asymmetry and emotion regulation strategies (Coan & Allen, 2003; Zhang et al., 2020). However, the similar levels of ED present across both groups suggest that both groups may have similar difficulties regulating emotion. Moreover, this study measures trait ED and does not provide information on how EEG activity relates to state ED in scenarios that require the use of emotion regulation skills during the EEG scan. Future studies should aim to assess this association in transdiagnostic samples.

Alternatively, it may be that the neural processes that underlie ED in the MDD-comorbid group may be different from the neurobiology associated with ED in the MDD-pure group. Specifically, ED in the MDD-comorbid group may be a result from neural patterns that subserve the comorbid disorders experienced by this group (i.e., ODD, DMDD). This is further strengthened by the externalizing nature of these comorbidities, and neural electrical activity that is consistent with externalizing symptoms, and not MDD (i.e., left frontal asymmetry). On the contrary, MDD is associated with greater right frontal asymmetry. However, due to the high levels of ED in the MDD-comorbid group and relatively lower severity of MDD, it seems like the clinically significant phenotype exhibited by this group is a result of difficulties with externalizing processes. Meanwhile, the neural correlates of ED in the MDD-pure group are characteristic of poor attentional control and difficulties in regulating emotions via attentional deployment. As such,

although both these groups of patients may be seeking care for their ED and MDD symptoms, the type of ED experienced by these two groups seems to be different at a biological level. Resultantly, these two groups require interventions that are tailored to their separate needs, where youth with MDD that is comorbid with externalizing disorders may require treatments that target their difficulties in externalizing symptoms, while youth with MDD only may benefit more from interventions aimed at helping them modulate and control their attention towards emotional stimuli.

3.5.3 Difficulties in Measurement

The results of this study demonstrate that the underlying neurobiological mechanisms of ED vary in youth from different disorder categories. Prior literature has also highlighted phenotypic differences in ED across different disorder categories (see Chapter 2). However, there has been extant debate as to what exactly is conceptualized by ED (Althoff et al., 2010). Previously, it has been described to conceptualize youth with highly comorbid psychopathology (Carlson 2007). However, the results of this study demonstrate that youth with MDD only and youth with MDD comorbid with behavioural disorders demonstrate similar levels of ED, as measured by the CBCL-DP. Other studies describe highly dysregulated youth to have pediatric bipolar disorder ("National Institute of Mental Health Research Roundtable on Prepubertal Bipolar Disorder" 2001; Staton, Volness, and Beatty 2008). Due to this variability, there exists some disagreement with regards to the assessment, classification, and treatment of ED in the field.

Due to this multifaceted nature of ED, conceptualizing and measuring ED using scale-based measures comes with its challenges. The CBCL-DP is one of the most extensively

used measures of ED (Achenbach and Rescorla 2001). In clinical settings, scales like the CBCL-DP demonstrate excellent reliability and validity in identifying youth with clinically significant levels of ED. However, in a study such as this, it may be difficult to delineate what exactly the CBCL-DP is measuring in this study sample, and what exactly is the construct that relates to the EEG asymmetry differences observed in this study. As a reminder, ED is measured by co-occurring elevations in internalizing and externalizing symptoms, and the comorbid emotional and behavioural disorders present in this sample make it so that youth in this sample are likely exhibiting several different internalizing and externalizing symptoms. As a result, it may be difficult to identify where the bulk of the clinical load is coming from. Moreover, the CBCL-DP consists of clinical symptoms, meaning that it is not a measure that is independent from measures of psychopathology. As such, it may be the case that ED measured by the CBCL-DP is simply a measure of general psychopathology. Resultantly, the comorbid disorders present in our sample influence scores on the CBCL-DP.

Another important consideration in the study of ED is state versus trait effects of emotion. According to the trait emotional intelligence theory, each individual has a unique emotional disposition with regards to how they perceive and appraise emotions, and how they react in emotion inducing situations (Petrides 2001). This provides the impetus for individual variability in personality and emotion. On the other hand, state-based emotions are measured within contexts and situations that illicit emotional reactions. Both state and trait emotions are related to HPA axis activity in both normative and clinical adult populations (Polk et al. 2005). Typically, measures of ED assess dispositional tendencies,

and the CBCL-DP is also a trait-based measure of ED (Lavender et al. 2017). One potential problem with relying on trait-based measures is that ED may not be a trait that remains consistent throughout various situational contexts. Instead, it may be that ED is context dependent and therefore fluctuates. In this case, more serious levels of ED may not be detected when measured in calm environments. This may be the case in samples with high clinical symptoms, such as the sample used in this study. As such, future studies should aim to measure ED using multiple different measures.

3.6 Limitations and Future Directions

One key limitation to this study is the disproportionate number of males versus females recruited for this study. This was especially the case for youth in the MDD-only group, as this group was 80% female. Prior literature has established sex-related differences in the prevalence of mood and anxiety disorders, and also in emotional experience and responsivity (Y. Deng et al., 2016; Domes et al., 2010; Frere et al., 2020; Naninck et al., 2011). The adolescent period coincides with puberty, and during puberty, gonadal hormones differentially promote sexual, neural, and behavioural maturation in males and females. Pubertal timing also plays a role in the development of psychopathology, making developmental stages an important consideration in the study of adolescent psychopathology (Graber, 2013). To account for sex differences in brain development, results from males and females of the same age should be compared to assess whether associations between ED and EEG asymmetry are different in males compared to females. Future studies should also include both age and pubertal stage, and potentially their interaction, as covariates.

Moreover, this study demonstrated differences in the relationship between EEG asymmetry and ED in youth with MDD-only, compared to youth with MDD comorbid with ODD or DMDD. From the limited number of clinical diagnoses present in this study's sample (i.e., MDD, ODD, DMDD), it is unclear whether this effect translates over to other disorders from the same categories (i.e., bipolar disorder, ADHD, conduct disorder). The conclusions of this study cannot be applied more broadly to encompass all emotional and behavioural dysregulation disorders. However, if it is the case that the correlates of ED reliably differ in different disorder categories, it would be imperative for clinicians to consider this when treating patients with ED. As such, future studies should aim to replicate this effect in study samples that include a broader range of mood and behavioural disorders, and in larger study samples with similar numbers of males and females.

Finally, another limitation of this study is the lack of diverse measures of ED. The CBCL-DP is a highly reliable and valid broadband measure of ED with high clinical utility (Aitken et al., 2019; Althoff et al., 2010). Due to the paucity in literature examining the correlation between frontal and parietal EEG asymmetry and ED, the CBCL-DP is an excellent starting point to explore potential relationships that may exist. However, after establishing preliminary evidence for a relationship between EEG asymmetry and ED, future studies should aim to use multiple measures of ED. This includes using a diverse combination of measures that assess chronic issues with emotion regulation, difficulties in social function, and a retrospective assessment of past emotional outbursts to ensure that the construct measured is indeed ED and not general psychopathology (Silverman et al.

2022; Althoff and Ametti 2021). Future studies should also aim to measure ED in emotion-inducing contexts to ensure that the full extent to a participant's ED symptoms is being assessed.

3.7 Conclusion

The ability to control the type, frequency, intensity, and duration of one's emotions, also known as emotion regulation, is an essential skill that develops early in life. Neural networks underlying social, cognitive, biological, and attentional processes work together to effectively regulate emotions (Theodore P. Beauchaine, 2015). The failure to learn or apply any one or more of these processes results in ED (Hilt, Hanson, and Pollak 2011). Effective emotion regulation is crucial to normative mental functioning, and ED is a common underlying feature of psychopathology in both youth and adult populations, and is associated with a higher likelihood of poor patient reported outcomes (D'Agostino et al. 2017). Its phenotype is highly variable, and no standard phenotypic description for ED exists. In clinical settings, care providers typically infer the presence of ED from co-occurring elevations in internalizing and externalizing symptoms. However, the relative contribution of each cluster of symptoms to a particular patient's ED phenotype is highly variable.

Biological measures can help alleviate some of these challenges associated with defining, measuring, and treating ED. Generally, when available, biological measures are considered more reliable than behavioural measures (Insel 2014). Frontal EEG asymmetry has been used as a correlate of internalizing and externalizing symptomology, while parietal EEG asymmetry has been shown to play a role in attentional processes that

may be involved in ED (Coan & Allen, 2003, 2004; Richard J. Davidson, 1994; Grimshaw & Carmel, 2014; Horato et al., 2022; McRae et al., 2010; Palmiero & Piccardi, 2017; Shomstein, 2012; Stewart et al., 2011). As such, this study aimed to explore the associations between frontal/parietal EEG asymmetries and ED scores measured by the CBCL-DP in a mixed clinical/control sample of adolescents, and whether these associations differed in youth with MDD only, compared to youth with MDD comorbid with ODD or DMDD, and controls.

The findings of this study suggest that ED is associated with rightward parietal asymmetry in a mixed community clinical sample of youth, and this effect is further pronounced in youth with MDD only. In youth with comorbid MDD with ODD or DMDD, ED was associated with left frontal asymmetry. It may be that the underlying neurobiological mechanisms of ED differ between youth with ED disorders only, compared to youth with comorbid emotion and behavioural dysregulation disorders. Several factors may contribute to this variation in underlying neurobiology, including sex-related differences in the genotype and phenotype of ED, sex-related differences in the maturation of the adolescent brain, differences in clinical phenotype, and difficulties in measuring ED. In clinical settings, this means that certain subsets of youth, despite having the same diagnosis of MDD, may benefit from different interventions. Further exploration of what ED looks like both biologically and phenotypically in different disorder categories will help inform the field whether particular biological or behavioural measures are better suited for one subset of patients over another. It will also help in

pinpointing the biological underpinnings that subserve dysregulation in a particular patient, allowing clinicians to provide targeted treatments.

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Chapter 4. Conclusion

Emotion regulation is an essential skill that begins developing at birth and continues developing throughout adolescence (Gross, 2013). Several emotion regulation strategies exist, however, for some individuals, maladaptive emotion regulation is socialized through negative reinforcement across development from family and peers. This leads to difficulties in effective modulation of behaviour in a goal directed manner, also known as ED (Theodore P. Beauchaine, 2015). Literature has established the role of ED in several different psychopathologies. Moreover, the role of ED in worsening patient outcomes has been highlighted in multiple different patient subpopulations, including individuals with histories of trauma, ADHD, borderline personality disorder, and anxiety disorders (Aldao & Nolen-Hoeksema, 2012; Biederman et al., 2012; Dugal et al., 2018; Esbjørn et al., 2012; Gratz et al., 2017; Pat-Horenczyk et al., 2015). This makes effective measurement and treatment of ED highly important.

In clinical settings, ED is assessed using scales-based measures of co-occurring elevations in internalizing and externalizing symptoms. However, it is difficult for these measures to identify the relative contribution of these heterotypic comorbidities to ED in a particular patient. Moreover, there is no standardized clinical description of ED, making it imperative for clinicians to have a valid and reliable biological marker of ED to reduce measurement error (Paulus et al., 2021). This is an important avenue for future research, as the transdiagnostic nature of ED means that it must be treated in a diverse population of patients. This diversity in clinical phenotype may call for a diversity in measurement and treatment approach. With this phenotypic heterogeneity in mind, the aim of the

systematic review described in chapter 2 was to assess the breadth of previously explored biological correlates of ED. To further explore how ED manifested in different disorder categories, chapter 2 also assessed how correlations between ED and various physiological variables differed in participants with ED disorders compared to behavioural dysregulation disorders.

Chapter 2 found that the most widely explored physiological correlate of ED is RSA. RSA is an indicator of cardiac vagal tone, and cardiac vagal tone has been extensively researched as a correlate of attention and emotion regulation, and is also a reliable indicator of internalizing and externalizing symptoms (T. Beauchaine, 2001; Grossman & Taylor, 2007; Paulus et al., 2021). To better understand the role of RSA in ED and the treatment of ED-related psychopathology, the neurobiological basis of ED must also be explored. Furthermore, to understand the unique set of emotion regulation related vulnerabilities that a particular patient has, the neurobiological measure being explored should also be able to tell us about the relative contribution of internalizing versus externalizing symptoms to a given patient or patient subgroup's phenotype. Resultantly, chapter 3 aimed to investigate the role of EEG asymmetry in ED.

There is a large body of literature that supports the role of frontal EEG asymmetry in approach and withdrawal related tendencies, which are associated with externalizing and internalizing related symptoms, respectively. Chapter 4 aimed to explore the relationship between EEG asymmetry and ED. To account for the role of attentional processes in regulating emotions, parietal EEG asymmetry was also used as an independent variable in this study. Relationships between these variables were assessed using correlational and

regression analyses in both the whole sample and in groups based on diagnostic categories. In the whole sample, ED was associated with right parietal asymmetry. When separate into groups comparing youth with MDD only, youth with MDD comorbid with ODD or DMDD, and typically developing controls, ED was associated with right parietal asymmetry in youth with MDD only, and with left frontal asymmetry in youth with comorbid MDD.

This research has important implications on how ED is measured and treated in clinical settings. Differences in the neural processes associated with ED across different disorder categories means that the ED in patients with distinct diagnoses cannot be treated the same. It seems like youth with MDD comorbid with DMDD or ODD exhibited ED characterized by higher rates of externalizing symptoms. As such, this subpopulation of youth with MDD may benefit from treatments that target their externalizing symptoms. For youth with MDD-only, ED was associated with right parietal asymmetry, suggesting that these youth may benefit from interventions that help effectively mediate attentional control in response to emotion-inducing stimuli.

The research undertaken in this thesis helps inform the field of several important avenues for future research. This includes a deeper look into how ED manifests both biologically and phenotypically in different disordered populations. It also provides the impetus for research examining the prevention and treatment of abnormalities in specific emotion regulation strategies, like attentional deployment, and how the efficacy of different interventions varies between different disordered populations. Future research should also assess correlations between EEG asymmetry and multiple different measures of ED to

improve the validity and reliability of the findings of this thesis. Finally, the use of EEG asymmetry can be further explored in its utility to detect ED in different disordered populations with the goal of developing more objective, biological measures of ED for use in clinical settings. EEG asymmetry remains stable across time and contexts and has been reliably linked to differences in affective style and processing (Coan & Allen, 2004), making it an excellent candidate for further exploration with regards to biological measures of ED.

CHAPTER 5. References

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