Received: 19 February 2018 | Revised: 13 September 2018 | Accepted: 14 September 2018

DOI: 10.1002/dev.21792

RESEARCH ARTICLE

WILEY Developmental Psychobiology

Temporally sensitive neural measures of inhibition in preschool children across a spectrum of irritability

Christen M. Deveney[1] | Margaret J. Briggs-Gowan[2] | David Pagliaccio[3] | Christopher R. Estabrook[4,5] | Elvira Zobel[4] | James L. Burns[4] | Elizabeth S. Norton[5,6] | Daniel S. Pine[3] | Melissa A. Brotman[3] | Ellen Leibenluft[3] | Lauren S. Wakschlag[4,5,7]

[1]Department of Psychology, Wellesley College, Wellesley, Massachusetts

[2]Department of Psychiatry, University of Connecticut School of Medicine, Farmington, Connecticut

[3]Emotion and Development Branch, National Institute of Mental Health, Bethesda, Maryland

[4]Department of Medical Social Sciences, Northwestern University, Chicago, Illinois

[5]Institute for Innovations in Developmental Sciences, Northwestern University, Chicago, Illinois

[6]School of Communication, Northwestern University, Evanston, Illinois

[7]Institute for Policy Research, Northwestern University, Chicago, Illinois

Correspondence
Margaret J. Briggs-Gowan, Department of Psychiatry, University of Connecticut Health Center, Farmington, CT.
Email: mbriggsgowan@uchc.edu

Present Address
David Pagliaccio, Division of Child and Adolescent Psychiatry, New York State Psychiatric Institute and the Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University, New York City, New York

Funding information
National Institute of Mental Health, Grant/Award Number: MAPS-1R01MH082830, MAPS-MHU010828320 and VEX study-MHU01090301

Abstract

Irritability is a prominent feature of chronic mental disorders and a developmental marker of their early emergence. The most salient feature of irritability in early childhood is temper tantrums. While temper tantrums are normative in young children, they can be clinically concerning when they are dysregulated, very frequent, and/or occur in unexpected contexts. The present study uses behavioral and event-related brain potential (ERP) measures to characterize the relationship between irritability and neural markers of response inhibition in very young children. Forty-six children (ages 4–7 years) completed a go/no-go task under nonfrustrating and frustrating conditions. ERPs elicited by go and no-go stimuli were examined as a function of frustration condition and irritability, operationalized via the well-validated Temper Loss scale of the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB). Higher Temper Loss scores were associated with larger $N2_{no\text{-}go}$ amplitudes and reduced no-go accuracy during frustration. This suggests that higher levels of irritability corresponded with increased conflict monitoring and poorer task performance during frustration. These findings add to a developing literature identifying the neurocognitive markers of varying levels of irritability in young children.

KEYWORDS
event-related brain potential, frustration, irritability, preschool, response inhibition

1 | INTRODUCTION

Children with severe and persistent irritability—a proneness to anger that may be associated with excessive and impairing temper outbursts (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017; Wakschlag et al., 2018)—experience high levels of impairment (Copeland, Brotman, & Costello, 2015) and increased risk for adverse outcomes throughout life (Copeland, Shanahan, Egger, Angold,

& Costello, 2014; Dougherty et al., 2013, 2015; Stringaris, Cohen, Pine, & Leibenluft, 2009). Irritability is a prominent feature of early childhood-onset neurodevelopmental conditions and a precursor to chronic mental disorders (Wakschlag et al., 2018). Identifying clinically significant irritability in very early childhood can facilitate prevention and treatment efforts targeting this common pathway to mental disorder. However, such early identification is challenged by the fact that one of the cardinal features of problematic irritability in children, temper tantrums, can represent either normative misbehavior or a marker of clinical concern in early childhood (Wakschlag et al., 2012). Across individuals, tantrums can vary considerably in their frequency, severity, and the context in which they occur (e.g., when hungry or tired vs. "out of the blue"; with parents vs. with other adults; Wakschlag et al., 2012). In young children, irritability can also manifest as long periods of angry or negative mood (e.g., "stays angry for a long time"; Wakschlag et al., 2012). While progress has been made in carefully cataloging the full range and characteristics of irritability in very young children (Biedzio and Wakschlag, in press; Wakschlag et al., 2015; Wakschlag et al., 2018; Wiggins et al., 2018), emerging evidence suggests that integrating neurocognitive measures can aid in identifying when a young child's irritability is likely to be associated with adverse long-term outcomes (Dougherty et al., 2018; Grabell et al., 2017; Grabell, Olson, Tardif, Thompson, & Gehring, 2016; Kessel, Dougherty, et al., 2016; Kessel, Meyer, et al., 2016; Li, Grabell, Wakschlag, Huppert, & Perlman, 2016; Perlman et al., 2015; Perlman, Luna, Hein, & Huppert, 2013). For example, interactions between early childhood irritability and neural measures of cognitive control predicted whether children developed internalizing or externalizing symptoms at age 9 (Kessel, Meyer, et al., 2016).

1.1 | Characterizing neurocognitive functioning across the spectrum of irritability

An important first step toward identifying markers of problematic irritability is to characterize the relationship between irritability and neurocognitive functioning across a spectrum of irritability severity. Many studies of school-aged children and adolescents (e.g., Adleman et al., 2011; Brotman et al., 2010; Deveney et al., 2013; Roy et al., 2013; Stoddard et al., 2016) involve categorical comparisons between children with clinically significant irritability and those with no psychiatric history. In contrast, studies of preschoolers have made strides in cataloging the relationship between irritability and neurocognitive functioning across the full spectrum of irritability. Recent work has linked anger during a laboratory task at age 12 months with poorer inhibitory control at age 3 years (Gagne & Goldsmith, 2011). Another laboratory has linked higher levels of preschool irritability with lateral and medial prefrontal cortex activation patterns during tests of cognitive control and cognitive flexibility (Li et al., 2016; Perlman et al., 2015, 2013). A series of studies emerging from a carefully characterized sample of children at risk for depression has revealed links between levels of preschool irritability and altered neural activation patterns and functional connectivity during reward and cognitive control tasks (Dougherty et al., 2018; Kessel, Dougherty, et al., 2016; Kessel, Meyer, et al., 2016). In one study, as irritability progressed from mild to moderate, lateral prefrontal activation during a cognitive control task increased. However, as irritability scores increased from moderate to severe, prefrontal activation decreased (Grabell et al., 2017). These findings further underscore the value of dimensional methods for capturing both linear and nonlinear associations.

To date, much of the existing neurocognitive research has focused on neurocognitive performance during neutral emotional contexts (c.f. Grabell et al., 2017). However, emerging research suggests that emotion–cognition interactions may be particularly important in the pathophysiology of irritability. Since clinically salient irritability was initially defined via disproportionate and prolonged reactions to blocked goal attainment (Leibenluft, 2011), it is likely that the motivational context of the neurocognitive task may be critical to understanding the neural mechanisms associated with irritability at all severity levels. Frustration is the affective state induced by blocked goal attainment and has been a particularly important affective condition in which to study irritability (Brotman et al., 2017; Leibenluft, 2017). In our prior work comparing attention flexibility between typically developing children/adolescents and those with clinically significant irritability, impaired performance in the clinical group was only discernible in a frustrating context (Deveney et al., 2013; Rich et al., 2011; c.f., Rich et al., 2007).

Thus, associations between irritability and neural activity in regions associated with emotion regulation, attention, and cognitive control may be particularly salient *during frustration*. Several studies provide preliminary support for this idea. In one study, children (ages 5–9 years) with temper outbursts characteristic of irritability had difficulty inhibiting negative emotional expressions during frustration, but not nonfrustration (Roy et al., 2013). Other research has linked irritability in young children (ages 3–7) with differing prefrontal activation patterns specifically during frustration conditions, including differentiation of children with irritability temperaments who were and were not impaired (Grabell et al., 2017; Perlman et al., 2013).

1.2 | Irritability and response inhibition

A small number of studies have linked irritability with inhibition deficits during neutral mood states in toddlers, school-age children, and adolescents (Adleman et al., 2011; Dickstein et al., 2007; Gagne & Goldsmith, 2011; c.f. Deveney et al., 2012); however, there are several limitations to this literature. First, the majority of studies have involved categorical comparisons between typically developing children and those with clinically significant irritability. Therefore, the relationship between irritability and response inhibition across a spectrum of irritability has not been explored. Second, none of these studies examined the relationship between irritability and response inhibition during frustration. This is a surprising gap given that pediatric irritability is often characterized by behaviors that suggest difficulties inhibiting responses when frustrated. Since irritability is a central cross-cutting feature of externalizing syndromes (Wakschlag et al., 2018), research with school-age children

displaying externalizing symptoms may be informative. These results from studies suggest that neural activation patterns during and/or when recovering from frustration differ among symptomatic children relative to those who are typically developing (Lewis & Stieben, 2004; Lewis, Lamm, Segalowitz, Stieben, & Zelazo, 2006; Stieben et al., 2007). Whether these frustration-related inhibitory deficits are identifiable at younger ages remains to be discovered.

In the present study of preschool-age children, we examine whether variations along the dimensional spectrum of irritability are associated with event-related brain potential (ERP) measures of response inhibition during a go/no-go task completed under nonfrustration and frustration conditions. The N2 component elicited by no-go trials is thought to index individuals' conflict detection, whereas the P3 component elicited by these trials is thought to index their response inhibition or evaluation of their success in inhibiting their response (Falkenstein, Hoormann, & Hohnsbein, 2002; Huster, Enriquez-Geppert, Lavallee, Falkenstein, & Herrmann, 2013). Although no ERP studies have related response inhibition specifically to irritability as a narrow-band phenotype in young children, children with externalizing syndromes broadly writ exhibit smaller N2 amplitudes (Buss, Dennis, Brooker, & Sippel, 2011; Dimoska, Johnstone, Barry, & Clarke, 2003; Grabell et al., 2016; Overtoom et al., 1998; Pliszka, Liotti, & Woldorff, 2000; Stieben et al., 2007) and possibly smaller P3 amplitudes (Overtoom et al., 1998). These reduced amplitudes are interpreted as evidence for reduced conflict monitoring and/or reduced mobilization of the resources required to inhibit a motor response in externalizing populations (Pliszka et al., 2000).

Here, we examine whether variations along the dimensional spectrum of irritability predict N2 and P3 amplitudes during a response inhibition task completed under nonfrustration and frustration conditions in preschoolers. We hypothesized that higher levels of irritability would be associated with impaired response inhibition as indicated by decreased no-go accuracy, ability to distinguish between go and no-go stimuli, and $N2_{no\text{-}go}$ and $P3_{no\text{-}go}$ amplitudes during frustration relative to nonfrustration conditions.

2 | METHODS

2.1 | Participants

Study participants were drawn from individuals participating in a larger longitudinal study of disruptive behaviors in preschoolers called the Multidimensional Assessment of Preschoolers Study (MAPS; Wakschlag et al., 2015). Briefly, MAPS recruited a large and diverse set of preschoolers from urban areas for a baseline assessment of disruptive behaviors. A subsample of those participants, chosen to oversample disruptive behaviors and other forms of psychopathology, participated in an intensive clinical and neurocognitive assessment that included an ERP session (see Nichols et al., 2015). For additional information about the MAPS study and the subset of children invited to participate in the laboratory sessions please, see Nichols et al., (2015); Wakschlag et al. (2015); and Supporting Information Appendix S1.

The present study reports on a further subset of participants who met eligibility criteria for the ERP session (at least 4 years of age; right-handed; and free of serious neurodevelopmental conditions and developmental delays or skin conditions that prevented electrode application) and who completed the go/no-go task (described below) with usable behavioral and ERP data. One hundred thirty children attempted the go/no-go task. Of those, 93 children completed the task with EEG data. As is common due to the challenges of EEG administration in young children, data from 27 children were excluded due to poor behavioral performance ($d' < 0.6$; $n = 7$) or having an insufficient number of trials to reliably estimate the ERP due to artifacts (<8 trials/trial type/block; $n = 20$). Of the remaining 66 children, 46 also had concurrent ratings of irritability. Therefore, the final sample consisted of 46 children ages 48.66–85.22 months ($M = 65.22$; $SD = 9.6$). Twenty children were male (43.5%), 18 identified as African American (39.1%), 19 as Hispanic (41.3%), and 9 as Caucasian (19.6%).

A series of analyses were conducted to determine whether the sample of children in the present study ($N = 46$) differed from other eligible children on sociodemographic, mood ratings, and behavioral performance variables. These analyses are described in detail in Supporting Information Appendix S1. Briefly, results indicate that while the 46 children in the present study adequately represent the proportion of boys and girls and the irritability severity of the larger sample, the present findings may be limited to children who are older, have better behavioral performance, and/or those who can tolerate multiple laboratory tasks including those involving EEG recordings and frustration manipulations. As such, they may underrepresent the relationship between irritability and response inhibition during frustration in young children. This limitation is considered in more depth in the discussion below.

Study protocols were approved by institutional review boards. Mothers provided informed consent. Parents were compensated for participation and transportation. Developmentally engaging approaches were used including appealing stimuli, rewards for participation and completion, rapid pacing, and breaks (see Methods section).

2.1.1 | Multidimensional assessment profile of disruptive behavior (MAP-DB)

Irritability was assessed with parent reports on the Temper Loss subscale of the MAP-DB, a measure specifically designed to differentiate normal: abnormal irritability in early childhood (Camacho, Wakschlag, & Perlman, in press; Wakschlag et al., 2010; Wakschlag et al., 2012; Wakschlag et al., 2018). Its 22 items include both normative misbehaviors (e.g. "loses temper or has a tantrum when tired, hungry, or sick") and qualitative features that distinguish clinically concerning expressions (e.g., "breaks or destroys things during a temper tantrum") and contexts (e.g., with parent, with other adult). The Temper Loss scale captures both irritable mood ("becomes

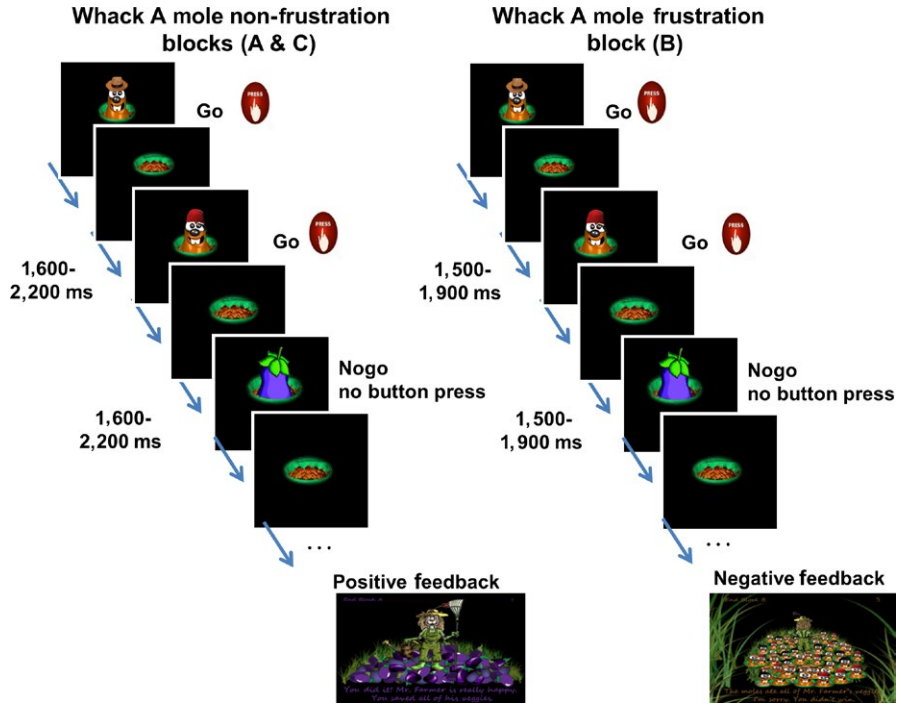

FIGURE 1 Whack-A-Mole Task. Children pressed a button when moles appeared (go trial; 70% of trials) but inhibited that response when an eggplant appeared (no-go trials; 30% of trials). Participants completed three blocks of trials. The first and third blocks (a and c) were nonfrustration blocks where the interstimulus (ISI) interval was randomized between 1,600 and 2,200 ms/trial and children received positive feedback after each set of 40 trials, regardless of performance. The second block was the frustration block (b). During this block, the ISI was shorter (1,500–1,900 ms) to promote errors and children received negative feedback after each set of 40 trials, regardless of performance

frustrated easily") and temper tantrums ("tantrums till exhausted"). The Temper Loss scale has been validated in a sociodemographically diverse set of participants with similar distributions across different sociodemographic factors including ethnicity and poverty (Wakschlag et al., 2014, 2012). In the present sample, internal consistency was excellent (Cronbach's α = 0.95). Scores ranged from 0 to 64.9 (M = 16.11, SD = 15.09) and were similar to scores observed in an independent sample of 1,490 children (Wakschlag et al., 2012).

The MAP-DB has been shown to distinguish young children with clinically significant irritability from those whose irritability falls into the normative range concurrently and longitudinally (Grabell et al., 2017; Wakschlag et al., 2015; Wiggins et al., 2018). Temper Loss scores above 25 have strong sensitivity and specificity in relation to external measures of clinical impairment (see Supporting Information Appendix S2 for details). Eleven children (24%) in the present sample had Temper Loss scores >25 reflecting clinically significant irritability.

2.2 | Whack-A-Mole Task

Participants completed a developmentally appropriate go/no-go task called the "Whack-A-Mole Task" (WAM) under different conditions (Figure 1) while ERP recordings were obtained. The WAM was based on the task developed by Sarah Getz and the Sackler Institute for Developmental Psychobiology (https://www.sacklerinstitute.org/cornell/assays_and_tools/WackAMole/mole_agree) and developmentally modified with permission to include a frustration manipulation similar the one used by Lewis and colleagues (Lamm & Lewis, 2010; Lewis & Stieben, 2004; Stieben et al., 2007). During the task, children helped Mr. Farmer save the vegetables in his garden by pressing a button to "whack" the moles (go trials; 140 trials/block), but avoid pressing a button when an eggplant appeared (no-go trials; 60 trials/block). Children had 1,500 ms to respond on each trial. A red and yellow flashing image appeared following commission errors (button press on no-go trials) and omission errors (lack of button press after 1,500 ms on go trials). No feedback was provided after correct responses. The first block (A) began with 40 go trials to build up a prepotent response.

Children completed the task in three blocks in the following order: nonfrustration (A), frustration (B), and nonfrustration (C). During the nonfrustration blocks (A and C), the interstimulus (ISI) interval ranged from 1,600 to 2,200 ms and children received positive feedback consisting of an image of a happy Mr. Farmer surrounded by eggplants after every 40 trials (a total of 5 feedback images were presented in each block). The research assistant told the participant that s/he saved Mr. Farmer's vegetables and the child won a puzzle piece that could be used to earn a prize from the treasure box at the end of the testing session. During the frustration block (B), the ISI was shortened to promote errors (1,500–1,900 ms). In addition, children received negative feedback consisting of a sad Mr. Farmer image after every 40 trials (a total of 5 feedback images were presented in this block). Children were told that they lost Mr. Farmer's

vegetables and would not win a puzzle piece. The feedback slides were presented at predetermined intervals and were not related to the child's task performance. All children won a prize at the end of the session.

Incorrect trials and trials with response times (RT) <100 ms were excluded from RT analyses. Mean RT for correct go trials and accuracy on go and no-go trials were calculated separately for each block. Discrimination sensitivity (d')—a measure of how well participants distinguished between the go and no-go stimuli—was calculated by comparing hit and false alarm rates during each block (Green & Swets, 1966). Larger d' values indicate better ability to distinguish between stimulus types.

2.3 | Frustration ratings

Children self-reported their mood on a 5-point Likert scale after each block. They were asked to "Point to the face that shows how you feel right now" using a pictorial scale depicting five faces ranging from 1 = smiling face/positive mood to 5 = unhappy face/negative/frustrated mood; see Supporting Information Appendix S3 for an example of the scale.

Research assistants rated perceived child frustration after each block using a 1–3 scale (1 = low, 2 = moderate, 3 = high; see Supporting Information Appendix S3 for an example of the scale). These ratings were based on the child's behavior during the block and in the break immediately following the block. Research assistants were instructed to base their ratings on observed child behavior without regard to the children's self-ratings. A frustration code of 1 indicates no or few occurrences of brief frustration, such as signing, pouting, whining, or saying the task is hard. A code of 2 indicates many occurrences of visible annoyance or irritation (e.g., nonverbal gestures, loud insistent whining or talking, groaning) without intense frustration throughout the block. A code of 3 indicates frequent frustration that predominates throughout the block or instances of extreme dysregulated frustration (e.g., tantrums, yelling, throwing the button box, banging on the table). Inter-rater agreement was acceptable (mean percent agreement was 82%). Research assistants were unaware of the individual child's Temper Loss scores or of the specific hypothesis being tested.

2.4 | Electroencephalographic data acquisition and analysis

EEG data were acquired using a SynAmp RT amplifier (Neuroscan) and a 32-channel Ag/AgCl Quick cap (Neuroscan). Electrooculographic signals were collected using Ag/AgCl electrodes placed above and below the left eye and bilaterally on the outer canthi. During recording, data were referenced to the right mastoid, filtered using a 100 Hz low-pass filter, and digitized at 1,000 Hz. Impedances were kept below 10 kΩ. Offline, EEG data were re-referenced to averaged mastoids and filtered using an FIR zero-phase shift low-pass 40 Hz filter. Data with amplitudes ±100 μV were removed using an automatic artifact rejection procedure, and eye blinks were removed using a regression procedure (Semlitsch, Anderer, Schuster, & Presslich, 1986). Artifact-free data were segmented into 1,200 ms epochs (including a 200 prestimulus baseline), baseline corrected, and averaged separately for go and no-go stimuli in each block. At least eight trials of each trial type per block were required to include in further analyses. Trials with incorrect behavioral responses were excluded from the analysis.

Consistent with prior studies (Ciesielski, Harris, & Cofer, 2004; Johnstone, Pleffer, Barry, Clarke, & Smith, 2005; Jonkman, 2006), the N2 and P3 components occurred later than typically observed in older children and adults. Following inspection of the grand average waveforms and guidance from previous research using related tasks and populations (Grabell et al., 2017; Lewis et al., 2006; Stieben et al., 2007), the N2 component was quantified as the mean amplitude between 300 and 500 ms averaged across frontocentral sites (F3, Fz, F4, FC3, FCz, FC4). The P3 component displayed a centroparietal distribution and was calculated as the mean amplitude between 500 and 800 ms averaged across centroparietal sites (CP3, CPz, CP4, P3, Pz, P4). Each component was calculated separately for each participant, trial type, and block.

2.5 | Statistical analyses

Frustration ratings, behavioral performance (RT, accuracy, d'), and ERP amplitudes (N2 and P3) across *block* (A, B, C) and, when applicable, *trial type* (go/no-go) were examined using repeated-measures analyses of covariance (ANCOVA) in SPSS. Age and gender were included as covariates in all analyses. The Greenhouse–Geisser correction was used when analyses violated sphericity assumptions. Post hoc analyses of main effects with more than two levels were conducted in SPSS using the pairwise comparisons option for repeated-measures ANCOVAs. A Bonferroni correction was applied to all pairwise comparisons (p values have been adjusted).

To test study hypotheses, the effects of irritability were examined using doubly repeated linear models in SAS which allow two dependent variables (e.g., go and no-go accuracy) to be analyzed in the same multilevel model. PROC MIXED was used for continuous outcomes (i.e., accuracy, response time, d', and ERP amplitudes). Block and trial type were used as predictors, and age and gender were included as covariates in both models. A direct (Kronecker) product of the unstructured covariance matrices was used for the repeated effects (trial type and block) for most analyses. Because the models did not converge for accuracy, unstructured covariance for trial type and autoregressive structure for the repeated block effect were used. For ordered categorical outcomes (i.e., frustration ratings), the SAS GENMOD procedure for general estimate equations was used with repeated block effect.

These models examined effects of MAP-DB Temper Loss scores in predicting changes in each primary dependent variable (e.g., $N2_{no\text{-}go}$) across blocks. Each model contained three planned contrast tests coded to examine a different pattern of change across frustration and nonfrustration blocks. The "Frustration" contrast tested our primary hypothesis that increases in Temper Loss scores would be

associated with reduced performance and impaired neural activation during frustration relative to the nonfrustration blocks. This was accomplished by assigning the frustration block (B) a weight of −1 and the nonfrustration blocks (A and C) weights of 0.5. Because the N2 amplitude is a negative deflection, more negative values reflect greater N2 amplitudes. The remaining contrasts were conducted to explore other potential relationships between irritability and response inhibition that may further the limited literature on this topic. The "Overall Deficit" contrast tested whether irritability was related to reductions in the dependent variable (e.g., N2 amplitude), irrespective of the frustration condition. This contrast weighted each block equally and was designed to help clarify whether irritability was associated with specific deficits during frustration, that is, a null overall deficit contrast combined with a significant frustration contrast would support the specificity of the frustration effect. The "Decline During the Task" contrast examined whether irritability was associated with changes in behavioral and neural performance over the course of the experiment. This contrast helped to identify whether irritability was associated with a decline in performance over the course of the task, perhaps reflecting greater fatigue and/or disengagement among children with higher levels of irritability. This contrast directly compared the first block (A) versus the final block (C; weights = −1 and 1, respectively).

One participant's P3 amplitude was > ±3.29 standard deviations from the group mean and was excluded from the P3 analyses. No other outliers existed for the N2 amplitude, temper loss, or any demographic, clinical, or behavioral measure.

Results focus on findings related to block and trial type, because we did not have any a priori hypotheses about age and gender effects (for a comprehensive summary of associations between age and gender and the primary dependent variables, please see Supporting Information Appendix S4).

3 | RESULTS

3.1 | Frustration ratings

No significant effect of block emerged for either child or research assistant frustration ratings across all 3 blocks (*F*s < 2.5, *p*s > 0.10). However, a direct comparison of blocks A and B indicated that the frustration manipulation elicited the intended negative emotions ($p < 0.001$). Temper Loss scores did not significantly predict child or research assistant frustration ratings. For detailed results of these analyses, please see Supporting Information Appendix S5.

3.2 | Response inhibition in preschoolers

The *block* × *trial type* ANCOVA predicting accuracy revealed a *block* × *trial type* interaction ($F_{2,86} = 3.99$, $p = 0.03$, $\eta_p^2 = 0.09$; Figure 2). Accuracy on go trials did not differ across the three task blocks ($p = 0.52$). In contrast, a significant effect of *block* emerged for no-go trial accuracy ($F_{2,86}$, $p = 0.01$, $\eta_p^2 = 0.10$). This effect suggested that no-go trial accuracy was lowest during block A versus the other two blocks, although these differences did not survive Bonferroni corrections for multiple comparisons. Finally, as shown in Figure 2, although the means were in the expected direction, accuracy did not differ significantly between go and no-go trials in any block within this small sample (*p*s > 0.19). RT and d' measures did not differ across blocks, *F*s < 2.20, *p*s > 0.13 (see Supporting Information Appendix S6 for a graphical depiction of these findings).

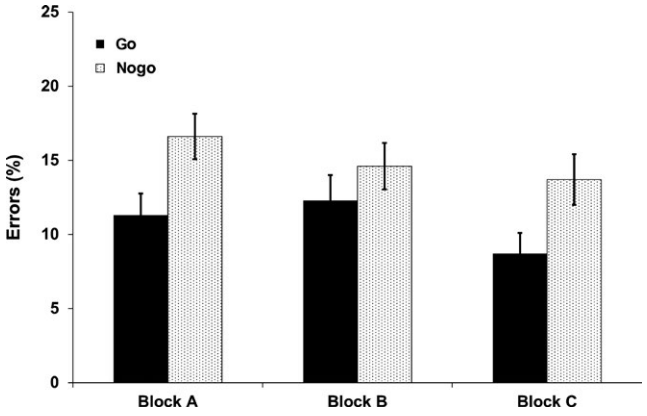

FIGURE 2 WAM Task accuracy. The number of errors committed during go and no-go trials during the task. Error bars reflect standard errors

An ad hoc analysis of the behavioral effects in a larger sample of children from this study ($N = 208$) suggests that some of null effects in the ERP sample may be due to limited statistical power and/or strict performance criteria ($d' \geq 0.6$) for who was included in the analysis. For detailed results of these analyses, please see Supporting Information Appendix S7.

Grand average waveforms and topographies are presented in Figures 3 and 4. No significant effects were observed for either N2 or P3 amplitudes, suggesting no impact of block or trial type on ERP amplitudes (*F*s < 1.0, *p*s > 0.30; see Supporting Information Appendix S8 for a graphical depiction of the mean N2 and P3 amplitudes in each block and trial type).

3.3 | Irritability and response inhibition

Temper Loss scores predicted no-go accuracy and go RT from the Frustration contrasts, consistent with hypotheses (Tables 1 and 2). This indicated that there were differences between no-go accuracy (and go RT) during frustration relative to nonfrustration as a function of Temper Loss. Greater irritability was associated with reduced no-go accuracy, but faster go RT during the frustration relative to the nonfrustration condition. Temper Loss scores did not, however, predict d' scores from the Frustration contrast. As expected, no significant findings between Temper Loss and RT or accuracy were observed for the Overall Deficit and Decline During the Task contrasts.

Temper Loss scores significantly predicted the Frustration contrast for $N2_{no\text{-}go}$ amplitudes (see Table 3). Every one-point increase in Temper Loss score was associated with a 0.09 μV increase (more negative value) in $N2_{no\text{-}go}$ amplitude during frustration versus

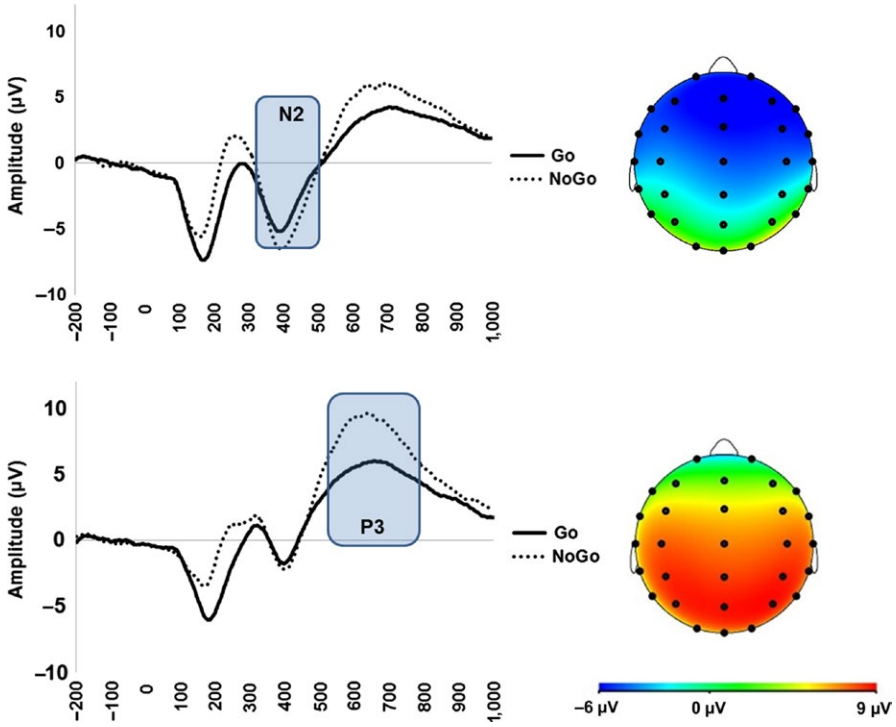

FIGURE 3 Grand average ERPs. The grand average ERP and scalp topography to go and no-go trials over the average frontocentral (F3, Fz, F4, FC3, FCz, FC4; top) and average centroparietal scalp sites (CP3, CPz, CP4, P3, Pz, P4; bottom)

nonfrustration, thus as irritability increased, there was a corresponding increase in $N2_{no\text{-}go}$ amplitude. Temper Loss scores were not significantly related to P3 amplitudes (Table 4). No significant associations between Temper Loss and N2 or P3 amplitudes were observed for the Overall Deficit and Decline During the Task contrasts (Tables 3 and 4).

4 | DISCUSSION

This study revealed novel evidence linking variations in irritability in young children with atypical response inhibition processes during frustration. Higher irritability was associated with larger $N2_{no\text{-}go}$ amplitudes, reduced no-go trial accuracy, and faster go trial response times during frustration. Irritability was unrelated to P3 amplitudes. The fact that irritability was related to behavioral and neural performance during frustration but not during nonfrustration conditions adds to an emerging body of evidence underscoring the utility of frustration tasks for elucidating neurocognitive deficits associated with irritability (Grabell et al., 2017). These frustration manipulation methods may be especially helpful in young children given the challenge when normative manifestations of irritability such as temper tantrums are so common.

4.1 | Irritability and neural markers of response inhibition

The present findings add to a growing literature relating response inhibition to pediatric irritability (Adleman et al., 2011; Dickstein et al., 2007; Gagne & Goldsmith, 2011; Roy et al., 2013) and extend these

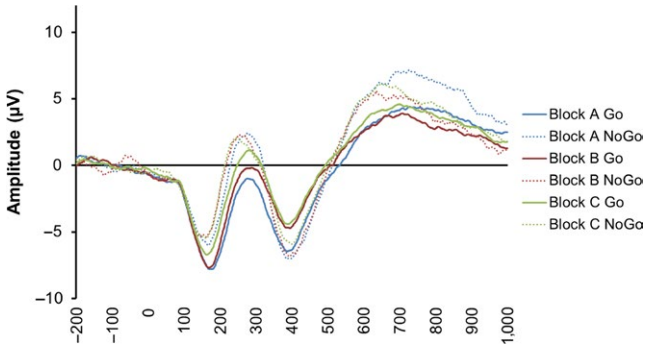

FIGURE 4 Grand average ERPs for each block and trial type

findings to preschool populations assessed using narrow-band, developmentally sensitive, dimensional assessments of irritability. Based on studies of children with ADHD and other externalizing symptoms (Dimoska et al., 2003; Overtoom et al., 1998; Pliszka et al., 2000; Stieben et al., 2007), we hypothesized that higher irritability would be associated with smaller $N2_{no\text{-}go}$ amplitudes during frustration. However, the opposite pattern was observed in this sample. Because increased $N2_{no\text{-}go}$ amplitudes during negative emotional conditions reflect the need to mobilize resources in order to successfully inhibit responses under challenging task conditions (Lewis et al., 2006), the observed $N2_{no\text{-}go}$ findings may represent a hyperresponsive conflict monitoring system during frustration. Given that irritability was associated with poorer response inhibition during frustration (as indicated by reduced no-go performance), one possibility is that this increased activation reflects neural inefficiency or perhaps a developmental lag among preschoolers with higher levels of irritability that make them more prone to engage in impulsive

TABLE 1 The relationship between one-unit increases in MAP-DB Temper Loss scores and accuracy after accounting for gender and age

	Estimate	Standard error	*t*
Go overall deficit contrast	−0.05	0.09	−0.54
Go decline during task contrast	−0.05	0.10	−0.50
Go frustration contrast	−0.07	0.05	−1.15
No-go overall deficit contrast	−0.08	0.10	−0.76
No-go decline during task contrast	0.15	0.10	1.40
No-go frustration contrast	0.11	0.06	1.96*

Note. Participant gender and age were covaried. The Frustration contrasts were set so that a one-unit increase in MAPDB Temper Loss score was associated with a more positive value during the nonfrustration blocks (A and C) and a more negative value during the frustration block (B).
*$p \leq 0.05$.

TABLE 2 The relationship between one-unit increases in MAP-DB Temper Loss scores and response time after accounting for gender and age

	Estimate	Standard error	*t*
Go overall deficit contrast	0.10	0.80	0.12
Go decline during task contrast	−0.53	0.63	−0.85
Go frustration contrast	0.90	0.39	2.31*

Note. Participant gender and age were included as covariates. The Frustration contrasts were set so that a one-unit increase in MAPDB Temper Loss score was associated with a more positive value during the nonfrustration blocks (A and C) and a more negative value during the frustration block (B).
*$p \leq 0.05$.

TABLE 3 The relationship between one-unit increases in MAP-DB Temper Loss scores and N2 amplitudes after accounting for gender and age

	Estimate	Standard error	*t*
Go overall deficit contrast	0.04	0.03	1.53
Go decline during task contrast	0.03	0.04	0.74
Go frustration contrast	0.01	0.03	0.42
No-go overall deficit contrast	0.02	0.04	0.62
No-go decline during task contrast	0.06	0.05	1.04
No-go frustration contrast	0.09	0.04	2.09*

Note. Participant gender and age were included as covariates. The Frustration contrasts were set so that a one-unit increase in MAPDB Temper Loss score was associated with a more positive value during the nonfrustration blocks (A and C) and a more negative value during the frustration block (B). Because the N200 amplitude is a negative deflection, a more negative value during frustration reflects an increase in N200 amplitude relative to the nonfrustration blocks.
*$p \leq 0.05$.

TABLE 4 The relationship between one-unit increases in MAP-DB Temper Loss scores and P3 amplitudes after accounting for gender and age

	Estimate	Standard error	*t*
Go overall deficit contrast	0.04	0.03	1.08
Go decline during task contrast	−0.03	0.05	−0.65
Go frustration contrast	−0.04	0.04	−1.02
No-go overall deficit contrast	−0.03	0.04	−0.68
No-go decline during task contrast	−0.02	0.07	−0.23
No-go frustration contrast	−0.08	0.05	−1.54

Note. Participant age and gender were included as covariates. The Frustration contrasts were set so that a one-unit increase in MAPDB Temper Loss score was associated with a more positive value during the nonfrustration blocks (A and C) and a more negative value during the frustration block (B).
None of the contrasts were significant at $p < 0.05$.

behaviors (e.g., yelling, hitting) when experiencing negative affect (Lewis et al., 2006). The enhanced $N2_{no\text{-}go}$ amplitudes might also reflect the adaptive mobilization of resources in order to cope with the negative affect elicited by the frustration manipulation and/or maximize performance despite the experience of negative affect. This pattern would align with Grabell et al.'s (2017) observation of a positive association between irritability and lateral prefrontal activation during a cognitive control task in children from low-to-moderate levels of irritability. Given that only 24% of children in our sample had scores reflecting clinically significant irritability, this seems a plausible interpretation. Critical next steps include clarifying the nature of the $N2_{no\text{-}go}$ results by repeating the study with a larger sample of children above the clinical threshold for irritability. Finally, irritability is a transdiagnostic symptom present in internalizing as well

as externalizing disorders (Wakschlag et al., 2018). Numerous studies indicate that children with anxiety and internalizing symptoms demonstrate enhanced ERP amplitudes (Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006; Stieben et al., 2007). Therefore, extending this work to other populations and examining whether irritability predicts similar or different ERP patterns depending on co-occurring internalizing symptoms will be important future work.

4.2 | The role of frustration in identifying irritability-related deficits

Consistent with our hypotheses, the effects of irritability were specific to comparisons of frustration and nonfrustration, rather than overall deficits or a decline during the course of the task. This is consistent with recent reviews highlighting irritability as an atypical response to frustrative nonreward (Brotman et al., 2017; Wakschlag et al., 2018) and our hypothesis that increased irritability in young children may be associated with atypical neurocognitive functioning *during frustration*. This also parallels findings that have shown that standardized observational paradigms designed to induce frustration in young children are important for clinical differentiation in early childhood (Wakschlag et al., 2008).

However, it is important to note that frustration-related deficits have not been thoroughly studied in populations experiencing clinical conditions that often involve irritability along with other symptoms (i.e., ADHD). Therefore, the extent to which these patterns are specific to irritability is unknown. While the majority of research on response inhibition in children with externalizing symptoms has not employed mood manipulations, one study found that children with both internalizing and externalizing symptoms have increased $N2_{no\text{-}go}$ amplitudes during frustration (Stieben et al., 2007) similar to what was observed in the present study. Such findings may point to shared mechanisms among children with irritability and associated symptoms.

In addition, future research might investigate whether relationships among irritability and behavioral and neural markers of inhibition are specific to frustration or whether they exist during other forms of pronounced negative affect, such as sadness or fear. Such findings would suggest that irritability in young children is associated with broader emotion regulation impairments rather than atypical responses to frustrative nonreward, specifically. This, in turn, may imply that irritability is associated with deficits in lateral prefrontal regulatory regions in addition to dysfunction in limbic and reward circuitry.

4.3 | P3

Irritability was unrelated to P3 amplitudes (Huster et al., 2013). Given the small sample size and the decision to include only successful inhibition trials in the ERP analyses, we do not advance any strong conclusions about the nonsignificant relationship between irritability and P3 amplitude but rather recommend continued investigation.

4.4 | Limitations

Neuroimaging studies in preschoolers are challenging. Tasks must be brief and engaging (Briggs-Gowan et al., 2015) yet have sufficient trials to reliably estimate brain activity after accounting for motion artifact common in children (Hoyniak, 2017). Despite our best efforts to engage and retain children, only a subset of eligible children completed the entire task with usable behavioral and ERP data (see Supporting Information Appendix S1 in Figure S1). Post hoc analyses indicated that preschoolers with and without useable data did not differ in levels of irritability. However, the children in the present study were somewhat older, performed better on the initial block of the task, and reported experiencing less frustration than those who were excluded (see Supporting Information Appendix S1). Therefore, these findings may underestimate the association between irritability and motor inhibition during frustration, especially in the youngest preschoolers, those with poorer response inhibition ability, and those who experience greater negative affect in response to frustration manipulations. In addition, our sample is more sociodemographically diverse than most of the published work on irritability, but is too small to examine sociodemographic effects. Thus, further research will be needed to determine whether patterns observed generalize to broader samples of young children. Finally, although versions of this task have been used in prior work (Fishbein et al., 2016; Lewis et al., 2006; Shapiro, Tassone, Choudhary, & Simon, 2014; Shapiro, Wong, & Simon, 2013; Stieben et al., 2007), this specific version of the WAM has not been used previously. Therefore, additional work must be done to evaluate the reliability, validity, and utility of this task to probe response inhibition in children from a range of sociodemographic backgrounds.

Although the means were in the predicted direction, the lack of a significant difference between N2 amplitude to no-go versus go stimuli is a potential limitation of the study. Specifically, it raises the question of whether the children differentiated between go and no-go trials. The strict performance criterion ($d' \geq 0.6$) indicates that the children were discriminating between go and no-go stimuli and were able to inhibit their responses on the appropriate trials. Therefore, an alternative explanation is that our relatively small sample size and the young age of our participants contributed to our failure to detect N2 amplitude differences between trial types at traditional significance levels. Although a recent meta-analysis (Hoyniak, 2017) indicated that differentiation between $N2_{no\text{-}go}$ and $N2_{go}$ amplitudes is observed in studies of children between the ages of 2 and 12 years, this same meta-analysis indicated that studies of very young children may not detect this effect due to difficulties obtaining high-quality neural data from very young children leading to increased variability and/or the ongoing maturation of the neural regions supporting response inhibition abilities during early childhood. Therefore, future research establishing normative neurocognitive functioning at different age ranges will be essential for establishing when disruptions in neurocognitive functioning first manifest in development.

5 | CONCLUSIONS

The present study joins emerging research linking dimensional assessments of irritability with neurocognitive functioning (Dougherty et al., 2018; Grabell et al., 2017, 2016; Kessel, Dougherty, et al., 2016; Kessel, Meyer, et al., 2016; Li et al., 2016; Perlman et al., 2015, 2013). We add to extant literature by providing evidence that higher levels of early irritability are associated with response inhibition impairments and enhanced activation of a conflict monitoring circuit during marked negative affect. Critical next steps will include replicating these findings in a larger sample with greater representation of clinically significant irritability, as well as longitudinal studies that test the incremental utility of behavioral and neurocognitive/neurophysiological measures for earlier identification of those young children most at risk for mental illness (Kessel, Meyer, et al., 2016). The significance of achieving a firmer grasp on irritability and its neural underpinnings in young children is underscored by rapidly accumulating evidence that irritability is an early life marker of mental health risk across the lifespan. The present findings bolster recent recommendations for joint consideration of brain: behavior atypicalities when pinpointing those young irritable children at highest clinical risk (Biedzio and Wakschlag, in press; Wakschlag et al., 2018).

ACKNOWLEDGMENTS

This study was supported by MAPS—1R01MH082830 and MHU010828320 (Wakschlag, Briggs-Gowan, Estabrook, and Norton) and by the VEX study—MHU01090301 (Briggs-Gowan and Wakschlag). Portions of this project were presented at the 72nd annual meeting of the Society of Biological Psychiatry in May 2017 in San Diego, CA. We gratefully acknowledge the contributions of Joel Voss, Ph.D., to the neuroscientific elements of the MAPS Study.

ORCID

Christen M. Deveney http://orcid.org/0000-0003-0244-8047

REFERENCES

Adleman, N. E., Kayser, R., Dickstein, D., Blair, R. J., Pine, D., & Leibenluft, E. (2011). Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *50*(11), 1173–1185, e1172. https://doi.org/10.1016/j.jaac.2011.07.011

Biedzio, D., & Wakschlag, L. S. (in press). Developmental emergency of disruptive behaviors beginning in infancy: Delineating normal: Abnormal boundaries to enhance early identification. In C. Zeenah (Ed.), *Handbook of infant mental health* (4th ed., pp. 407–425). New York, NY: Guilford.

Briggs-Gowan, M. J., Pollak, S. D., Grasso, D., Voss, J., Mian, N. D., Zobel, E., … Pine, D. S. (2015). Attention bias and anxiety in young children exposed to family violence. *Journal of Child Psychology and Psychiatry*, *56*(11), 1194–1201. https://doi.org/10.1111/jcpp.12397

Brotman, M. A., Kircanski, K., Stringaris, A., Pine, D. S., & Leibenluft, E. (2017). Irritability in youths: A translational model. *American Journal of Psychiatry*, *174*(6), 520–532. https://doi.org/10.1176/appi.ajp.2016.16070839

Brotman, M. A., Rich, B. A., Guyer, A. E., Lunsford, J. R., Horsey, S. E., Reising, M. M., … Leibenluft, E. (2010). Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. *American Journal of Psychiatry*, *167*(1), 61–69. https://doi.org/10.1176/appi.ajp.2009.09010043

Buss, K. A., Dennis, T. A., Brooker, R. J., & Sippel, L. M. (2011). An ERP study of conflict monitoring in 4–8-year old children: Associations with temperament. *Developmental Cognitive Neuroscience*, *1*(2), 131–140. https://doi.org/10.1016/j.dcn.2010.12.003

Camacho, M. C., Wakschlag, L. S., & Perlman, S. B.. (in press). Early childhood irritability: Using a neurodevelopmental framework to identify clinical concern. In A. K. Roy, M. A. Brotman, & E. Leibenluft (Eds.), *Irritability in pediatric psychopathology*. Oxford: Oxford University Press.

Ciesielski, K. T., Harris, R. J., & Cofer, L. F. (2004). Posterior brain ERP patterns related to the go/no-go task in children. *Psychophysiology*, *41*(6), 882–892. https://doi.org/10.1111/j.1469-8986.2004.00250.x

Copeland, W. E., Brotman, M. A., & Costello, E. J. (2015). Normative irritability in youth: Developmental findings from the great smoky mountains study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(8), 635–642. https://doi.org/10.1016/j.jaac.2015.05.008

Copeland, W. E., Shanahan, L., Egger, H., Angold, A., & Costello, E. J. (2014). Adult diagnostic and functional outcomes of DSM-5 disruptive mood dysregulation disorder. *American Journal of Psychiatry*, *171*(6), 668–674. https://doi.org/10.1176/appi.ajp.2014.13091213

Deveney, C. M., Connolly, M. E., Haring, C. T., Bones, B. L., Reynolds, R. C., Kim, P., … Leibenluft, E. (2013). Neural mechanisms of frustration in chronically irritable children. *American Journal of Psychiatry*, *170*(10), 1186–1194. https://doi.org/10.1176/appi.ajp.2013.12070917

Deveney, C. M., Connolly, M. E., Jenkins, S. E., Kim, P., Fromm, S. J., Brotman, M. A., & Leibenluft, E. (2012). Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. *Biological Psychology*, *89*(1), 148–155. https://doi.org/10.1016/j.biopsycho.2011.10.003

Dickstein, D. P., Nelson, E. E., McClure, E. B., Grimley, M. E., Knopf, L., Brotman, M. A., … Leibenluft, E. (2007). Cognitive flexibility in phenotypes of pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*(3), 341–355. https://doi.org/10.1097/chi.0b013e31802d0b3d

Dimoska, A., Johnstone, S. J., Barry, R. J., & Clarke, A. R. (2003). Inhibitory motor control in children with attention-deficit/hyperactivity disorder: Event-related potentials in the stop-signal paradigm. *Biological Psychiatry*, *54*(12), 1345–1354. https://doi.org/10.1016/S0006-3223(03)00703-0

Dougherty, L. R., Schwartz, K. T. G., Kryza-Lacombe, M., Weisberg, J., Spechler, P. A., & Wiggins, J. L. (2018). Preschool and School-Age Irritability Predict Reward-Related Brain Function. *Journal of the American Academy of Child & Adolescent Psychiatry*, *57*(6), 407–417. e2. https://doi.org/10.1016/j.jaac.2018.03.012

Dougherty, L. R., Smith, V. C., Bufferd, S. J., Kessel, E., Carlson, G. A., & Klein, D. N. (2015). Preschool irritability predicts child psychopathology, functional impairment, and service use at age nine. *Journal of Child Psychology and Psychiatry*, *56*(9), 999–1007. https://doi.org/10.1111/jcpp.12403

Dougherty, L. R., Smith, V. C., Bufferd, S. J., Stringaris, A., Leibenluft, E., Carlson, G. A., & Klein, D. N. (2013). Preschool irritability: Longitudinal associations with psychiatric disorders at age 6 and parental psychopathology. *Journal of the American Academy of Child and*

Adolescent Psychiatry, *52*(12), 1304–1313. https://doi.org/10.1016/j.jaac.2013.09.007

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (2002). Inhibition-related ERP components: Variation with modality, age, and time-on-task. *Journal of Psychophysiology*, *16*(3), 167–175. https://doi.org/10.1027//0269-8803.16.3.167

Fishbein, D. H., Domitrovich, C., Williams, J., Gitukui, S., Guthrie, C., Shapiro, D., & Greenberg, M. (2016). Short-term intervention effects of the PATHS curriculum in young low-income children: capitalizing on plasticity. *Journal of Primary Prevention*, *37*(6), 493–511. https://doi.org/10.1007/s10935-016-0452-5

Gagne, J. R., & Goldsmith, H. H. (2011). A longitudinal analysis of anger and inhibitory control in twins from 12 to 36 months of age. *Developmental Science*, *14*(1), 112–124. https://doi.org/10.1111/j.1467-7687.2010.00969.x

Grabell, A. S., Li, Y., Barker, J. W., Wakschlag, L. S., Huppert, T. J., & Perlman, S. B. (2017). Evidence of non-linear associations between frustration-related prefrontal cortex activation and the normal: Abnormal spectrum of irritability in young children. *Journal of Abnormal Child Psychology*, *46*(1), 137–147. https://doi.org/10.1007/s10802-017-0286-5

Grabell, A. S., Olson, S. L., Tardif, T., Thompson, M. C., & Gehring, W. J. (2016). Comparing self-regulation-associated event related potentials in preschool children with and without high levels of disruptive behavior. *Journal of Abnormal Child Psychology*, *45*(6), 1119–1132. https://doi.org/10.1007/s10802-016-0228-7

Green, D. M., & Swets, J. A. (1966). *Signal detection theory and psychophysics*. New York, NY: Wiley.

Hoyniak, C. (2017). Changes in the NoGo N2 event-related potential component across childhood: A systematic review and meta-analysis. *Developmental Neuropsychology*, *42*(1), 1–24. https://doi.org/10.1080/87565641.2016.1247162

Huster, R. J., Enriquez-Geppert, S., Lavallee, C. F., Falkenstein, M., & Herrmann, C. S. (2013). Electroencephalography of response inhibition tasks: Functional networks and cognitive contributions. *International Journal of Psychophysiology*, *87*(3), 217–233. https://doi.org/10.1016/j.ijpsycho.2012.08.001

Johnstone, S. J., Pleffer, C. B., Barry, R. J., Clarke, A. R., & Smith, J. L. (2005). Development of inhibitory processing during the Go/NoGo task – A behavioral and event-related potential study of children and adults. *Journal of Psychophysiology*, *19*(1), 11–23. https://doi.org/10.1027/0269-8803.19.1.11

Jonkman, L. M. (2006). The development of preparation, conflict monitoring and inhibition from early childhood to young adulthood: A Go/Nogo ERP study. *Brain Research*, *1097*(1), 181–193. https://doi.org/10.1016/j.brainres.2006.04.064

Kessel, E. M., Dougherty, L. R., Kujawa, A., Hajcak, G., Carlson, G. A., & Klein, D. N. (2016). Longitudinal associations between preschool disruptive mood dysregulation disorder symptoms and neural reactivity to monetary reward during preadolescence. *Journal of Child and Adolescent Psychopharmacology*, *26*(2), 131–137. https://doi.org/10.1089/cap.2015.0071

Kessel, E. M., Meyer, A., Hajcak, G., Dougherty, L. R., Torpey-Newman, D. C., Carlson, G. A., & Klein, D. N.. (2016). Transdiagnostic factors and pathways to multifinality: The error-related negativity predicts whether preschool irritability is associated with internalizing versus externalizing symptoms at age 9. *Development and Psychopathology*, *28*(4pt1), 913–926. https://doi.org/10.1017/S0954579416000626

Ladouceur, C. D., Dahl, R. E., Birmaher, B., Axelson, D. A., & Ryan, N. D. (2006). Increased error-related negativity (ERN) in childhood anxiety disorders: ERP and source localization. *Journal of Child Psychology and Psychiatry*, *47*(10), 1073–1082. https://doi.org/10.1111/j.1469-7610.2006.01654.x

Lamm, C., & Lewis, M. D. (2010). Developmental change in the neurophysiological correlates of self-regulation in high- and low-emotion conditions. *Developmental Psychology*, *35*(2), 156–176. https://doi.org/10.1080/87565640903526512

Leibenluft, E. (2011). Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *American Journal of Psychiatry*, *168*, 129–142. https://doi.org/10.1176/appi.ajp.2010.10050766

Leibenluft, E. (2017). Pediatric irritability: A systems neuroscience approach. *Trends in Cognitive Sciences*, *21*(4), 277–289. https://doi.org/10.1016/j.tics.2017.02.002

Lewis, M. D., Lamm, C., Segalowitz, S. J., Stieben, J., & Zelazo, P. D. (2006). Neurophysiological correlates of emotion regulation in children and adolescents. *Journal of Cognitive Neuroscience*, *18*(3), 430–443. https://doi.org/10.1162/089892906775990633

Lewis, M. D., & Stieben, J. (2004). Emotion regulation in the brain: Conceptual issues and directions for developmental research. *Child Development*, *75*(2), 371–376. https://doi.org/10.1111/j.1467-8624.2004.00680.x

Li, Y., Grabell, A. S., Wakschlag, L. S., Huppert, T. J., & Perlman, S. B. (2016). The neural substrates of cognitive flexibility are related to individual differences in preschool irritability: A fNIRS investigation. *Developmental Cognitive Neuroscience*, https://doi.org/10.1016/j.dcn.2016.07.002

Nichols, S., Briggs-Gowan, M., Estabrook, R., Henry, D., Burns, J., Kestler, J., & Wakschlag, L. (2015). Punishment insensitivity in early childhood: A developmental, dimensional approach. *Journal of Abnormal Child Psychology*, *43*, 1011–1023.

Overtoom, C. C. E., Verbaten, M. N., Kemner, C., Kenemans, J. L., van Engeland, H., Buitelaar, J. K., … Koelega, H. S. (1998). Associations between event-related potentials and measures of attention and inhibition in the continuous performance task in children with ADHD and normal controls. *Journal of the American Academy of Child and Adolescent Psychiatry*, *37*(9), 977–985. https://doi.org/10.1097/00004583-199809000-00018

Perlman, S. B., Jones, B. M., Wakschlag, L. S., Axelson, D., Birmaher, B., & Phillips, M. L. (2015). Neural substrates of child irritability in typically developing and psychiatric populations. *Developmental Cognitive Neuroscience*, *14*, 71–80. https://doi.org/10.1016/j.dcn.2015.07.003

Perlman, S. B., Luna, B., Hein, T. C., & Huppert, T. J. (2013). fNIRS evidence of prefrontal regulation of frustration in early childhood. *Neuroimage.*, *85*(Pt 1), 326–334. https://doi.org/10.1016/j.neuroimage.2013.04.057

Pliszka, S. R., Liotti, M., & Woldorff, M. G. (2000). Inhibitory control in children with attention-deficit/hyperactivity disorder: Event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biological Psychiatry*, *48*(3), 238–246. https://doi.org/10.1016/S0006-3223(00)00890-8

Rich, B. A., Carver, F. W., Holroyd, T., Rosen, H. R., Mendoza, J. K., Cornwell, B. R. … Leibenluft, E. (2011). Different neural pathways to negative affect in youth with pediatric bipolar disorder and severe mood dysregulation. *Journal of Psychiatric Research*, *45*(10), 1283–1294. https://doi.org/10.1016/j.jpsychires.2011.04.006

Rich, B. A., Schmajuk, M., Perez-Edgar, K. E., Fox, N. A., Pine, D. S., & Leibenluft, E. (2007). Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. *Am J Psychiatry*, *164*(2), 309–317.

Roy, A. K., Klein, R. G., Angelosante, A., Bar-Haim, Y., Leibenluft, E., Hulvershorn, L. … Spindel, C. (2013). Clinical features of young children referred for impairing temper outbursts. *Journal of Child and Adolescent Psychopharmacology*, *23*(9), 588–596. https://doi.org/10.1089/cap.2013.0005

Semlitsch, H. V., Anderer, P., Schuster, P., & Presslich, O. (1986). A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology*, *23*(6), 695–703. https://doi.org/10.1111/j.1469-8986.1986.tb00696.x.

Shapiro, H. M., Tassone, F., Choudhary, N. S., & Simon, T. J. (2014). The development of cognitive control in children with chromosome 22q11.2 deletion syndrome. *Frontiers in Psychology*, *5*, 566. https://doi.org/10.3389/fpsyg.2014.00566

Shapiro, H. M., Wong, L. M., & Simon, T. J. (2013). A cross-sectional analysis of the development of response inhibition in children with chromosome 22q11.2 deletion syndrome. *Frontiers in Psychiatry*, *4*, 81. https://doi.org/10.3389/fpsyt.2013.00081

Stieben, J., Lewis, M. D., Granic, I., Zelazo, P. D., Segalowitz, S., & Pepler, D. (2007). Neurophysiological mechanisms of emotion regulation for subtypes of externalizing children. *Development and Psychopathology*, *19*(2), 455–480. https://doi.org/10.1017/S0954579407070228

Stoddard, J., Sharif-Askary, B., Harkins, E. A., Frank, H. R., Brotman, M. A., Penton-Voak, I. S., … Leibenluft, E. (2016). An open pilot study of training hostile interpretation bias to treat disruptive mood dysregulation disorder. *Journal of Child and Adolescent Psychopharmacology*, *26*(1), 49–57. https://doi.org/10.1089/cap.2015.0100

Stringaris, A., Cohen, P., Pine, D. S., & Leibenluft, E. (2009). Adult outcomes of youth irritability: A 20-year prospective community-based study. *American Journal of Psychiatry*, *166*(9), 1048–1054. https://doi.org/10.1176/appi.ajp.2009.08121849

Wakschlag, L. S., Briggs-Gowan, M. J., Choi, S. W., Nichols, S. R., Kestler, J., Burns, J. L., … Henry, D. (2014). Advancing a multidimensional, developmental spectrum approach to preschool disruptive behavior. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53(1), 82–96*, e83. https://doi.org/10.1016/j.jaac.2013.10.011

Wakschlag, L. S., Briggs-Gowan, M. J., Hill, C., Danis, B., Leventhal, B. L., Keenan, K. … Carter, A. S. (2008). Observational assessment of preschool disruptive behavior, Part II: Validity of the disruptive behavior diagnostic observation schedule (DB-DOS). *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*(6), 632–641. https://doi.org/10.1097/CHI.0b013e31816c5c10

Wakschlag, L. S., Briggs-Gowan, M. J., Tolan, P., Hill, C., Danis, B., & Carter, A. S. (2010). The Multidimensional Assessment of Preschool Disruptive Behavior (MAP-DB) Questionnaire. (Unpublished measure)

Wakschlag, L. S., Choi, S. W., Carter, A. S., Hullsiek, H., Burns, J., McCarthy, K. … Briggs-Gowan, M. J. (2012). Defining the developmental parameters of temper loss in early childhood: Implications for developmental psychopathology. *Journal of Child Psychology and Psychiatry*, *53*(11), 1099–1108. https://doi.org/10.1111/j.1469-7610.2012.02595.x

Wakschlag, L. S., Estabrook, R., Petitclerc, A., Henry, D., Burns, J. L., Perlman, S. B. … Briggs-Gowan, M. L. (2015). Clinical implications of a dimensional approach: The normal: Abnormal spectrum of early irritability. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(8), 626–634. https://doi.org/10.1016/j.jaac.2015.05.016

Wakschlag, L. S., Perlman, S. B., Blair, R. J., Leibenluft, E., Briggs-Gowan, M. J., & Pine, D. S. (2018). The neurodevelopmental basis of early childhood disruptive behavior: Irritable and callous phenotypes as exemplars. *American Journal of Psychiatry*, *175*(2), 114–130. https://doi.org/10.1176/appi.ajp.2017.17010045

Wiggins, J. L., Briggs-Gowan, M. J., Estabrook, R., Brotman, M. A., Pine, D. S., Leibenluft, E., & Wakschlag, L. S. (2018). Identifying clinically significant irritability in early childhood. *Journal of the American Academy of Child & Adolescent Psychiatry*, *57*(3), 191–199.e2. https://doi.org/10.1016/j.jaac.2017.12.008

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Deveney CM, Briggs-Gowan MJ, Pagliaccio D, et al. Temporally sensitive neural measures of inhibition in preschool children across a spectrum of irritability. *Developmental Psychobiology*. 2019;61:216–227. https://doi.org/10.1002/dev.21792