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Joint Consideration of Inhibitory Control and Irritability in Young Children: Contributions to Emergent Psychopathology

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Abstract

Deficits in self-regulation capacity have been linked to subsequent impairment and clinical symptomology across the lifespan. Prior work has identified difficulty regulating angry emotions (i.e., irritability) as a powerful transdiagnostic indicator of current and future clinical concerns. Less is known regarding how irritability intersects with cognitive features of self-regulation, in particular inhibitory control, despite its mental health relevance. A promising avenue for improving specificity of clinical predictions in early childhood is multi-method, joint consideration of irritability and inhibitory control capacities. To advance early identification of impairment and psychopathology risk, we contrast group- and variable-based models of neurodevelopmental vulnerability at the interface of irritability and inhibitory control in contexts of varied motivational and emotional salience. This work was conducted in a longitudinal study of children recruited at well-child visits in Midwestern pediatric clinics at preschool age (N = 223, age range = 3–7 years). Group-based models (clustering and regression of clusters on clinical outcomes) indicated significant heterogeneity of self-regulation capacity in this sample. Meanwhile, variable-based models (continuous multiple regression) evidenced associations with concurrent clinical presentation, future symptoms, and impairment across the broad spectrum of psychopathology. Irritability transdiagnostically indicated internalizing and externalizing problems, concurrently and longitudinally. In contrast, inhibitory control was uniquely associated

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Compliance with Ethical Standards

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with attention-deficit/hyperactivity symptoms. We present these findings to advance a joint consideration approach to two promising indicators of neurodevelopmental vulnerability and mental health risk. Models suggest that both emotional and cognitive self-regulation capacities can address challenges in characterizing the developmental unfolding of psychopathology from preschool to early childhood age.

Keywords

Self-regulation; Irritability; Inhibitory control; Early childhood

Introduction

Development of the capacity for self-regulation–in emotional and cognitive arenas–is characterized by significant and rapid change during early childhood, with critical implications for mental health outcomes across the lifespan. Self-regulation represents the set of internal processes that individuals employ to modulate emotional and cognitive responses to stimuli (Blair & Raver, 2015; Murray et al., 2015). To improve understanding of how these internal processes inform early mental health risk prediction, we looked across two often disparate lines of research: emotional and cognitive self-regulation, i.e., irritability and inhibitory control, as risk predictors.

Irritability, defined as difficulty regulating angry and frustrated emotions, is a highly salient marker of dysregulation (Bilgin & Wolke, 2020; Wakschlag et al., 2019). In fact, irritability is currently the most robust early marker of neurodevelopmental vulnerability to common and modifiable forms of internalizing and externalizing psychopathology, and there is increasing interest in defining the typical:atypical spectrum of this domain (Biedzio & Wakschlag, 2019; Martel et al., 2013; Smith et al., 2019; Wakschlag et al., 2018). Extensive work in this arena has supported the transdiagnostic nature of irritability (Beauchaine & Tackett, 2020; Wiggins et al., 2018). Despite the demonstrated promise of irritability as a predictor, there remains a need for science that captures the full typical:atypical spectrum of irritability in a manner that is developmentally sensitive, given that our ability to measure irritability and early psychopathology is often constrained by the rapid change and development characteristic of early childhood (Krogh-Jespersen et al., 2021).

Another clinically predictive feature of self-regulation is cognitive, i.e., inhibitory control. Inhibitory control is the ability to inhibit a pre-potent or practiced response, expressed clinically as poor self-control (Nigg, 2017; Wiebe et al., 2015). Of note, inhibitory control is likely contextually bound, with certain contexts having higher motivational salience than others; we hereafter refer to the ability to regulate across contexts as *inhibitory modulation* (Wiebe et al., 2015). Like irritability, deficits in inhibitory control have been found to possess high transdiagnostic relevance in assessing early mental health risk, with direct assessments of this capacity in early childhood having been well validated in the field (Berger & Buttelmann, 2022; Dougherty et al., 2015; Haynes et al., 2015; McGrath et al., 2016; Nigg, 2017; Sonuga-Barke, 2002).

While both irritability and inhibitory control have been repeatedly found to possess clinical utility in identifying neurodevelopmental vulnerabilities, these constructs have rarely been considered jointly and the behavioral intersection of irritability with inhibitory control in young children is poorly understood (Healey et al., 2008; Martel et al., 2013). While prior work has established that the capacities captured by emotionally charged tasks have unique behavioral and cognitive sequelae (Hongwanishkul et al., 2005), there remains a need for research investigating how and whether measurement of these constructs might intersect in clinically useful ways. This includes a need for more extensive work exploring inhibitory modulation as a means of examining irritability and inhibitory control jointly (Wiggins et al., 2018). As the most salient clinical feature of irritability is dysregulated tantrums/emotional outbursts (Wakschlag et al., 2012), it follows that impairments in inhibitory control may manifest differently depending on the emotional and motivational context and models which leverage this difference may provide useful insight into the intra-individual variation that distinguishes typical:atypical self-regulation. Related work suggests that the specific capacity assessed in an emotionally charged context–to regulate behavior and emotions under varied motivational conditions–may be particularly important to identifying early indicators of self-regulatory risk (Geeraerts et al., 2015; Sonuga-Barke, 2002). In looking at the inhibitory control:irritability interface of self-regulation, a natural next step is the development of models of neurodevelopmental vulnerability which capture inhibitory control in both high-motivational (frustrative) and low emotional/motivational contexts, and the ability to modulate response in switching between the two.

Challenges to and Merits of Joint Consideration

A significant challenge to joint consideration of cognitive and emotional self-regulation lies in both the *measurement* and the *modeling* of these capacities. Measurement is complicated by the significant inter- and intra-individual variability in acquisition and consolidation of self-regulation in early childhood (Zelazo & Carlson, 2012), which make it difficult to differentiate normative variability in regulatory abilities from clinically concerning dysregulation (Wakschlag et al., 2010). Furthermore, the extant literature on early development of emotional self-regulation has employed temperament as the primary measure of this capacity (Karalunas et al., 2019). This proves a notable limitation in predicting to clinical symptoms, as measures of temperament are limited in their ability to capture the full range of the typical:atypical spectrum of irritability (Leibenluft & Stoddard, 2013).

In determining the best approaches for modeling how these constructs may relate to each other, we look to prior work employing data-driven (e.g., “bottom-up”) approaches to conceptualizing regulatory capacities. Prior work ascertaining latent “natural groupings” of regulatory capacities within the context of early childhood development show promise, particularly in capturing the full heterogeneity of cognitive features of neurodevelopmental vulnerability to behavioral disorders (Bathelt et al., 2018). In related clinical science work, such bottom-up approaches have elucidated the relation of irritability and hypervigilance in the prediction of psychopathology (Salum et al., 2017). Similar work by Karalunas et al. (2014) has deepened our understanding of early childhood disorder via establishing the irritable-ADHD subtype with implications for intervention and impairment

trajectories. Of note, there has been a recent call in the field for greater attention to transdiagnostic approaches in studying neurodevelopmental risk, given significant inter-individual heterogeneity even within a single disorder–of which the irritable-ADHD subtype is only one example–which may limit our ability to conceptualize the clinical utility of our predictors (Astle et al., 2022). Clustering methods in particular have been identified as a promising method for conducting this work, alongside other group-based models of latent factors as a means of addressing and reducing the not insignificant problem of measurement variance (Gärtner & Strobel, 2021).

Within this larger context of establishing methods for modeling heterogeneity, there remains the question of how best to model jointly two capacities (i.e., irritability and inhibitory control) with different behavior sequelae and presentations. Such inquiry is worthwhile, as a joint-modeling approach to irritability and inhibitory control capacity has the promise to improve specificity of risk identification and clinical prediction (Grabell et al., 2018). Several studies support the potential value of joint consideration in clinical identification models, as an indicator of increased symptom severity specifically for ADHD in the presence of increased irritability (Healey et al., 2011; Rabinovitz et al., 2016). Meanwhile, executive function deficits reflective of reduced inhibitory control capacity have uniquely predicted later expression of disruptive behavior symptoms among preschool age children considered “high-irritable” (Kessel et al., 2016). Others have applied this approach meaningfully to explicate how a child’s early capacity for inhibiting worried thoughts mediates the relation between fearful emotionality and symptoms of anxiety (Gramszlo et al., 2018). Prior work in this arena has limited its examination to specific disorders or domains (i.e., internalizing or externalizing disorder groups only), with a focus on clinical *outcomes* rather than early *predictors* (e.g., (Karalunas et al., 2019). An important next step in the field is the application of these methods to broad, well-characterized samples, as early in the clinical sequence as possible for maximal impact (i.e., before a clinical referral or diagnosis is merited; (Smith et al., 2019).

The Present Study

This paper builds on and extends foundational work in the arenas of transdiagnostic prediction, early developmental identification, and measurement and analytic methodology for joint consideration of target constructs. A novel contribution of this work is in its prediction of promising early indicators to the *broad spectrum of psychopathology*, specifically predicting irritability (a key transdiagnostic indicator in early development), inhibitory control, and inhibitory modulation to a full range of internalizing and externalizing syndromes. In fact, the extant research most similar to the present study, which clustered phenotypes of clinical risk, was restricted to prediction of ADHD (Healey et al., 2011). Likewise, work by Healey et al. (2011); see also (Rabinovitz et al., 2016) comprises the only other study to our knowledge that examines covariation of executive function and emotion regulation in young children to predict to psychopathology of any kind. We extend this work in preschoolers while predicting to a full range of internalizing and externalizing outcomes. Furthermore, we leverage tools for measuring our target constructs in dimensional, developmentally sensitive ways. Of note, we employ the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB), which was designed to measure

the typical:atypical spectrum of irritability, as opposed to measures of temperament which have been frequently used in similar research (Healey et al., 2011; Karalunas et al., 2019). Furthermore, we capture inhibitory control in two contexts of motivational salience via inclusion of an inhibitory modulation construct, which allows us to assess intra-individual variation in regulatory capacities across contexts. Finally, we contrast modeling and analytic methods pioneered for use in developmental clinical science by others in the field (i.e., clustering, see Karalunas et al., 2014, 2019) with a regression approach in the same sample.

In this study, we employ developmentally sensitive measures of our core constructs, and compare and contrast analytic approaches to jointly considering and modeling inhibitory control and irritability. We present an exploratory analysis using hierarchical clustering techniques to delineate naturally occurring groups along measures of irritability, inhibitory control, and inhibitory modulation at preschool age. We then examine the incremental clinical utility of our approaches for identifying children's neurodevelopmental vulnerability to later disorder via multiple regression. Using the group assignment derived from the clustering approach as well as more traditional person-based models, we present both group- and variable-based multiple regression models testing the relation of measures of self-regulation to present and future clinical concerns (both specific symptomology and general impairment). We investigate the promise of joint consideration of key constructs via the following: inclusion of a measure of inhibitory modulation in our models, interaction terms in the variable-based regression analyses, and group-based regression analysis, in which groups are derived from *k-means* cluster analysis.

The aims of this study are twofold:

1. To model whether and how emotional and cognitive expressions of self-regulation relate in early childhood via both an exploratory hierarchical clustering model and continuous (variable-based) multiple regression, and
2. To assess the clinical utility of such methods of joint consideration for identification and prediction of clinical outcomes.

We hypothesized that such joint consideration could improve clinical prediction. While we in fact find that meaningful clusters can be derived from such data, the relation between cluster and symptom type is complex, indicating the need for continued research at the intersection of inhibitory control and irritability in early childhood.

Method

Participants

The broad analytic ($N = 242$ cross-sectional, $N = 223$ longitudinal) sample was derived from a larger longitudinal study of early childhood irritability and disruptive behavior. The recruitment process for this larger study has been described at length in related work (e.g., Wakschlag et al., 2012). In brief, recruitment in this larger study stratified participants by race/ethnicity and a range of SES membership to ensure a diverse sample; children were oversampled for psychopathology risk via parent-report measures of disruptive behavior and family adversity. Consent and assent were obtained from a primary caregiver and

participating child, respectively, at the first study visit and at each event during which data were collected, via trained research assistants who reviewed consent/assent forms with each participating child/adult one-on-one. All recruitment and study procedures were approved by the Northwestern University's Institutional Review Board (**IRB#STU00083564**) prior to the start of study activities. In the present study, exploratory modeling was conducted with those children who evidenced reliable completion of all three blocks of a computer-based inhibitory control task, the Whack-A-Mole (WAM) and had complete irritability data ($N = 262$; $\mu = 4.4$, $SD = 0.75$, range 3–6 years). Of note, this sample excluded 9 children who exhibited disengagement from the WAM task, as reported by the experimenter and confirmed by the authors (see Fig. S1 in the supplementary materials for details). Implications of task disengagement are expanded on in the discussion of study results; details and rationale for determination of disengagement/engagement are described in greater detail in "Measures".

Modeling and analyses consisted of three components, each with slightly different sample sizes due to data availability: 1) cluster modeling, in which we used the entire eligible sample with usable data available at preschool age ($n = 262$), 2) cross-sectional regression ($n = 248$), and 3) longitudinal regression ($n = 223$). Varying sample sizes across the modeling and analytic components of the present study are due to missing data on key parent-report measures (14 missing at preschool age, 39 missing at early school age).

For the analytic components of the present study, group- and variable-based multiple regression models are restricted to those participants for whom we have complete impairment and clinical symptom data at preschool and early school ($\mu = 7.3$, $SD = 1.02$, range 4–9 years) ages. The analytic sample was racially/ethnically diverse: children were 47% African American/black, 29% Hispanic, 22% Caucasian/white, and 2% reported race/ethnicity as "Other." The sample was also SES diverse; at the time of recruitment, 43% of participating families were designated at or below the poverty level according to an income-to-needs ratio, 14% near-threshold, and 43% above threshold. Participants included in the analytic sub-samples did not vary significantly in demographic composition from the original study sample.

Measures

All core measures tapping irritability and inhibitory control capacity were collected at the preschool age time point of the study. Impairment was captured by the Family Life Impairment Scale (FLIS) at three time points: the preschool age visit, a 9-month follow-up survey ($\mu = 5.7$, $SD = 0.75$, range = 3–7 years), and the early school age visit ($\mu = 7.3$, $SD = 1.02$, range = 4–9 years). Symptoms of psychopathology were assessed at preschool and early school age using validated clinical interviews.

Inhibitory control and modulation.—The Whack-A-Mole (WAM; Casey et al., 1997; see also Deveney et al., 2019) is a computerized Go/No-Go task using child-friendly animation (e.g., moles) to gameify the task and engage participants; scores on this task have been found to correlate significantly with neural activation and location of related regions during task-based fMRI. The WAM has been widely used in both typically developing

and neurodivergent preschool age populations to measure working memory and inhibitory control (Casey et al., 2011). In this task, children were presented with animations of a mole (the Go trial) and vegetables (the No-Go trial) and instructions to press the button only when the mole appeared, as quickly and accurately as possible. The task consisted of 140 Go trials and 60 No-Go trials. A three-block iteration of this task including a rigged block (inserted between two "typical" iterations of the task) was meant to induce frustration and measure ability to recover from the frustration. Rate of presentation during the non-rigged blocks ranged from 1,600 to 2,200 ms and children received positive feedback from both the task and the research assistant administering it. During the rigged block, trials were presented at slightly shorter intervals (1,500 to 1,900 ms) and children received negative feedback on task performance that was not related to actual accuracy of Go and No-Go trials. *Block 1* was the standard task, which was designed to capture inhibitory control, and provided children with accurate feedback about their performance. *Block 2* of the task was a "rigged" version of the same task in which the task responded at a delay such that children received feedback indicating an incorrect response (i.e., that they had missed the target during the Go trial) regardless of their actual performance, intended to be frustrating for all children. Children were not informed of the difference in conditions specific to this block. *Block 3* was designed to assess recovery after frustration and, as in Block 1, provided accurate performance feedback.

Determination of useable data: Observed task engagement on the WAM determined usability of participant data. Because we wanted to avoid excluding children who simply struggled with the task and thus fell below typical accuracy cut-offs, we checked the entire sample for outliers and flagged participants for evaluation if they met dual criteria of task accuracy below 80% and errors of commission (i.e., "false alarm" responses) above 50%. We reviewed video-recordings of these sessions were reviewed to ascertain the validity of task data based on recommendations of co-author Dr. Perlman, an expert in inhibitory control. Scores were considered a valid representation of participants' abilities for those who were deemed "on task" (i.e., looking at the screen and operating the controller as instructed) by a trained research assistant. Our approach here is consistent with clinical approaches to similar tasks (e.g., CPT; Huang-Pollock et al., 2012).

Data reduction of the WAM: We calculated a change score using the d' scores on the first and third blocks of the WAM task. Block 1 assessed inhibitory control within a low motivational context in a standard Go/No-Go task format. Block 2 was rigged for failure with the intent of inducing frustration and provided participants with false negative feedback about their performance. Due to the alterations made to Block 2 and the implications of these alterations for interpretation of scores during the rigged condition, we calculated a change score from the first to third block of the WAM reflecting *inhibitory modulation*, i.e., the ability to recover following frustration. The aforementioned change score is calculated as the *d'* value on Block 1 subtracted from that achieved on Block 3. Thus, a positive change score indicates improved performance on the WAM across the three blocks, and a negative score indicates lower performance relative to the first exposure. Both the inhibitory control and modulation (i.e., change) *d'* scores were ultimately standardized as z-scores for

analyses, and thus reflect the relative abilities and improvement of participants within the sample.

Irritability.—The Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB; Wakschlag et al., 2014) is a developmentally sensitive parent-report survey designed to differentiate the normative misbehavior of early childhood from that which portends clinical risk across multiple dimensions, with high internal consistency within the Temper Loss scale ($\alpha = 0.97$). The analyses conducted in this study are restricted to this 14-item scale, as it uniquely measures the typical:atypical spectrum of irritability (Wakschlag et al., 2012, 2014). Parents rated the frequencies of child's behaviors on a 6-point Likert-type scale ranging from 0 ("Never in the past month") to 5 ("Multiple times per day") in order to reduce bias by including objective rather than subjective frequency scales. This measure was designed to capture the range of irritability from developmentally expectable to clinically concerning across multiple contexts (Deveney et al., 2019; Wakschlag et al., 2012). Item-response theory (IRT) methods were used to generate the typical:atypical spectrum of irritability (see Wakschlag et al., 2012). As IRT scores tend to have a standard deviation less than one, z-scores were created to maintain consistency with the MAP-DB and WAM data used in all models.

Impairment trajectories.—The Family Life Impairment Scale (FLIS; Mian et al., 2018) was used to determine the level and type of functional impairment experienced as a result of children's behavior in three areas: child functioning, family functioning, and parental functioning. The FLIS is a 19-item parent-report survey with a 3-point Likert-type scale in which parents endorse agreement with specific statements of activities that may be difficult for the child or family to complete, and has evidenced high internal consistency in preschool and early school age populations (α ranging from 0.74 to 0.85). The FLIS was administered at all three time points, enabling us to model impairment trajectories. In order to do this, we fitted multi-indicator growth models with random intercepts and slopes across three time points (i.e., at recruitment, at the preschool-age visit, and again at early school age; Wiggins et al., 2018). Intercepts were centered at 5 years of age. At each observed time, a latent variable for impairment was measured by the five observed indicator items, which were modeled as an ordinal variable. Growth was modeled from the three latent variables, using age as time scores. Parameters were estimated by robust maximum likelihood in Mplus, version 6.11. Trajectory scores are individual estimates of the slopes of impairment in the model across the three time points, indicating both the direction and magnitude of impairment for participating children.

Clinical symptoms.—Developmentally specified DSM-based clinical interviews were used to obtain symptom counts collected via semi-structured parent interview at preschool (the Preschool Age Psychiatric Assessment, PAPA; (Egger & Angold, 2004) and early school age (the Kiddie Schedule for Affective Disorders and Schizophrenia, K-SADS; Kaufman et al., 1997). These semi-structured interviews were chosen for their high test–retest reliability (intraclass correlation coefficients for each PAPA scale ranged from 0.61 to 0.80, see Egger et al., 2006, and kappas for each K-SADS scale range from 0.77 to 1.00, Kaufman et al., 1997) and correlation with widely used diagnostic measures (e.g., Child

Behavior Checklist). Clinical outcomes for our models consisted of continuous symptom counts for common internalizing and externalizing disorders: separation anxiety, generalized anxiety, depression, attention deficit/hyperactivity, and oppositional-defiant syndromes. Multiple regression analyses for these outcomes were conducted separately at both time points.

Analytic Overview

We employed two analytic approaches to joint consideration of inhibitory control and irritability: hierarchical and follow-on *k-means* cluster analysis with regression of cluster assignment against outcomes, and multiple regression (both with and without interaction terms) against those same outcome variables.

Analysis 1: Clustering.—Clustering techniques were used to determine whether natural groupings existed in our sample along inhibitory control and irritability domains, and if so, to characterize those groups along these domains. This analytic approach was applied to test whether children's scores across these domains fall together in ways that indicate a behavioral pattern of (dys)regulation across our measures, indicating which children are consistently more or less regulated than the others in the analytic sample. Given the exploratory nature of the initial question, hierarchical clustering was conducted to perform a bottom-up analysis of the data. Next, a k-means confirmatory analysis was employed with the *adegenet* package of R (last updated for version 2.1.1) to gather metrics of validity (Norusis, 2008).

Participant data were clustered on three variables: (1) performance on the WAM Block 1 (prior to frustration induction) as captured by *d'*, (2) change in performance on the WAM between Block 3 and Block 1 (i.e., *after* versus *before* frustration induction; also *d'*) and (3) parent-reported irritability (i.e., the Temper Loss scale of the MAP-DB). Because cluster analysis is highly sensitive to differences in variance in scale in the data (Liu et al., 2010), all variables were standardized as z-scores prior to conducting the cluster analysis (Milligan & Cooper, 1988). Hierarchical cluster analysis in our sample generated the number of clusters that *best fit* extant groups within the data, rather than imposing an assumed number of groups on the data. Ward's method was used as we did not assume that groups would be of equal size.

Analysis 2: Hierarchical regression.—We conducted multiple regression for both cluster assignment (group-based) and continuous scores (variable-based) as independent variables along irritability, inhibitory control, and inhibitory modulation measures (Laursen & Hoff, 2006). In the individual-based multiple regression multiples, interaction terms for *inhibitory control* x *irritability* and *inhibitory modulation* x *irritability* were included and examined as a mean conceptualization of joint consideration. Unstandardized betas indicating the number of symptoms associated with either group membership (group-based) or single unit increases in our irritability, inhibitory control, and inhibitory modulation measures (variable-based).

Analysis 2.a. Group-based.: Cluster assignment was a categorical independent variable regressed to two sets of outcomes: impairment (the FLIS) and clinical symptom counts (the PAPA) on *k* clusters in the data. These models allowed us to test the clinical utility of the clusters.

Analysis 2.b. Variable-based.: This analysis consisted of multiple regression models including the same outcome variables as Analysis 2.a, but instead used inhibitory control task performance and irritability scores continuously. Joint consideration was attempted analytically via the inclusion of two interaction terms for children's *inhibitory control* x *irritability* and *inhibitory modulation* x *irritability*. In addition to testing the predictive utility of jointly considering inhibitory control and irritability to later impairment, comparison of the models in Analyses 2.a and 2.b provided insight on the relative clinical utility of cluster analysis (i.e., our second analytic objective).

Results

Analysis 1: Cluster analysis.

The cluster analysis consisted of several sets of related analyses, to verify the accuracy and validity of the final generated groups. All models were fit to three variables: irritability (MAP-DB Temper Loss score), inhibitory control (performance on WAM prior to frustration induction), and inhibitory modulation (change in performance on the WAM *after* frustration induction). We first ran a hierarchical cluster analysis indicating 4 clusters. We then verified the fit of this four-cluster solution using the Carlinski-Harabaz index, as recommended by Liu et al. (2010). This is a conservative estimate of validity based on within- and between-cluster distances. In applying this index, the highest value indicated that the four-cluster solution best fit our data. Follow-on analyses indicated that the largest proportion of the *total* variance explained by the clusters (61.5%) with the measure of irritability. The four clusters (see Fig. 1) indicate slight overlap when participants are clustered into four groups.[1] Clusters did not vary significantly in demographic composition.

The resulting clusters are comprised of different demonstrated ability across the three domains of regulatory capacity (e.g., irritability, inhibitory control, and inhibitory modulation). Table 1 indicates the mean scores of irritability, inhibitory control, and inhibitory modulation associated with each of the clusters (see Table S1 in the supplementary materials for a comparison of both standardized and unstandardized mean scores by cluster). The mean scores in Table 1 were calculated from standardized values and thus can be interpreted in terms of each group's average performance relative to the mean of the sample (i.e., a score of 0 is at the sample mean, 1 is a full standard deviation above the sample mean).

Cluster One is our "well-regulated" group, comprised of children who possess average inhibitory control, high inhibitory modulation in the context of frustration, and low irritability. This group improved the most on the WAM following the emotion-induction

[1]Clusters are presented in Fig. 1 along WAM (inhibitory control), WAM change (inhibitory modulation), amd MAP-DB (irritability) score axes.

block (i.e., had the highest change score; μ_{EI1} = 1.766), scoring nearly 2 standard deviations above the sample mean. While this group exhibited average inhibitory control (μ_{IC1} = 0.02), their irritability was low (μ_{I1} = −0.55). Meanwhile, Cluster Four, the "dysregulated" group, is comprised of those participants who scored the highest in irritability of the sample (μ_{I4} = 0.99), nearly 1 standard deviation above the mean, and were also relatively low in baseline inhibitory control performance (μ_{IC4} = −0.39). They exhibited moderately low inhibitory modulation, performing slightly worse on the inhibitory control task following frustration induction (μ_{EC4} = −0.18).

We also found two "intermediate" groups who exhibited similarly poor inhibitory modulation but were differentiated by their inhibitory control scores and irritability. These clusters are here described in terms of regulation ability within the context of frustration: "contextually bound" (Cluster Two) and "poor cross-contextual" (Cluster Three) regulation. The contextually bound regulation group is comprised of children with average levels of irritability (μ_{I2} = 0.10) who also performed the highest on the inhibitory control task (μ_{IC2} = 1.18). Notably, this group scored below the sample mean for improvement from the first to the third and final block (μ_{EI2} = −0.32), indicating diminished inhibitory control following frustration induction.[2] Thus, this group is considered high in inhibitory control but with moderate levels of irritability, which may impede their ability to modulate response to frustration. Cluster Three, those with comparatively poor cross-contextual regulation, exhibited similar inhibitory modulation to the contextually bound regulation group, but with notable differences in baseline inhibitory control and irritability. These children were the least irritable in the sample, at nearly one standard deviation below the mean (μ_{I3} = −0.90). However, this group performed worse on the third block relative to the well-regulated group (μ_{EI3} = −0.36) and was comprised of participants who exhibited low initial performance on the inhibitory control task (μ_{IC3} = −0.35). Thus, the poor cross-contextual regulation group was low in both inhibitory control and irritability, with the caveat that their ability to recover from frustration was poor and hindered expression of their inhibitory control relative to the other children in the sample.

Taken together, all four groups in the sample represent the heterogeneity of profiles of preschool-age inhibitory control, modulation, and irritability.

Analysis 2.a: Cluster regression.

Impairment and number of symptoms of separation anxiety, generalized anxiety, depression, attention-deficit/hyperactivity (ADHD), and oppositional-defiant (ODD) disorders were separately regressed on cluster membership. The well-regulated group was used as the comparison group for this analysis. Main effects (unstandardized beta) alongside R^2 values for this analysis are presented in Table 2 below. The cut-off for statistical significance was set at 0.01 following a post-hoc Bonferroni correction for multiple comparisons (Bonferroni, 1936). A small positive-but-not-significant association was found between trajectories of parent and family impairment across the preschool and early school years and the dysregulated group as compared with the well-regulated group (β = 0.65, p =

[2]Of note, the *unstandardized* mean change score of this population is slightly above 0, which indicates minimal objective improvement between the first and last trials of the WAM; z-scores speak to relative improvement (or lack thereof) within the analytic sample.

0.028; $\beta = 0.14$, $p = 0.047$, respectively), reflecting pathways of increasing impairment between preschool and early school ages. Cluster membership was significantly associated with higher symptom counts for both externalizing and internalizing syndromes for the dysregulated vs. well-regulated groups across the two time points. In particular, children in the dysregulated cluster had significantly more symptoms of separation anxiety ($\beta = 0.76$, $p = 0.006$), generalized anxiety ($\beta = 0.91$, $p = 0.002$), depression ($\beta = 0.85$, $p = 0.004$), ODD ($\beta = 1.76$, $p = 0.000$), and ADHD ($\beta = 2.72$, $p = 0.001$) at preschool age. At early school age, membership in this cluster was associated significantly with more symptoms of ODD ($\beta = 2.84$, $p = 0.000$; i.e., 2.8 more symptoms of ODD as compared with those in the "well regulated" cluster) only, at a higher magnitude than the cross-sectional preschool-age ODD model. Children designated as having poor cross-contextual regulation (Cluster Three) had fewer symptoms of depression ($\beta = -1.54$, $p = 0.013$) at early school age relative to the group that was most well-regulated overall. This same group was not significantly associated with reduced number of symptoms at preschool age.

Analysis 2.b. Continuous multiple regression.

This analysis consisted of a multiple regression of the same variables used to generate the aforementioned clusters. Beta and R^2 values for each model are presented in Table 3. Interaction terms (*inhibitory control* x *irritability*, *inhibitory modulation* x *irritability*) were also tested with no significant (or sizable) interaction found, and thus were excluded from the final models. Covariates in all models were family socioeconomic status, child age, gender, race/ethnicity, and performance on a direct, untimed cognitive assessment (i.e., the Differential Ability Scales, Picture Similarities Subtest; Elliott, 1990).

Clinical symptom prediction—We found main effects of irritability on the number of DSM-based symptoms (i.e., PAPA, K-SADS scores) for multiple internalizing and externalizing syndromes at both preschool and early school age. Unstandardized beta (β) values represent the number of symptoms on each syndrome subscale within the age-appropriate psychopathology measure. Irritability was associated with symptoms of separation anxiety, depression, attention deficit/hyperactivity, and oppositionality reported at both preschool and early school age. Better inhibitory control performance was significantly associated with lower number of ADHD symptoms at both preschool ($\beta = -0.835$, $p = 0.006$) and early school age ($\beta = -2.695$, $p = 0.001$). Neither inhibitory modulation nor the interaction of irritability and inhibitory control were associated significantly with number of symptoms across any internalizing or externalizing syndromes. An additional model testing the interaction between inhibitory control and inhibitory modulation, as well as the interaction between irritability and inhibitory modulation, yielded no significant effects on symptom score count.

Impairment trajectory prediction—Irritability was associated with trajectories of child, parent, and family impairment from preschool to early school age; however, inhibitory control and inhibitory modulation were not significantly associated with impairment trajectories. As with our models predicting to clinical symptoms, interaction terms proved insignificant.

Discussion

In this paper, we examined patterns at the intersection of young children's irritability and contextually varied inhibitory control, with the aim of evaluating the contributions of each to clinical identification, both individually and together. We compared two potential methods of conducting this work: group- and variable-based regression. In so doing, we demonstrate two primary findings of note: 1) Hidden heterogeneity can be elucidated in part with measures of cognitive and emotion regulation, and 2) Joint consideration of these constructs preliminarily evidences incremental utility in identifying children's neurodevelopmental vulnerability to future psychopathology.

Our findings demonstrate that irritability and inhibitory control in two contexts of emotional salience (e.g., including inhibitory modulation) *do* intersect in varied ways in their prediction of clinical outcomes. The exploratory cluster analysis demonstrated that there is heterogeneity in self-regulation capacity, which we would miss if looking only at the components comprising our clusters as distinct indicators. Within our sample, there are children for whom the story is more complex than being simply well or poorly regulated. Of note, contextual variation (i.e., inhibitory modulation) did identify children who appear phenotypically different from others in this sample. It is worth considering the confirmation of hidden heterogeneity within our cluster analysis alongside the lack of significant interaction effects according to the variable-based regression method. In the latter analysis, performance on the inhibitory control task uniquely and significantly predicted future ADHD symptomology, while irritability proved transdiagnostic, consistent with prior work in this arena (Wakschlag et al., 2018). When considered alongside cognitive features of self-regulation (i.e., inhibitory control and inhibitory modulation), the specificity of these predictions appears to improve.

We note that irritability provided the most meaningful input to the formation of our clusters and was the strongest predictor of both number of symptoms and severity of impairment when making predictions at the individual level. It is important to note that this may in part reflect method variance as both irritability and clinical outcomes were assessed via parent-report whereas inhibitory control assessment was task-based. However, we note that inclusion of parents as reporters is vital to the utility of the present study, as parent perspectives are the primary drivers of clinical identification at this age (Blackwell et al., 2020; Owens et al., 2015). Furthermore, the MAP-DB survey used here has been validated in multiple large and diverse community samples of preschoolers, with demonstrated generalizability across demographic sub-groups, alongside predictive validity and mechanistic utility (Wakschlag et al., 2015).

Comparison of the clinical outcomes of the clusters revealed several meaningful patterns, indicating the potential clinical utility of such an approach. Consistent with the literature on irritability as a transdiagnostic indicator of risk, the dysregulated cluster (i.e., the most irritable, with greatest deficits in inhibitory control and lowest capacity to modulate in the context of frustration) had pervasively *increased* internalizing/externalizing symptoms at preschool age as well as escalating impairment over time relative to the well-regulated group. Notably, this dysregulated group was also at increased risk for symptoms (see

unstandardized β values) of oppositional-defiant disorder at early school age, a disorder in which dysregulation is a core feature. In contrast, the poor cross-contextual regulation group, representing children with the lowest irritability, evidenced good inhibitory control under low motivational conditions but poor inhibitory control in the frustrative context. The children in this poor cross-contextual group were associated with *reduced* risk for depression at early school age relative to the well-regulated group. This isolated pattern was unexpected, especially as it was not seen at preschool age. However, it may reflect a set of children who react irritably when frustrated, which can be normative, but do not have the chronic irritable mood (e.g., grumpiness) that subserves depressive patterns. These children represent the opposite end of the theorized regulatory spectrum and the potential protectiveness of greater self-regulation ability (Flouri et al., 2014; Mischel et al., 2011). The puzzling nature of this finding underscores the importance of replication in other samples and future work that captures cross-contextual regulation more directly.

Limitations of the present design and methods constrain interpretation. First, there are inherent limits of measurement that attempts to "induce" frustration experimentally as we did in the WAM: such tasks will not be equally frustrating for all children and deducing the degree to which children actually experienced frustration in the "rigged"/false-feedback condition is an additional challenge. We further note that the change scores calculated to represent children's inhibitory modulation (i.e., responses to emotion induction) are subject to a ceiling effect for those who performed very well in the pre-frustration context, in that there is little room for them to improve relative to others in the sample. Additionally, applying a categorical (i.e., cluster) approach to our data, while valuable in the exploration of how our latent construct relates to concurrent and future psychopathology, reduces the explanatory power of those models in which cluster assignment is a predictor. This poses a fundamental challenge to comparing our models to each other in terms of variance explained by each. While the categorical variables derived from clustering methods are at a methodological disadvantage when contrasted with continuous variables, collapsing the sample into groups via a clustering approach informs our understanding of sub-groups of children who may have different developmental trajectories over time, particularly in characterizing the task-based performance and parent reports on an "at-risk" dysregulated group of children. Finally, the use of parent report data for our measure of irritability as well as impairment and symptom data presents both advantages and challenges. Parent response data with such a young population confers *high* ecological validity, as parents know their children best and ultimately determine whether or not to pursue and implement clinical treatment in real-world contexts. At the same time, the absence of direct observation of irritability and/or another informant on psychopathology is a limitation. We do note however, that both parent report measures (i.e., MAP-DB and PAPA) query about contextual information, including behavior both in out of home contexts (Egger & Angold, 2004; Wakschlag et al., 2015).

Despite the limitations noted above, this work demonstrates that patterns of inhibitory control under varied motivational contexts do not always move in tandem. Multi-method approaches examining and inducing real-time frustration are an important area for future research. This might include physiological indicators of heightened negative emotions (e.g., heart rate) during the inhibitory control task as well as direct observation of

irritability, such that a physiologic indicator of arousal can complement task performance and observed behavior data. We have used this method successfully with direct observation and neuroimaging methods in our other work (Fishburn et al., 2019). In addition, although our sample was moderately sized, future investigations should draw on yet larger samples to yield increased numbers of children in each cluster for sufficient variability. For example, the well-regulated cluster had fewer than 40 children and even the largest (dysregulated) cluster had an *n* of 80. This precludes explication of individual differences (such as sex or age differences or environmental variation) that may obscure the utility of the clusters.

We consider the present work an important step toward joint consideration of multiple facets of self-regulation in the developmental unfolding of psychopathology. Future work can benefit from applying and extending the analytic approaches outlined here in larger broad population samples, and beginning in earlier development to examine the developmental unfolding of these processes and their intersection. Additional work clustering multiple facets of self-regulation capacity more directly should employ multimodal measurement of irritability and inhibitory control across varied emotional and motivational contexts, as well as exploring the differential effects of these variables on an outcome. These approaches may improve conceptualization of the constructs in question and increase the discriminatory power of the clusters that emerge from such analyses, as well as elucidating the mechanisms driving the heterogeneity observed in the population of the present study. Such work would elucidate the multi-faceted nature of clinical pathways within the context of neurodevelopment to differentiate further typical variation in self-regulation from that which is an early marker of neurodevelopmental vulnerability and concern.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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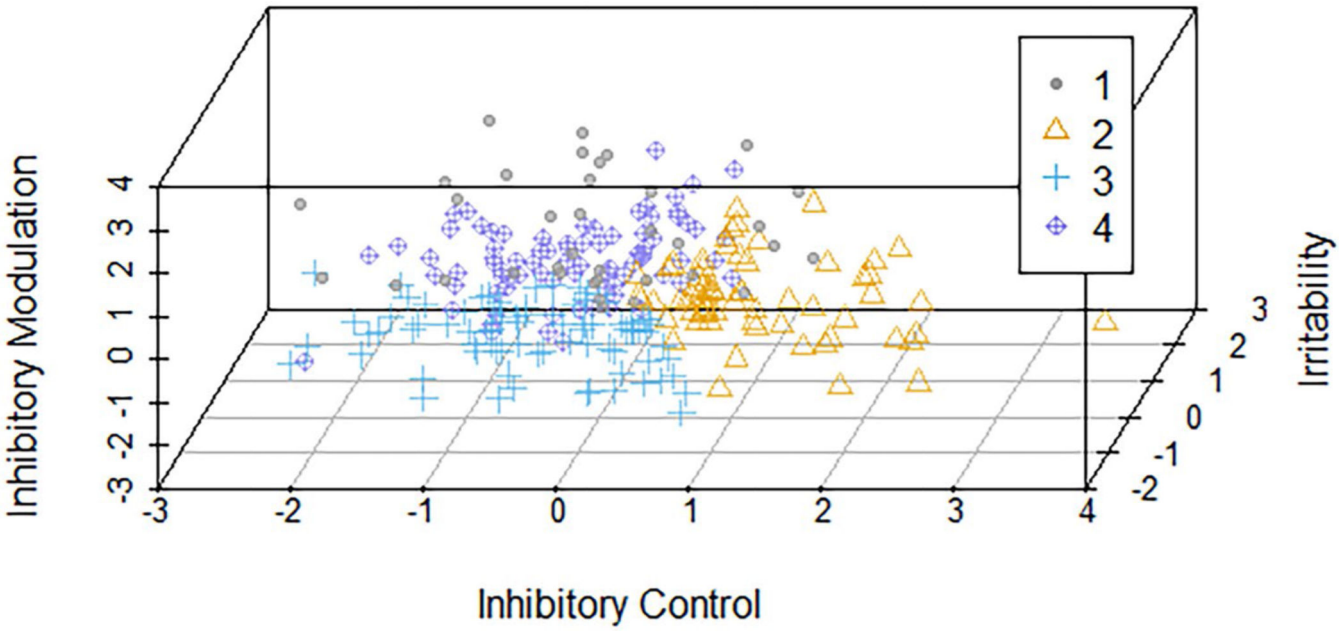

Fig. 1.
Clustering of Inhibitory Control, Modulation (d' WAM scores), and Irritability (MAP-DB)

Table 1

Means of Target Variables by Cluster

Cluster #	Cluster Name	Irritability	Inhibitory Control	Inhibitory Modulation	*n*
1	Well-Regulated Group	−0.552	0.017	1.766	36
2	Contextually Bound Regulation Group	0.092	1.183	−0.319	66
3	Poor Cross-Contextual Regulation Group	−0.903	−0.354	−0.359	80
4	Dysregulated Group	0.987	−0.387	−0.177	80

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Table 2

Analysis 2.a. Cluster Regression Model β Values

	Psychopathology Symptoms										Impairment Trajectory		
	Separation Anxiety		Generalized Anxiety		Depression		Attention Deficit/ Hyperactivity		Oppositional-Defiant		Child	Parent	Family
Cluster #	PSA	ESA	PSA	ESA	PSA	ESA	PSA	ESA	PSA	ESA			
2	0.153	−0.665	0.420	0.101	0.288	−1.133	0.984	−2.510	0.661	1.041	0.248	0.420	0.144
3	−0.184	−0.921	0.267	−0.146	−0.150	−1.535 *	−0.051	−3.860	−0.359	−0.030	−0.314	−0.484	−0.128
4	0.761 **	0.738	0.907 **	0.801	0.844 **	−0.311	2.718	2.526	1.759 ***	2.840 **	0.452	0.650 *	0.465
R^2	0.12	0.12	0.08	0.03	0.11	0.07	0.13	0.11	0.26	0.11	0.11	0.15	0.12

PSA Pre-School Age, *ESA* Early School Age

* p < 0.05;

** p < 0.01;

*** p < 0.001

Table 3

Analysis 2.b. Continuous Multiple Regression β Values

	Psychopathology Symptoms										Impairment Trajectory		
	Separation Anxiety		Generalized Anxiety		Depression		Attention Deficit/Hyperactivity		Oppositional-Defiant		Child	Parent	Family
	PSA[a]	ESA[b]	PSA	ESA	PSA	ESA	PSA	ESA	PSA	ESA			
Irritability	0.374***	0.601**	0.512***	0.344	0.595***	0.633**	1.667***	2.909***	0.345***	−1.390***	0.429***	0.572***	0.339***
Inhibitory Control	−0.189	−0.258	−0.163	−0.068	−0.142	0.011	−0.835**	−2.695***	−0.134	−0.551	0.011	0.040	−0.101
Inhibitory Modulation	0.031	0.092	0.010	−0.14	0.102	0.566*	0.094	0.649	0.002	−0.338	0.053	0.106	−0.004
R^2	0.13	0.12	0.17	0.03	0.20	0.07	0.23	0.11	0.18		0.16	0.20	0.14

PSA Pre-School Age, *ESA* Early School Age

* p < 0.05;

** p < 0.01;

*** p < 0.001