2021 Gatlinburg Conference Symposium Submission

Symposium Title: Emotion Regulation in Autism Spectrum Disorder: Novel Clinical and Treatment Outcomes Measures

Chair: Debra Reisinger, Ph.D.

Discussant: Rebecca Shaffer, Psy.D.

Overview: Emotional impairments in childhood and adolescence can have lasting impacts across the lifespan including loneliness, greater social impairment, lower quality of life, and psychiatric diagnoses and psychotropic medication use. These clinical issues are hypothesized to arise from difficulties in *emotion regulation* (ER), or the ability to modulate the experience, expression, and intensity of emotions in a socially-acceptable and contextually-appropriate manner. Addressing ER during childhood and adolescence is critically important to improving outcomes that lead to successful transition to adulthood, especially in autism spectrum disorder (ASD). Deficits in ER are associated with higher rates of comorbid diagnoses and maladaptive behavior in both ASD and Non-ASD populations. Multiple characteristics associated with ASD may predispose these individuals to have impaired ER. Further, individuals with ASD may have altered neural mechanisms underlying reduced ER. The goal of this symposium is to identify and discuss biological and behavioral characteristics associated with ER in ASD in addition to innovative biobehavioral methods used to assess treatment outcomes. The first two presentations explore ER in the broader clinical context, with one exploring differences in ER across three clinical groups in addition to the impact of ASD symptoms on ER and the other examining subgroup differences during two resting state networks in relation to ER symptoms and clinical outcomes. The last two presentations examine the utility of two innovative measurement techniques during a treatment designed to address ER in children and adolescents with ASD: 1) physiological data in relation to clinical outcomes and 2) a probabilistic reversal learning task to assess cognitive flexibility outcomes. These presentations highlight the array of methodologies to examine multiple key aspects associated with ER, including novel methods to better assess targeted ER treatment outcomes.

Paper 1 of 4

Paper Title: Exploring the link between ASD symptoms and emotion regulation in toddlers and preschoolers

Authors: Deanna Swain, Ph.D., Shuting Zheng, Ph.D., Somer Bishop, Ph.D., So Hyun Kim, Ph.D.

The first author is a postdoctoral fellow and will be applying for the Theodore Tjossem Postdoctoral Award.

Introduction: ER has been posited to underlie various forms of child psychopathology, including ASD and other neurodevelopmental disorders (NDD) such as ADHD (Aldao, Gee, De Los Reyes, & Seager, 2016). Within ASD, researchers suggest that heightened ER impairments are associated with increased ASD symptom severity (White et al., 2016) as well as increased rates of comorbidities such as anxiety and depression (Weiss, 2014). However, a recent systematic review of ER findings in young children with ASD (Cibralic et al., 2019) found mixed evidence supporting the relationship between ASD symptoms and ER impairments in young children with ASD. The current study compares emotion regulation (ER) levels across three diagnostic groups (i.e. neurotypical, ASD, and non-ASD), controlling for key demographic variables. We also examine the influence of ASD symptoms on ER in ASD-only and ASD-referred samples.

Methods: Participants included children between the ages of 1.5 and 5 years (M = 48 months, SD = 14 months) seen at ASD-specialty clinics for clinical or research purposes. Children were categorized by diagnosis into one of the following groups: NT (*n* = 96), ASD (*n* = 539), Non-ASD (*n* = 106), which included children with other NDD, such as ADHD, as well as internalizing and externalizing psychopathology. ASD symptoms were measured by the ADOS-2 Calibrated Severity Scores for Social Affect (CSS-SA) and Restricted and Repetitive Behavior domains (CSS-RRB). Emotion regulation was quantified by parent report on the Child Behavior Checklist - Emotion Dysregulation Inventory (CBCL-EDI; Berkovits, Eisenhower, & Blacher, 2017). For Aim 1, an ANCOVA was run to compare differences in ER across diagnostic groups controlling for age, gender, NVIQ, VIQ, and maternal education. For Aim 2, separate hierarchical linear regressions were run to examine predictors of ER in two samples (ASD and Non-ASD combined

and ASD-only). Predictors were entered into three blocks: 1) gender, age, maternal education; 2) NVIQ, observed spontaneous language level; 3) CSS-SA and CSS-RRB.

Results: Results from the ANCOVA suggest significant group differences in ER ($F[2, 554]= 37.35$, $p < .001$). Post-hoc analyses reveal significantly higher ER impairment in ASD compared to NT group ($p < .001$) and Non-ASD compared to NT group ($p < .001$). There were no differences in ER between the ASD and Non-ASD groups. When predicting ER difficulties in both ASD and Non-ASD samples combined, significant predictors included maternal education ($\beta = .20$, $p < .001$), language level ($\beta = .33$, $p < .001$), and NVIQ ($\beta = -.14$, $p = .04$; before block 3 variables were included). When entered in the final block, ASD symptoms were not significant predictors and NVIQ was no longer significant. Results were replicated when run in the ASD-only sample; however, NVIQ remained a significant predictor in the final model.

Discussion: Both children with ASD and those with other developmental disorders (e.g., ADHD, language disorders, anxiety) have significantly more impairments in ER compared to neurotypical children. This supports the hypothesis that ER impairments represent a transdiagnostic construct of psychopathology that is not unique to the ASD population. Autism symptom severity in both children with ASD as well as those with other developmental disorders was not associated with ER, whereas language levels and maternal education appeared to play a critical role in the development of ER in these populations.

Paper 2 of 4

Paper Title: Utilizing Data-Driven Brain Connectivity Subgroups to Examine Emotion Regulation Patterns in Adolescents with Autism, Social Anxiety, and Controls

Authors: Marika Coffman, Ph.D., Ligia Antezana, M.S.

Introduction: The ability to modulate the intensity of one's emotional responses in order to adaptively fit the context or one's goals is known as emotion regulation (ER; Mazefsky et al., 2013). ER difficulties are associated with various mental health outcomes in adolescence (Weinberg and Klonsky, 2009), although measurement of ER difficulties, especially in ASD, is complicated by difficulties with self-report, and conflation with ASD symptoms. Examining the association between resting state brain networks and ER difficulties may reveal neural signatures underlying ER deficits. Two resting state networks, the salience network (SN), which relates to attention allocation, and default mode network (DMN), which underlies self-referential cognitions and inflexible thinking, may play a role in ER difficulties, i.e., repetitive negative thinking (Burrows et al., 2017). Thus, we aimed to determine whether SN-DMN connectivity subgroups relate to common and distinct patterns of ER difficulties in a sample of typically developing adolescents and those with social anxiety with and without comorbid autism.

Methods: Participants (N=48, Age: M[SD]= 15.65[2.23]; IQ: M[SD]= 105.20[11.26]) underwent a resting state functional Magnetic Resonance Imaging (fMRI) and completed the Difficulties in ER Scale (DERS). Higher scores on the DERS indicate greater difficulties in ER. Resting-state preprocessing was conducted using the Configurable Pipeline Analysis of Connectomes (C-PAC; https://fcp-indi.github.io/). A total of seven 5mm spherical regions of interest (ROIs) were extracted for each participant (four DMN and three SN nodes) were chosen using Neurosynth (http://neurosynth.org/) Group Iterative Multiple Model Estimation (GIMME), a graph theory approach (Gates and Molenaar, 2012), was applied on time series resting state data in order to identify individual connectivity patterns. Subsequently, a community detection algorithm identified subgroups characterized by distinctive SN-DMN connectivity patterns.

Results: Two data-driven subgroups were identified: Subgroup A (n=30) was characterized by an additional within-DMN path, while Subgroup B (n=18) was characterized by two additional within-SN paths, one additional within-DMN path, and one additional between SN-DMN path. Data-driven subgroups did not differ in IQ, age, diagnostic grouping, or DERS scores ($ps>.16$). To examine whether subgroups differed on their DERS scores by diagnostic group, a multivariate ANOVA was conducted, with controls in Subgroup B demonstrating greater difficulties in ER Clarity than those in Subgroup A ($p<.001$). Additionally, in ASD, a trend ($p<.10$)

emerged between subgroups for Goals, such that adolescents with ASD in Subgroup B had greater difficulties in goal-directed behavior. No subgroup differences existed within the social anxiety group (*p*s>.20)

Discussion: These results suggest that hyperconnectivity within and between salience and default mode networks may be associated with specific difficulties in emotion regulation abilities during adolescence. More specifically, adolescent controls that demonstrated hyperconnectivity had difficulties in clearly identifying their emotions, whereas adolescents with ASD with hyperconnectivity had a trend toward greater difficulties in goal-directed behavior. Thus, although similar neural patterns of increased connections of SN-DMN may index specific ER difficulties, these patterns likely relate to differential ER difficulties by diagnostic group. These findings may be important in identifying neural markers for ER-targeted treatments (e.g., mindfulness, neurofeedback) and tailoring ASD-specific ER treatments that may not be observed based on behavior alone.

Paper 3 of 4

Paper Title: Examining the Utility of a Biobehavioral Approach on 'Emotion Regulation' Treatment Outcomes in Children and Adolescents with Autism Spectrum Disorder

Authors: Debra Reisinger, Ph.D., James Heathers, Ph.D., Paul Horn, Ph.D., Shelley Randall, B.A., Lauren Schmitt, Ph.D., Matthew Goodwin, Ph.D., Rebecca Shaffer, PhD

Introduction: Deficits in emotion regulation (ER) have been linked to significantly higher rates of hospitalizations, suicidal ideation, school disciplinary action, rejection by peers, failed transitions into adulthood, comorbid psychiatric diagnoses, and increased use of psychotropic medications in individuals with autism spectrum disorder (ASD) compared to their peers without ER difficulties (Conner et al., 2019; Cai et al., 2018; Goldsmith & Kelley, 2018). Interventions for ER deficits in ASD are currently emerging in the field; however, outcome data for these interventions typically rely on caregiver reports to determine treatment outcomes. Therefore, a critical need remains in the ASD field to include objective, quantitative measures that document differential intervention outcomes and identify responder characteristics to provide adequate and timely intervention. In the general population, heart rate variability (HRV) is a robust and objective ER biomarker wherein greater physiological regulation associates with fewer behavioral problems in youth (Calkins, 1997). Within ASD, the literature has highlighted atypical physiological arousal, including the theory that problem behaviors are functionally related to homeostatic regulation (Klusek et al., 2015; Lydon et al., 2016). In sum, HRV may be an important predictor signaling whether individuals with ASD will benefit from intervention, while also providing information about the biological mechanisms associated with therapeutic gains. The present study demonstrates pilot data examining the feasibility of utilizing HRV as a biomarker in a treatment trial addressing ER deficits in ASD in addition to the relationship between HRV and other clinical outcome measures.

Methods: Participants included a subset (*N*=17; 86% male) of individuals ages 8 to 18 years diagnosed with ASD who were a part of a larger treatment trial focused on emotion regulation called 'Regulating Together' (Shaffer et al., 2019). We evaluated participants at an initial baseline/screening visit (Week 0), a second baseline/treatment visit five weeks later (Week 5) immediately before the start of the intervention, at treatment end (Week 10), and at two follow-up visits (Week 15, Week 20). Participants wore an ambulatory Faros cardiovascular monitor while completing the following three conditions: (1) baseline measurement while watching a video (Baseline); (2) a direction to relax however they would like at a table (Task 1); and (3) breathing exercises (Task 2). We calculated change in HRV (as measured by root mean square of the successive differences [RMSSD] between neighboring RR intervals) from Baseline to Task 1 and Baseline to Task 2. Participants' caregivers also completed a series of clinical measures at each time point including Emotion Dysregulation Inventory (EDI), Clinical Global Impression Scale (CGI-I), Aberrant Behavior Checklist (ABC), and the Flexibility Scale. We also examined associations between changes in HRV and the aforementioned clinical outcome measures.

Results: The present study obtained very high feasibility rates as indicated by 100% tolerability and 100% data collection success rate (*N*=201 recordings) across participants. Analyses demonstrate that change in HRV for Task 1 was significantly related to our

clinical outcome measures including the EDI-Reactivity ($F(1, 5) = 10.30$, $p = 0.024$) and EDI-Dysphoria ($F(1,5)=7.31$, $p=0.04$). In addition, Task 1 had an interaction with time on the ABC-Irritability ($F(4, 23)=2.79$, $p=0.05$) and the CGI-I ($F(3,14)=3.21$, $p=0.05$). Task 2 had a significant interaction between HRV and time on a subscale of the Flexibility Scale, Generativity ($F(4,24)=3.58$, $p=0.02$). Task 2 also had a interaction with time predicting improvement on the CGI-I ($F(3,14)=2.87$, $p=0.07$) and the Flexibility Total Score ($F(4,23)=2.27$, $p=0.09$). Finally, HRV for Task 1 was sensitive to change over time in a small number of participants ($N=11$) who completed the treatment program.

Discussion: Given the need for objective and reliable biomarkers to further examine treatment outcomes and responses in ASD, the present study demonstrates preliminary evidence for the high feasibility of obtaining physiological indices in children and adolescents with ASD. Additionally, the present study suggests construct validity with several clinical outcome measures relating to core ER deficits, including reactivity, dysphoria, irritability, flexibility, and overall clinical improvement. Despite our small sample of participants, the present study supports the predictive utility of HRV on improvement in clinical outcomes and sensitivity to change across time during the intervention. Overall, ambulatory HRV appears to be a promising biomarker for identifying biological mechanisms associated with therapeutic gains for use in future treatment trials that aim to promote emotion regulation in ASD.

Paper 4 of 4

Paper Title: Emerging Evidence of Enhanced Flexibility Using a Probabilistic Reversal Learning Task Following Intervention Targeting Emotion Regulation in Youth with ASD

Authors: Lauren M. Schmitt, Ph.D., John A. Sweeney, Ph.D., Craig A. Erickson, M.D., Rebecca Shaffer, Ph.D.

Introduction: Cognitive flexibility is a critical aspect of emotion regulation (ER), involving both the ability to inhibit previously preferred coping behaviors or cognitive sets and switching to more adaptive coping strategies and thought processes (Schreiter & Best, 2020; Mazefsky et al., 2013). Yet, the ability to strategically and flexibly adapt to situational demands, especially in the context of uncertainty and/or high emotional saliency, is impaired in ASD. Thus, failure to flexibly use different coping or change thoughts may lead to the maintenance of maladaptive coping and long-term ED in ASD. We conducted a within-subjects trial of Regulating Together (RT), a group-based, parent-integrated behavioral intervention targeting ED for individuals with ASD aged 8-18 years (Shaffer et al., 2019), including specific curricula focused on enhancing cognitive flexibility. Using a probabilistic reversal learning (PRL) task of cognitive flexibility previously validated for use in ASD (D'Cruz et al., 2016), we examined the feasibility and efficacy of PRL as an outcome measure in a behavioral intervention trial for ASD.

Methods: Thirty-one participants (8-18 years, 80% males) completed RT and attempted the PRL task during Screening, Visit, and Follow-up (10-weeks post-intervention). During PRL, participants are instructed to choose one of two identical stimuli (i.e., animals) positioned in different locations on the screen. Participants were reinforced (i.e., coin) on 80% of correct responses and on 20% of incorrect responses. During acquisition, participants chose one of two stimulus locations until they identified the correct location on 8 of 10 consecutive trials. Then, they proceeded to the reversal phase in which the correct location is switched without warning, and participants had to identify the new correct location. Testing was discontinued if they do not reach criterion within 50 trials of either phase. We computed total number of trials to reach criterion and number of errors (i.e., selecting the incorrect location). Caregivers completed the Aberrant Behavior Checklist (ABC), Emotion Dysregulation Inventory (EDI), and Flexibility Scale (FS) at each time point; scores were used in exploratory correlational analyses with PRL outcomes.

Results: Successful completion of the PRL task was demonstrated by the majority of participants (n=25, 88%) at initial visits and all participants at the follow-up visit. Compared to baseline, participants needed fewer number of trials to reach PRL criterion 10-weeks following intervention ($F(1,20)=5.42$, $p=.031$, Cohen's $d=.69$), this was particularly pronounced in the child age group (8-12 yr) ($t=2.34$, $p=.030$, $d=.96$). At the 10 weeks follow-up visit, greater improvement on PRL as indicated by fewer total trials or total errors related to less severe parent-rated rigidity and broader symptoms associated with ED. Together, our findings demonstrate the ability of the PRL task to detect change following an intensive treatment focused on enhancing ER, thus supporting its use as a

behavior-based outcome measure intervention trials with individuals with ASD. The child age group demonstrated greater reductions than the adolescent group (13-18 yr) for perseverative ($F(1,20)=6.514$, $p=.019$, $d=1.04$), but the two groups showed similar reductions in regressive errors ($F(1,20)=.274$, $p=.607$, $d=.25$). A greater reduction in total trials needed to reach criterion from baseline to follow-up related to less severe parent-rated routines ($r=-.680$, $p=.001$) and interests ($r=-.470$, $p=.036$) at follow-up. Additionally, fewer total errors related to lower irritability ($r=.427$, $p=.047$), hyperactivity ($r=.514$, $p=.021$), and speech abnormalities ($r=.581$, $p=.005$) at the 10 Week Follow-up.

Discussion: We demonstrate the initial feasibility and utility of a probabilistic reversal learning task as an outcome measure of cognitive flexibility following a within subjects trial of a group-based, parent-integrated intervention targeting ER in children and adolescents with ASD. Compared to baseline, participants needed fewer number of trials to reach PRL criterion 10-weeks following intervention. At the 10 weeks follow-up visit, greater improvement on PRL as indicated by fewer total trials or total errors related to less severe parent-rated rigidity and broader symptoms associated with ED. Together, our findings demonstrate the ability of the PRL task to detect change following an intensive treatment focused on enhancing ER, thus supporting its use as a behavior-based outcome measure intervention trials with individuals with ASD.