Inhibition Predicts the Course of Depression and Anxiety Symptoms Among Adolescents

The Moderating Role of Familial Risk

Elizabeth S. Stevens, PhD, Carter J. Funkhouser, MA,* Randy P. Auerbach, PhD,†‡ Ardesheer Talati, PhD,†‡ Marc G. Gameroff, PhD,†‡ Jonathan E. Posner, MD,†‡ Myrna M. Weissman, PhD,†‡ and Stewart A. Shankman, PhD§*

Abstract: Numerous theoretical models suggest that inhibition difficulties—the inability to moderate automatic responses—contribute to the onset and/or maintenance of internalizing symptoms. Inhibition deficits and internalizing disorders run in families and share overlapping genetic risk factors, suggesting that inhibition deficits may be particularly prognostic of internalizing symptoms in those with high familial risk. This study tested this hypothesis in a longitudinal sample during the transition from adolescence to early adulthood. As hypothesized, prospective associations between inhibition and anxiety and depressive symptoms 8 years later were moderated by familial risk for depression. Specifically, poorer inhibition prospectively predicted greater anxiety and depressive symptoms in those at high (but not low) familial risk for major depressive disorder. These findings provide preliminary support for impaired inhibition as an indicator of risk for later internalizing symptoms in those at high familial risk.

Key Words: Depression, anxiety, inhibitory control, vulnerability, adolescence

(*J Nerv Ment Dis* 2022;00: 00–00)

Anxiety and depression symptoms are highly prevalent, frequently co-occur (Kessler et al., 2005; Shankman and Klein, 2003), and are associated with high socioeconomic and disease burden (Greenberg et al., 2003; Kessler et al., 2009). These symptoms often begin during adolescence or young adulthood (Kessler et al., 2007), suggesting that identifying early vulnerability factors may help mitigate potential personal and societal costs. This goal is also consistent with the National Institute of Mental Health's Research Domain Criteria initiative, which seeks to identify shared and/or unique vulnerabilities for psychopathologies with the goal of informing intervention and prevention efforts (Zalta and Shankman, 2016).

Individual differences in inhibition abilities may be one such vulnerability marker for depression and anxiety symptoms (Snyder et al., 2019). Inhibition can be defined as the ability to modulate prepotent/automatic responses to a) respond in a goal-congruent manner and/or b) limit the influence of distracting stimuli on task performance (Friedman and Miyake, 2004; Miyake et al., 2000; Nigg, 2000). Inhibition is one executive function (Friedman and Miyake, 2004; Miyake et al., 2000), a set of higher-order processes that coordinate or integrate lower-level cognition and behavior and help individuals allocate optimal levels of attention to salient stimuli and facilitate effective responding across contexts.

*Department of Psychology, University of Illinois at Chicago, Chicago, Illinois; †Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University; ‡Division of Translational Epidemiology, New York State Psychiatric Institute, New York, New York; and §Department of Psychiatry and Behavioral Sciences, Northwestern University, Chicago, Illinois.

Send reprint requests to Stewart A. Shankman, PhD, Department of Psychiatry and Behavioral Sciences, Northwestern University, 680 N Lake Shore Drive, Chicago, IL 60611. E-mail: stew.shankman@northwestern.edu.

ISSN: 0022-3018/22/0000–0000
DOI: 10.1097/NMD.0000000000001584

Inhibitory control is closely linked to emotion regulation, which is implicated in the development of symptoms of anxiety and depression (Cisler et al., 2010; Joormann and Gotlib, 2010). Numerous studies and theoretical models (for review, see De Raedt and Koster, 2010; Eysenck et al., 2007) posit a central role of compromised inhibitory processes and the related constructs of attentional control and emotion (dys)regulation in anxiety and depressive symptoms. For example, individuals with elevated anxiety symptoms exhibit poorer attentional control and/or inhibition as measured via self-report (*e.g.*, Cox and Olatunji, 2017) or behavioral tasks (*e.g.*, Stroop task, go-no-go tasks; Gorlin and Teachman, 2015; Zainal and Newman, 2018). Anxiety symptoms are also associated with attentional biases that may reflect underlying attentional control deficits (Bar-Haim et al., 2007). Similar results have been found for major depressive disorder (MDD; Gotlib and Joormann, 2010), particularly in youth, with one meta-analysis finding that inhibition (measured via the Stroop Interference Test) was the facet of executive functioning most strongly associated with depression ($d = 0.77$; Wagner et al., 2015). Longitudinal studies further support inhibitory functioning as a vulnerability factor for internalizing psychopathology. Among children and adolescents, poorer performance on behavioral tasks indexing inhibitory control predicted greater likelihood of developing MDD (Bufferd et al., 2014; Stange et al., 2016) and anxiety disorders (Muris, 2006; Oldehinkel et al., 2007; Zainal and Newman, 2018). In addition, longitudinal neuroimaging studies have demonstrated that greater activation in brain regions associated with inhibition (*e.g.*, medial prefrontal cortex) predict course of illness (Langenecker et al., 2018; White et al., 2018). Emotion (dys)regulation may play a mechanistic role in the association between inhibitory control deficits and psychopathology. For instance, difficulty inhibiting negative or goal-irrelevant information and removing this information from working memory may lead to maladaptive emotion regulation strategies (*e.g.*, repetitive negative thinking; Joormann and Gotlib, 2010), which in turn are thought to increase risk for multiple psychopathologies (Snyder et al., 2019).

Inhibition may also represent a *familial* vulnerability factor for anxiety and depression symptoms. Twin and family studies have shown that performance on neurocognitive tasks measuring inhibitory functioning (Friedman et al., 2018; Routledge et al., 2017) and anxiety and depressive symptoms (Kendler et al., 2003) are significantly heritable. Moreover, twin studies indicate that these symptoms and inhibition share partially *overlapping* genetic risk factors (Friedman et al., 2018; Gustavson et al., 2019; Routledge et al., 2017), suggesting that some genetic factors increase risk for both anxiety/depressive symptoms and inhibition difficulties. Given that inhibition may be a familial vulnerability factor, the prognostic association between inhibition and internalizing psychopathology may be specific to (or stronger for) those with a family history of psychopathology. Davidovich et al. (2016) found that adolescents who had reduced inhibitory control during an affective go/no go task and parents with recurrent MDD reported more depressive symptoms themselves compared with adolescents with

intact inhibitory control. This study, however, was cross-sectional and no study to our knowledge has examined the interactive effect of family history and inhibition deficits on longitudinal outcomes.

The aims of the present study were the following. First, we examined concurrent and prospective associations between inhibitory control and symptoms of anxiety and depression, hypothesizing that impaired inhibitory control would be associated with greater symptoms. Second, we examined familial risk as a moderator, hypothesizing that the prospective associations between poorer inhibitory control and greater anxiety and depressive symptoms would be stronger in individuals at high familial risk for psychopathology.

METHODS

Participants

Participants were enrolled in a longitudinal, three-generation cohort study of families at high or low risk for MDD. Details of the sample have been reported elsewhere (Weissman et al., 2016). Briefly, probands (*i.e.*, generation 1; G1) with a history of MDD were recruited from outpatient psychiatric clinics. Inclusion criteria required that probands within this group had at least one depressive episode that lasted at least 4 weeks, was at least moderate in severity, caused noticeable role impairment, and prompted outpatient treatment. Exclusion criteria for this group included a history of bipolar disorder, schizophrenia, or primary substance abuse disorder (Weissman et al., 2016). All G1s in this group had onset of MDD before age 40, and most before age 30. A second group of probands with no history of psychiatric illness/treatment were simultaneously selected from the same community. Offspring of G1s (*i.e.*, G2s) were also enrolled. Participants completed up to seven waves of interviews and assessments over 30 years, and biological grandchildren of G1 probands (*i.e.*, G3) were assessed beginning at wave 3. There were no cases of bipolar disorder or schizophrenia in any of the three generations. Procedures and training remained similar across all waves to minimize method variance. All study procedures were approved by the institutional review board at New York State Psychiatric Institute/Columbia University. Written informed consent was obtained from adults for themselves and minors, and verbal assent was obtained from minors.

The present study focused on G3s, as they were in the prime risk window for onset/escalation of internalizing psychopathology (mean [SD] age, 16.1 [5.2] years; Kessler et al., 2005). Participants whose grandparents had no lifetime history of MDD were categorized as "low risk" for psychopathology, whereas participants with one or more grandparent with a history of MDD were categorized as "high risk" for psychopathology (Weissman et al., 2016).* G3s who completed both the Simon task (described below) and diagnostic interviews were included in the present sample. One participant was excluded for poor Simon task data quality, yielding a final sample consisting of 21 high-risk and 27 low-risk participants ($N = 48$). Demographic and clinical characteristics are presented in Table 1.

Measures

Psychiatric Assessments

The present study used data from waves 5 and 6, completed approximately 8 years apart. Diagnoses were obtained at all waves using age-appropriate versions of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (Kaufman et al., 1997; Mannuzza et al., 1986; Orvaschel et al., 1982) using best estimate procedures (Leckman et al., 1982), which involved an independent review of all assessments by experienced, doctoral-level clinicians. Parents and children separately rated symptoms for participants younger than 18 years. Interviews assessed the time period since the previous interview (or since birth, for initial interviews), facilitating the ascertainment of lifetime diagnoses.

Current depression and anxiety symptoms were also assessed at baseline and 8 years after baseline. Depressive symptoms were measured using the Hamilton Rating Scales for Depression (Ham-D; Hamilton, 1967) if the participant was an adult or the Children's Depression Rating Scale (CDRS; Poznanski et al., 1985) if the participant was a minor. Anxiety symptoms were assessed using either the Hamilton Rating Scales for Anxiety (Ham-A; Hamilton, 1959) for adults or the Revised Child Manifest Anxiety Scale (RCMAS; Perrin and Last, 1992) for minors. To merge the adult and child assessments of the same construct, the adult's and children's measures were combined into variables reflecting either depression symptom severity or anxiety symptom severity by standardizing the corresponding adult and child scores (*e.g.*, the Ham-D and CDRS for depression) within the sample and merging them.

Cognitive Functioning

Processing speed was assessed at wave 6 (*i.e.*, 8 years after baseline) using the Coding subtest from the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler et al., 2004) or Adults (WAIS-IV; Wechsler, 2008), depending on the participant's age. Processing speed was included as a covariate to minimize the confounding effect of processing speed in Simon performance. Coding scores on the WISC and WAIS were converted to age-adjusted standard scores, then combined and standardized to create a single index of processing speed.

Simon Task

The Simon task, a widely used behavioral measure of inhibition, was administered during an functional magnetic resonance imaging scan at baseline (*i.e.*, wave 5). Visual stimuli were presented via E-Prime software 1.1 (Psychology Software Tools, Inc, Sharpsburg, PA) in 10 blocks of 102 trials each. For each trial, an arrow pointing either left or right was displayed either to the left or to the right of a fixation cross positioned at midline. Participants were instructed to indicate the direction of the arrow as quickly as possible by pressing a response box button, and reaction time (RT) was recorded. Each arrow was presented for 1300 milliseconds, with an interstimulus interval of 350 milliseconds. Most trials were "congruent," wherein arrows pointed in the same direction as their position on the screen (*e.g.*, right-pointing arrow presented to the right of midline). Approximately

TABLE 1. Sample Demographic and Clinical Characteristics

Characteristic		
Sex, female, *n* (%)	23 (47.9)	
High familial risk, *n* (%)	21 (43.8)	
	Baseline	Follow-up
Age, y	16.05 (5.22)	24.40 (5.34)
Lifetime anxiety disorder, *n* (%)	21 (43.8)	21 (43.8)
Lifetime MDD, *n* (%)	9 (18.8)	16 (33.3)
Anxiety symptoms, mean (SD)[a]	4.51 (5.18)	1.56 (2.78)
Depression symptoms, mean (SD)[b]	3.95 (4.61)	2.05 (3.52)
Processing speed standard score, mean (SD)	–	10.15 (2.64)

Processing speed was assessed from WISC/WAIS coding.

[a] Hamilton Rating Scales for Anxiety/RCMAS.

[b] Ham-D/CDRS.

*We also tested whether prospective associations differed between participants with ($n = 34$ [70.8%]) vs without ($n = 14$ [29.2%]) a parental history of MDD. Parental MDD history did not moderate any of the prospective associations between the ex-Gaussian parameters and anxiety or depressive symptoms (p values > 0.557).

7% of trials were "incongruent," wherein arrows pointed in the direction opposite their position on the screen (*e.g.*, left-pointing arrow presented to the right of midline). The incongruent condition is cognitively more difficult and taps inhibitory control, whereas the congruent condition indexes general task performance. Incongruent trials were spaced pseudorandomly every 13 to 16 congruent trials. There were relatively few incorrect responses in each condition (mean [SD]: congruent, 13.3 [19.4]; incongruent, 13.9 [9.03]). Only correct trials were used in analyses to increase the homogeneity of included trials.

RTs were averaged separately for the congruent and incongruent conditions. Analyses of RT averages assume that RT data are normally distributed. However, research suggests that RT data are not normally distributed and instead are best fit by an exponentially modified Gaussian ("ex-Gaussian") distribution that reflects a combination of a normal (*i.e.*, Gaussian) distribution and an exponential distribution that rises rapidly on the left side of the distribution and has a long tail to the right (*e.g.*, Balota and Spieler, 1999). Ex-Gaussian distributions can be characterized using three parameters (mu, sigma, and tau) thought to reflect distinct (albeit correlated) processes. Mu represents the mean of the normal portion of the distribution and reflects average response time. Sigma represents the standard deviation of the normal portion of the distribution and reflects variability in response time. Tau captures the mean of the exponential portion of the distribution and reflects extreme (*i.e.*, slow) responses at the tail of the distribution. Tau is thought to be influenced by attentional lapses and central decision-making processes (Hohle, 1965) and be especially reflective of inhibitory control abilities. Supporting this interpretation, tau (but not mu or sigma) has consistently discriminated between groups that are known to differ in inhibitory control (*e.g.*, young adults versus older adults, individuals with versus without attention deficit/hyperactivity disorder; West et al., 2002; Leth-Steensen et al., 2000).

An ex-Gaussian distribution was fit to each participant's data using the R package retimes (Massidda, 2013). Following procedures from studies examining RT data from a similar task (Bondy et al., 2018), ex-Gaussian parameters were estimated for each participant and condition via a bootstrapping approach (5000 iterations) using maximum likelihood and implementing the Simplex method to establish the minimum of the objective function. Mu was obtained with a Gaussian kernel estimator (Van Zandt, 2000), and tau was then selected within the bootstrapped values based on maximum likelihood criterion. Sigma was not examined in this study because it has demonstrated poor retest reliability and validity (Bondy et al., 2018).

Data Analyses

Analyses were a series of multiple regression models. All models adjusted for participants' age, sex, and processing speed (WISC/WAIS Coding standard scores) as these variables were associated with average RT in the incongruent condition ($|r|$s = 0.10–0.43). Processing speed was also moderately associated with tau in the congruent condition ($r = -0.39$, $p = 0.006$) and mu in the incongruent condition ($r = -0.37$, $p = 0.011$), but was not significantly related to tau in the incongruent condition ($r = -0.09$, $p = 0.557$) or mu in the congruent condition ($r = -0.21$, $p = 0.156$; see Table 2). This approach increased the specificity of our findings to inhibitory control separate from processing speed. We also included the corresponding parameter from the congruent condition as a covariate to control for general task performance. Unsurprisingly, participants' mean RTs in congruent and incongruent trials were highly correlated ($r = 0.87$, $p < 0.001$). Neither tau ($r = 0.00$, $p = 0.977$) nor mu ($r = 0.12$, $p = 0.406$) was significantly correlated across congruent and incongruent trials, however, supporting the inclusion of the two conditions as separate predictors when examining the effects of tau or mu. All longitudinal models additionally adjusted for baseline symptom severity by covarying for baseline scores on the dependent variable (*i.e.*, either anxiety or depressive symptoms). All predictor variables were standardized.

Separate models were run for anxiety and depression and for tau and mu. In the first set of models, we examined cross-sectional associations between tau or mu and symptoms by regressing baseline anxiety symptoms (Ham-A/RCMAS) or depressive symptoms (Ham-D/CDRS) on the above covariates and tau or mu. Second, to examine prospective associations between tau or mu and subsequent symptoms, we ran similar models predicting anxiety symptoms (Ham-A/RCMAS) or depressive symptoms (Ham-D/CDRS) approximately 8 years later. The prospective models included covariates (age, sex, processing speed, and participants' personal and familial risk status) and tau or mu as predictors. Subsequent models testing the moderating effects of familial risk included the interaction between tau or mu and familial risk as an additional predictor. Simple slopes testing was used to probe significant interactions.

Finally, half of the sample ($n = 24$) met lifetime criteria for an anxiety disorder (panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, or separation anxiety disorder) or MDD at baseline. Examining individuals with and without a personal history of an internalizing disorder obfuscates whether inhibitory control deficits are a risk marker versus a state or scar marker observed in individuals with a history of anxiety or depression (Zeiss and Lewinsohn, 1988). To examine whether inhibitory control deficits might be a risk marker for anxiety and/or depressive symptoms, we conducted exploratory sensitivity analyses testing these cross-sectional and prospective associations only in participants who had not did not meet lifetime criteria for an anxiety disorder or MDD at baseline.

RESULTS

Cross-Sectional and Prospective Associations Between Inhibitory Control and Symptoms

Table 3 contains results for the cross-sectional models. Independent of tau in the congruent condition, tau in the incongruent condition was positively associated with anxiety symptoms ($\beta = 0.31$, 95% confidence interval [CI], 0.01–0.60; $p = 0.047$). The association between tau in the incongruent condition and depressive symptoms was not significant ($\beta = 0.24$, 95% CI, −0.07 to 0.55; $p = 0.136$). Mu in the incongruent condition was unrelated to anxiety or depressive symptoms (p values > 0.188). Cross-sectional associations between symptoms and tau or mu in the congruent condition were nonsignificant, with the exception that mu in the congruent condition was associated with depressive symptoms ($\beta = 0.41$, 95% CI, 0.10–0.72; $p = 0.012$).

Longitudinal models (Table 4) indicated that greater tau in the incongruent condition predicted greater subsequent anxiety symptoms at follow-up ($\beta = 0.33$, 95% CI, 0.02–0.64; $p = 0.042$). As in the cross-sectional models, tau in the incongruent condition did not significantly predict depressive symptoms at follow-up ($\beta = 0.27$, 95% CI, −0.05 to 0.59; $p = 0.104$). Mu in the incongruent condition did not prospectively predict anxiety or depressive symptoms (p values > 0.624). Tau and mu in the congruent condition did not prospectively predict anxiety or depressive symptoms, with the exception that mu in the congruent condition significantly predicted anxiety symptoms ($\beta = 0.49$; 95% CI, 0.18–0.80; $p = 0.003$).

Familial Risk as a Moderator of Associations Between Inhibitory Control and Symptoms

Finally, we tested whether inhibitory control interacted with familial risk for MDD to prospectively predict symptoms of anxiety and/or depression. In models prospectively predicting anxiety symptoms, familial risk interacted with tau in the incongruent condition ($\beta = 0.45$, 95% CI, 0.10–0.80; $p = 0.017$), but not mu in the incongruent condition ($\beta = 0.17$, 95% CI, −0.18 to 0.52; $p = 0.343$). Simple slopes (see Fig. 1) indicated

TABLE 2. Correlations Between Study Variables

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Baseline anxiety Sx	–	–	–	–	–	–	–	–	–	–	–
2. Baseline depressive Sx	0.72***	–	–	–	–	–	–	–	–	–	–
3. Follow-up anxiety Sx	0.27	0.31†	–	–	–	–	–	–	–	–	–
4. Follow-up depressive Sx	0.05	0.22	0.64***	–	–	–	–	–	–	–	–
5. Tau congruent	0.04	−0.23	−0.09	0.06	–	–	–	–	–	–	–
6. Tau incongruent	0.29†	0.24	0.39*	0.34*	0.00	–	–	–	–	–	–
7. Mu congruent	0.13	0.31†	0.47**	0.31†	−0.25†	0.14	–	–	–	–	–
8. Mu incongruent	−0.21	−0.30†	−0.03	0.08	0.54***	−0.42**	0.12	–	–	–	–
9. Sex	−0.36*	−0.38*	−0.08	0.07	0.28†	0.06	0.00	0.32*	–	–	–
10. Baseline age	0.07	0.05	−0.02	0.06	−0.03	0.12	−0.34*	−0.21	0.35*	–	–
11. Processing speed	0.06	0.02	−0.13	−0.27†	−0.39**	−0.09	−0.21	−0.37*	0.10	0.17	–

Correlations involving sex are point biserial correlations; all other correlations are Pearson correlations.
Sx indicates symptoms.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
†$p < 0.10$.

that poorer inhibition (tau) prospectively predicted greater anxiety symptoms in high-risk individuals ($\beta = 0.81$, 95% CI, 0.30–1.33; $p = 0.004$), but not low-risk individuals ($\beta = 0.09$, 95% CI, −0.25 to 0.43; $p = 0.597$). In models prospectively predicting depressive symptoms, familial risk interacted with tau in the incongruent condition ($\beta = 0.42$, 95% CI, 0.02–0.82; $p = 0.041$), but not mu in the incongruent condition ($\beta = 0.27$, 95% CI, −0.13 to 0.67; $p = 0.187$). Follow up-simple slopes analysis yielded similar patterns of results to those for anxiety symptoms: poorer inhibitory control (tau) prospectively predicted greater depressive symptoms in high-risk ($\beta = 0.72$, 95% CI, 0.14–1.30; $p = 0.020$), but not low-risk ($\beta = 0.06$, 95% CI, −0.32 to 0.43; $p = 0.769$), individuals.

Associations Between Inhibitory Control and Symptoms in Individuals Without a Personal History

Neither tau nor mu in the incongruent condition was cross-sectionally or prospectively associated with anxiety or depressive symptoms when examined only in individuals without a personal history of an anxiety disorder or MDD at baseline (p values > 0.120).

DISCUSSION

The present study examined cross-sectional and prospective associations between inhibitory control and symptoms of anxiety or

TABLE 3. Cross-Sectional Associations Between Inhibitory Control and Internalizing Symptoms

	Relation With Anxiety Symptoms			Relation With Depression Symptoms		
Predictor	**β**	**95% CI**	**p**	**β**	**95% CI**	**p**
Tau						
Covariates						
Sex	−0.40	−0.71 to −0.08	**0.017**	−0.29	−0.62 to 0.04	0.085*
Age	0.12	−0.19 to 0.43	0.452	0.10	−0.22 to 0.43	0.527
Processing speed	0.18	−0.15 to 0.51	0.287	−0.03	−0.37 to 0.32	0.881
Tau congruent	0.20	−0.13 to 0.53	0.232	−0.17	−0.52 to 0.17	0.326
Inhibitory control						
Tau incongruent	0.31	0.01 to 0.60	**0.047**	0.24	−0.07 to 0.55	0.136
Mu						
Covariates						
Sex	−0.33	−0.64 to 0.01	0.062*	−0.30	−0.62 to 0.03	0.074*
Age	0.21	−0.14 to 0.57	0.241	0.23	−0.11 to 0.56	0.180
Processing speed	0.07	−0.27 to 0.41	0.683	0.00	−0.34 to 0.35	0.982
Mu congruent	0.23	−0.11 to 0.56	0.181	0.41	0.10 to 0.72	**0.012**
Task performance speed						
Mu incongruent	−0.08	−0.44 to 0.28	0.669	−0.23	−0.56 to 0.11	0.188

Processing speed was assessed from WISC/WAIS coding. $p < 0.05$ is denoted by data in bold.
*$p < 0.10$.

TABLE 4. Longitudinal Associations Between Inhibitory Control and Internalizing Symptoms Approximately 8 Years Later

	Predicting Anxiety Symptoms			Predicting Depression Symptoms		
Predictor	***β***	**95% CI**	***p***	***β***	**95% CI**	***p***
Tau						
Covariates						
Sex	0.21	−0.14 to 0.56	0.246	0.24	−0.13 to 0.60	0.203
Age	−0.25	−0.58 to 0.08	0.146	−0.12	−0.47 to 0.24	0.519
Processing speed	−0.24	−0.57 to 0.09	0.152	−0.33	−0.67 to 0.02	0.073*
Baseline Anx or Dep Sx	0.21	−0.12 to 0.53	0.219	0.18	−0.16 to 0.52	0.300
Familial MDD risk	0.47	0.16 to 0.79	**0.006**	0.40	0.06 to 0.74	**0.026**
Tau congruent	−0.24	−0.57 to 0.10	0.165	−0.07	−0.42 to 0.29	0.711
Inhibitory control						
Tau incongruent	0.33	0.02 to 0.64	**0.042**	0.27	−0.05 to 0.59	0.104
Mu						
Covariates						
Sex	0.11	−0.23 to 0.45	0.533	0.19	−0.20 to 0.57	0.340
Age	−0.03	−0.37 to 0.31	0.861	0.02	−0.37 to 0.42	0.904
Processing speed	−0.13	−0.44 to 0.18	0.409	−0.29	−0.64 to 0.06	0.110
Baseline Anx or Dep Sx	0.16	−0.14 to 0.46	0.293	0.15	−0.22 to 0.52	0.425
Familial MDD risk	0.45	0.15 to 0.76	**0.006**	0.39	0.05 to 0.73	**0.031**
Mu Congruent	0.49	0.18 to 0.80	**0.003**	0.28	−0.10 to 0.65	0.149
Task performance speed						
Mu incongruent	−0.08	−0.41 to 0.25	0.624	−0.01	−0.39 to 0.36	0.945

Processing speed was assessed from WISC/WAIS coding. $p < 0.05$ is denoted by data in bold.

Anx indicates anxiety; Dep, depression; Sx, symptoms.

*$p < 0.10$.

depression, and whether these associations depended on familial risk. Consistent with hypotheses, initial results indicated that tau in the incongruent condition—which reflects lapses in attention consistent with poorer inhibitory control—was cross-sectionally and prospectively associated with anxiety symptoms. Cross-sectional and prospective associations between inhibitory control and depressive symptoms were not significant. Average speed of responding (mu) in the incongruent condition was not significantly associated with symptoms. Moderation analyses revealed that inhibitory control deficits at baseline predicted greater anxiety and depression symptoms 8 years later in those with high (but not low) familial risk for MDD. Previous studies examining similar questions in preschool and school-aged children have similarly found that inhibition-related constructs (*i.e.*, executive control) predicted anxiety and depression symptoms (Gramszlo et al., 2018; Nelson et al., 2018) even up to 7 years later (Kertz et al., 2016), whereas general cognitive abilities did not. The current study extends these findings to a critical risk window for developing internalizing pathology: the transition from adolescence to young adulthood.

Consistent with the partially overlapping genetic variance between performance on neurocognitive tasks measuring inhibition and internalizing psychopathology (Friedman et al., 2018; Gustavson et al., 2019; Routledge et al., 2017), the prospective associations between inhibitory control and anxiety and depressive symptoms were moderated by familial risk for MDD. Inhibitory control deficits predicted higher future anxiety/depression symptoms for individuals at high, but not low, familial risk for MDD. Low inhibitory control may therefore compound preexisting (familial) vulnerability to internalizing symptoms, perhaps by impairing cognitive or emotion regulation abilities. Multiple studies have shown that individuals reporting high trait negative affectivity and low inhibitory control evidence greater information processing biases (*e.g.*, attentional bias to threat) and anxiety symptoms, whereas those with higher inhibitory control exhibit weaker or nonsignificant relationships between such dispositional factors and anxiety (for a review, see Lonigan et al., 2004). The critical impact of familial risk has been shown in other studies with this multigenerational sample (Weissman et al., 1987, 2016). Given that inhibitory control abilities have also been shown to be genetic/familial (*e.g.*, Liu et al., 2021), the present findings suggest that inhibitory control may be a *familial* vulnerability factor for internalizing psychopathology. However, it is worth noting that familial risk for MDD did not moderate prospective associations between inhibitory control and internalizing symptoms when familial risk was operationalized using parental history rather than grandparental history. Statistical power was lower when defining familial risk using parental history rather than grandparental history due to a greater imbalance in group sizes. Thus, the nonsignificant moderating effects of parental history may have been type II errors.

Importantly, the effects for inhibitory control (as indexed by tau in the incongruent condition) were independent of tau in the congruent condition. The incongruent condition is more cognitively difficult and likely to tap inhibitory control abilities than the congruent condition, but controlling for the congruent condition adds specificity and additional rigor to the analyses. We also controlled for general processing speed (WAIS/WISC), increasing confidence that our findings are specific to inhibitory control. Relatedly, the use of ex-Gaussian parameters versus standard RT measures may achieve more reliable and/or valid indices of inhibitory control (McAuley et al., 2006).

The patterns of effects observed in this study were generally similar across anxiety and depressive symptoms, although some associations were only statistically significant for anxiety symptoms. The similar patterns of results are unsurprising given the frequent co-occurrence of anxiety and depressive symptoms (Kessler et al., 2005; Shankman and Klein, 2003) and suggests that inhibitory control is a *transdiagnostic* prospective predictor of internalizing symptoms in individuals with high familial risk for MDD. These findings broadly align with theoretical

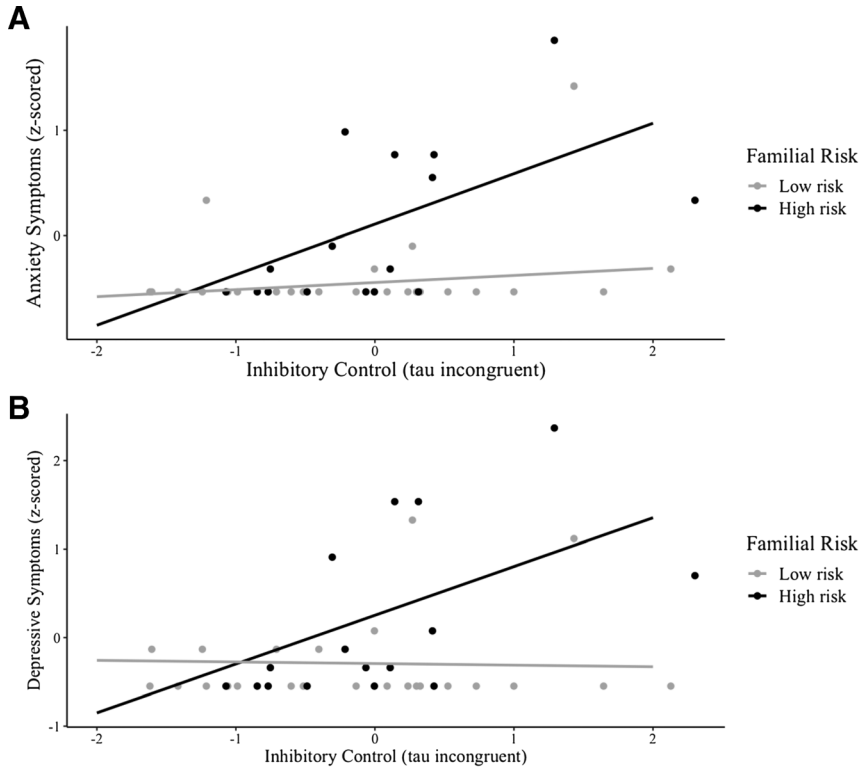

FIGURE 1. Prospective associations between inhibitory control and symptoms of anxiety (A) and depression (B).

models of anxiety and depression in which poor inhibitory control relates to or exacerbates worry/rumination (De Raedt and Koster, 2010; Eysenck et al., 2007; Joormann and Gotlib, 2010) and may be one mechanism by which negative affect and internalizing symptoms are maintained or exacerbated over time. The fact that these associations were independent of participants' baseline symptom severity further supports the interpretation that inhibitory control predicts development or exacerbation of symptoms. That said, exploratory analyses indicated that inhibitory control was not associated with internalizing symptoms when estimated only in individuals without a personal history of an internalizing disorder at baseline, suggesting that inhibitory control deficits may be a correlate or scar (rather than risk factor) of internalizing symptoms. These analyses were underpowered and effects were generally in the same direction as in the primary analyses, however. Examining whether inhibitory control is a risk factor for internalizing symptoms in higher-powered studies would be a valuable future direction.

If replicated, these findings may facilitate identifying and intervening with adolescents at risk for developing internalizing psychopathology. Inhibitory functioning tests are commonly administered to at-risk adolescents (*e.g.*, in schools), and our findings indicate that these tests could be utilized to identify those who would benefit from screening for current or future internalizing symptoms. Although still in early phases, research indicates that increasing abilities related to inhibitory control positively impacts internalizing symptoms (*e.g.*, Sari et al., 2016). Early interventions involving training inhibitory control abilities could potentially improve resilience to internalizing symptoms. This could functionally mimic cognitive behavioral therapy and related strategies that aim to increase cognitive flexibility, which promotes adaptive responding to future life stressors (Hoppitt et al., 2014).

The present study had several strengths, including use of a multigenerational, diagnostically well-characterized, high-risk sample, multiple experimental controls to strengthen specificity of the effects, and longitudinal follow-up over 8 years. There were also several notable limitations. First, the sample was small, which likely impacted statistical power to detect significant associations. Second, although most participants were adolescents at baseline and analyses covaried for age, the age range was relatively large. Examining similar questions in a more homogeneously aged sample could facilitate more nuanced interpretations regarding the relevance of developmental stage to the associations between inhibitory control, familial risk, and internalizing symptoms. Third, although the Simon task allowed for examination of the relationship between nonaffective inhibitory control and symptoms, future studies should consider additionally utilizing tasks measuring inhibitory control using affective stimuli. Fourth, psychiatric treatment history was not accounted for and it is possible that familial risk for MDD was confounded with treatment (*e.g.*, exposure to psychotropic medications). Fifth, although we considered both anxiety and depressive symptoms, it is unclear whether these associations are specific to these symptoms. For example, inhibitory control is also associated with externalizing symptoms (Leth-Steensen et al., 2000), and it is important to determine whether the moderating effect of familial risk extends to externalizing symptoms. In addition, these symptoms are common in numerous depressive and anxiety disorders as well as other psychopathologies (Kessler et al., 2005), precluding inferences regarding diagnostic specificity. Sixth, we used data from a study that began data collection in 1982 and followed up participants over the ensuing decades and generations. Because of this long follow-up period, the assessments administered to the original G1 participants are now somewhat outdated. Seventh, although this study focused on inhibitory control, there are other potential moderators that might interact with familial risk to play a role in the development of anxiety and depressive symptoms (*e.g.*, peer functioning; Funkhouser et al., 2022). Elucidating that other moderators is an important future direction. Eighth, the moderating effect of familial risk may further vary as a function of the characteristics

of familial depression (*e.g.*, age of onset, recurrence, comorbidities). The small sample size and the homogeneity of the G1 participants with MDD made it infeasible to consider these various characteristics in this study, but this would be an important future direction given the typical heterogeneity of MDD. Ninth, there were relatively few incorrect responses during the inhibitory control task, suggesting the task may not have been sensitive enough to detect unsuccessful inhibitory control. The relevance of inhibitory control to internalizing dimensions should be evaluated in subsequent studies with more challenging paradigms.

CONCLUSIONS

In sum, this study found that inhibitory control (as measured by the ex-Gaussian parameter tau) prospectively predicted anxiety and depressive symptoms 8 years later in individuals with high (but not low) familial risk for MDD. These findings suggest that inhibitory control may be a familial vulnerability factor for internalizing psychopathologies.

DISCLOSURE

This work was supported by the National Institute of Mental Health (grants R01MH036197, R01MH119771, and F31MH123042). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or of any other sponsor.

All authors have read and approved the submitted manuscript. Dr Stevens and Mr Funkhouser initially conceptualized the paper, conducted all the statistical analyses, and drafted the initial manuscript. Dr Auerbach contributed the analytic plan. Drs Talati, Gameroff, Posner, and Weissman designed and acquired the data and critically evaluated the paper for intellectual content. Dr Shankman oversaw the overall development of the paper and interpretation of the results.

This study was conducted according to acceptable research standards, received institutional review board/ethics approval, and obtained informed consent of study subjects.

Dr Weissman has received research funding from the Brain and Behavior Foundation and the Templeton Foundation and has received royalties from Perseus Press, Oxford Press, APA Publishing, and Multihealth Systems. Dr Posner has received research funding from Takeda and Aevi Genomics and received a consultancy from Innovation Science. None of these represent a conflict of interest for this paper, and the other authors have no potential conflicts of interest to disclose.

REFERENCES

Balota DA, Spieler DH (1999) Word frequency, repetition, and lexicality effects in word recognition tasks: Beyond measures of central tendency. *J Exp Psychol Gen*. 128:32–55.

Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IJzendoorn MH (2007) Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychol Bull*. 133:1–24.

Bondy E, Stewart JG, Hajcak G, Weinberg A, Tarlow N, Mittal VA, Auerbach RP (2018) Emotion processing in female youth: Testing the stability of the late positive potential. *Psychophysiology*. 55:10.1111/psyp.12977.

Bufferd SJ, Dougherty LR, Olino TM, Dyson MW, Laptook RS, Carlson GA, Klein DN (2014) Predictors of the onset of depression in young children: A multimethod, multi-informant longitudinal study from ages 3 to 6. *J Child Psychol Psychiatry*. 55:1279–1287.

Cisler JM, Olatunji BO, Feldner MT, Forsyth JP (2010) Emotion regulation and the anxiety disorders: An integrative review. *J Psychopathol Behav Assess*. 32:68–82.

Cox RC, Olatunji BO (2017) Linking attentional control and PTSD symptom severity: The role of rumination. *Cogn Behav Ther*. 46:421–431.

Davidovich S, Collishaw S, Thapar AK, Harold G, Thapar A, Rice F (2016) Do better executive functions buffer the effect of current parental depression on adolescent depressive symptoms? *J Affect Disord*. 199:54–64.

De Raedt R, Koster EHW, Joormann J (2010) Attentional control in depression: A translational affective neuroscience approach. *Cogn Affect Behav Neurosci*. 10:1–7.

Eysenck MW, Derakshan N, Santos R, Calvo MG (2007) Anxiety and cognitive performance: Attentional control theory. *Emotion*. 7:336–353.

Friedman NP, du Pont A, Corley RP, Hewitt JK (2018) Longitudinal relations between depressive symptoms and executive functions from adolescence to early adulthood: A twin study. *Clin Psychol Sci*. 6:543–560.

Friedman NP, Miyake A (2004) The relations among inhibition and interference control functions: A latent-variable analysis. *J Exp Psychol Gen*. 133:101–135.

Funkhouser CJ, Ashaie SA, Gameroff MJ, Talati A, Posner J, Weissman MM, Shankman SA (2022) Prospectively predicting adult depressive symptoms from adolescent peer dysfunction: A sibling comparison study [published online ahead of print]. *Res Child Adolesc Psychopathol*. doi: 10.1007/s10802-022-00906-4.

Gorlin EI, Teachman BA (2015) Inhibitory control as a moderator of threat-related interference biases in social anxiety. *Cogn Emot*. 29:723–735.

Gotlib IH, Joormann J (2010) Cognition and depression: Current status and future directions. *Annu Rev Clin Psychol*. 6:285–312.

Gramszlo C, Geronimi EMC, Arellano B, Woodruff-Borden J (2018) Testing a cognitive pathway between temperament and childhood anxiety. *J Child Family Stud*. 27:580–590.

Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle P (2003) The economic burden of depression in the United States: How did it change between 1990 and 2000? *J Clin Psychiatry*. 64:1465–1475.

Gustavson DE, Franz CE, Panizzon MS, Reynolds CA, Xian H, Jacobson KC, Toomey R, Lyons MJ, Kremen WS (2019) Genetic and environmental associations among executive functions, trait anxiety, and depression symptoms in middle age. *Clin Psychol Sci*. 7:127–142.

Hamilton M (1959) The assessment of anxiety states by rating. *Br J Med Psychol*. 32: 50–55.

Hamilton M (1967) Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 6:278–296.

Hohle RH (1965) Inferred components of reaction times as functions of foreperiod duration. *J Exp Psychol*. 69:382–386.

Hoppitt L, Illingworth JL, MacLeod C, Hampshire A, Dunn BD, Mackintosh B (2014) Modifying social anxiety related to a real-life stressor using online cognitive bias modification for interpretation. *Behav Res Ther*. 52:45–52.

Joormann J, Gotlib IH (2010) Emotion regulation in depression: Relation to cognitive inhibition. *Cognit Emot*. 24:281–298.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997) Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 36:980–988.

Kendler KS, Prescott CA, Myers J, Neale MC (2003) The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry*. 60:929–937.

Kertz SJ, Belden AC, Tillman R, Luby J (2016) Cognitive control deficits in shifting and inhibition in preschool age children are associated with increased depression and anxiety over 7.5 years of development. *J Abnorm Child Psychol*. 44:1185–1196.

Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Ustün TB, Wang PS (2009) The global burden of mental disorders: An update from the WHO world mental health (WMH) surveys. *Epidemiol Psichiatr Soc*. 18:23–33.

Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustün TB (2007) Age of onset of mental disorders: A review of recent literature. *Curr Opin Psychiatry*. 20:359–364.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005) Prevalence, severity, and comorbidity of 12-month *DSM-IV* disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 62:617–627.

Langenecker SA, Jenkins LM, Stange JP, Chang YS, DelDonno SR, Bessette KL, Passarotti AM, Bhaumik R, Ajilore O, Jacobs RH (2018) Cognitive control neuroimaging measures differentiate between those with and without future recurrence of depression. *Neuroimage Clin*. 20:1001–1009.

Leckman JF, Sholomskas D, Thompson D, Belanger A, Weissman MM (1982) Best estimate of lifetime psychiatric diagnosis: A methodological study. *Arch Gen Psychiatry.* 39:879–883.

Leth-Steensen C, Elbaz ZK, Douglas VI (2000) Mean response times, variability, and skew in the responding of ADHD children: A response time distributional approach. *Acta Psychol (Amst).* 104:167–190.

Liu H, Funkhouser CJ, Langenecker SA, Shankman SA (2021) Set shifting and inhibition deficits as potential endophenotypes for depression. *Psychiatry Res.* 300:113931.

Lonigan CJ, Vasey MW, Phillips BM, Hazen RA (2004) Temperament, anxiety, and the processing of threat-relevant stimuli. *J Clin Child Adolesc Psychol.* 33:8–20.

Mannuzza S, Fyer AJ, Klein DF, Endicott J (1986) Schedule for Affective Disorders and Schizophrenia–Lifetime version modified for the Study of Anxiety Disorders (SADS-LA): Rationale and conceptual development. *J Psychiatr Res.* 20:317–325.

Massidda D (2013) Retimes: Reaction time analysis. *R package [computer software].* Available at: https://rdrr.io/cran/retimes/. Accessed March 4, 2019.

McAuley T, Yap M, Christ SE, White DA (2006) Revisiting inhibitory control across the life span: Insights from the ex-Gaussian distribution. *Dev Neuropsychol.* 29:447–458.

Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A (2000) The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cogn Psychol.* 41:49–100.

Muris P (2006) The pathogenesis of childhood anxiety disorders: Considerations from a developmental psychopathology perspective. *Int J Behav Dev.* 30:5–11.

Nelson TD, Kidwell KM, Nelson JM, Tomaso CC, Hankey M, Espy KA (2018) Preschool executive control and internalizing symptoms in elementary school. *J Abnorm Child Psychol.* 46:1509–1520.

Nigg JT (2000) On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychol Bull.* 126:220–246.

Oldehinkel AJ, Hartman CA, Ferdinand RF, Verhulst FC, Ormel J (2007) Effortful control as modifier of the association between negative emotionality and adolescents' mental health problems. *Dev Psychopathol.* 19:523–539.

Orvaschel H, Puig-Antich J, Chambers W, Tabrizi MA, Johnson R (1982) Retrospective assessment of prepubertal major depression with the kiddie-SADS-e. *J Am Acad Child Psychiatry.* 21:392–397.

Perrin S, Last CG (1992) Do childhood anxiety measures measure anxiety? *J Abnorm Child Psychol.* 20:567–578.

Poznanski E, Mokros HB, Grossman J, Freeman LN (1985) Diagnostic criteria in childhood depression. *Am J Psychiatry.* 142:1168–1173.

Routledge KM, Burton KLO, Williams LM, Harris A, Schofield PR, Clark CR, Gatt JM (2017) The shared and unique genetic relationship between mental well-being, depression and anxiety symptoms and cognitive function in healthy twins. *Cognit Emot.* 31:1465–1479.

Sari BA, Koster EHW, Pourtois G, Derakshan N (2016) Training working memory to improve attentional control in anxiety: A proof-of-principle study using behavioral and electrophysiological measures. *Biol Psychol.* 121(pt B): 203–212.

Shankman SA, Klein DN (2003) The relation between depression and anxiety: An evaluation of the tripartite, approach-withdrawal and valence-arousal models. *Clin Psychol Rev.* 23:605–637.

Snyder HR, Friedman NP, Hankin BL (2019) Transdiagnostic mechanisms of psychopathology in youth: Executive functions, dependent stress, and rumination. *Cognit Ther Res.* 43:834–851.

Stange JP, Connolly SL, Burke TA, Hamilton JL, Hamlat EJ, Abramson LY, Alloy LB (2016) Inflexible cognition predicts first onset of major depressive episodes in adolescence. *Depress Anxiety.* 33:1005–1112.

Van Zandt T (2000) How to fit a response time distribution. *Psychon Bull Rev.* 7: 424–462.

Wagner S, Müller C, Helmreich I, Huss M, Tadić A (2015) A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *Eur Child Adolesc Psychiatry.* 24:5–19.

Wechsler D (2008) *Wechsler Adult Intelligence Scale: Administration and Scoring Manual.* San Antonio, TX: The Psychological Corporation.

Wechsler D, Kaplan E, Fein D, Kramer J, Morris R, Delis DC (2004) *Wechsler Intelligence Scale for Children–Integrated: Technical and interpretative manual* (4th ed). San Antonio, TX: The Psychological Corporation.

Weissman MM, Berry OO, Warner V, Gameroff MJ, Skipper J, Talati A, Pilowsky DJ, Wickramaratne P (2016) A 30-year study of 3 generations at high risk and low risk for depression. *JAMA Psychiatry.* 73:970–977.

Weissman MM, Gammon GD, John K, Merikangas KR, Warner V, Prusoff BA, Sholomskas D (1987) Children of depressed parents. Increased psychopathology and early onset of major depression. *Arch Gen Psychiatry.* 44: 847–853.

West R, Murphy KJ, Armilio ML, Craik FIM, Stuss DT (2002) Lapses of intention and performance variability reveal age-related increases in fluctuations of executive control. *Brain Cogn.* 49:402–419.

White SF, Costanzo ME, Thornton LC, Mobley AM, Blair JR, Roy MJ (2018) Increased cognitive control and reduced emotional interference is associated with reduced PTSD symptom severity in a trauma-exposed sample: A preliminary longitudinal study. *Psychiatry Res Neuroimaging.* 278:7–12.

Zainal NH, Newman MG (2018) Executive function and other cognitive deficits are distal risk factors of generalized anxiety disorder 9 years later. *Psychol Med.* 48: 2045–2053.

Zalta AK, Shankman SA (2016) Conducting psychopathology prevention research in the RDoC era. *Clin Psychol (New York).* 23:94–104.

Zeiss AM, Lewinsohn PM (1988) Enduring deficits after remissions of depression: A test of the scar hypothesis. *Behav Res Ther.* 26:151–158.