

6-2018

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Brian W. Bauer

University of Southern Mississippi, brian.bauer@usm.edu

Hanna C. Gustafsson

Oregon Health and Science University

Joel Nigg

Oregon Health and Science University

Sarah L. Karalunas

Oregon Health and Science University

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Recommended Citation

Bauer, Brian W.; Gustafsson, Hanna C.; Nigg, Joel; and Karalunas, Sarah L., "Working Memory Mediates Increased Negative Affect and Suicidal Ideation in Childhood Attention-Deficit/Hyperactivity Disorder" (2018). *Student Publications*. 17.
https://aquila.usm.edu/student_pubs/17

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Published in final edited form as:

J Psychopathol Behav Assess. 2018 June ; 40(2): 180–193. doi:10.1007/s10862-017-9635-5.

Working memory mediates increased negative affect and suicidal ideation in childhood attention-deficit/hyperactivity disorder

Brian W. Bauer,

University of Southern Mississippi, 118 College Drive #5025, Hattiesburg, MS 39406, Phone: (206) 612-3122

Hanna C. Gustafsson,

Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Multnomah Pavilion, Suite 1505, Mail Code: UHN-80R1 Portland, OR 97239, Phone: (503) 418-8402

Joel Nigg, and

Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Multnomah Pavilion, Suite 1513, Mail Code: UHN-80R1 Portland, OR 97239, Phone: (503) 418-8498

Sarah L. Karalunas

Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Multnomah Pavilion, Suite 1513, Mail Code: UHN-80R1, Portland, OR 97239, Phone: (503) 494-5780

Abstract

Objective—Children with attention-deficit/hyperactivity disorder (ADHD) are at greater risk for suicidal ideation and suicide attempts compared to those without ADHD. Increased risk is at least partially attributable to a subset of children with ADHD and comorbid depression or disruptive behavior disorders; however, the early predictors and mechanisms driving increased risk are not well understood. Here, we investigate the contributions of two candidate mechanisms for increased suicidal ideation in children with ADHD: executive function and negative affect.

Methods—623 clinically well-characterized, community-recruited children classified by research criteria as ADHD ($n=388$) or typically-developing controls ($n=253$) participated. Parent-report on the Temperament in Middle Childhood Questionnaire provided a measure of negative affectivity. Children completed laboratory tasks to measure response inhibition and working memory. Suicidal ideation was evaluated by parent report during a semi-structured interview and child responses on the Children's Depression Inventory.

Results—Compared to typically developing controls, children with ADHD had higher rates of suicidal ideation, more negative affect, slower stop signal reaction times, and weaker working

Correspondence to: Brian W. Bauer.

Conflict of Interest: Brian Bauer, Hanna Gustafsson, Joel Nigg, and Sarah Karalunas declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

memory. Statistical path-model analyses confirmed the hypothesis that weaker working memory in ADHD statistically mediated increased negative affect. Weaker working memory also mediated and increased suicidal ideation in these cross sectional data. Findings were not attributable to comorbid disruptive behavioral disorders. Poor response inhibition did not reliably mediate negative affect or suicidal ideation.

Conclusion—Impairment in working memory is an important early risk factor for suicidal ideation in children with ADHD, and may help in identifying children for prevention and early intervention efforts.

Keywords

ADHD; Executive Functioning; Suicide; Negative Affect

From 1999 through 2014, suicide rates rose 24% (10.5 to 13.0 per 100,000) in the United States (Centers for Disease Control and Prevention [CDC], 2016), and rose dramatically for children ages 10-14. It is the second leading cause of death in the US for this age group, and the third leading cause of death among adolescents up to age 19 years (Cash & Bridge, 2009; Centers for Disease Control and Prevention, 2014; Curtin, Warner, Hedegaard; 2016). Rates of deaths by suicide in Attention Deficit Hyperactivity Disorder (ADHD) are potentially three times higher than rates in those without ADHD (Chronis-Tuscano et al., 2010; James, Lai, & Dahl, 2004; Ljung, Chen, Lichtenstein, & Larsson, 2014). In addition, ADHD has recently been found to be the most common mental disorder for children under the age of 12 who die by suicide (Sheftall et al., 2016). This increased risk is partly attributable to a subset of children with ADHD and comorbid depression, anxiety, or conduct disorder (Agosti, Chen, Levin, 2011; Haavisto et al., 2005; Impey & Heun, 2012; James, Lai, & Dahl, 2004; Jarrett & Ollendick, 2008; Nigg, 2013; Sourander et al., 2009). However, in most cases ADHD onsets prior to comorbid conditions, and earlier risk factors for suicide that exist prior to comorbid disorder onset are not well-characterized.

Suicide-related ideation is important to understanding suicidal behaviors (Beck, Kovacs, & Weissman, 1979; Brown, Beck, Steer, & Grisham, 2000; Kessler, Borges, & Walters, 1999; Kovacs & Garrison, 1985; Lewinsohn, Rohde, & Seeley, 1996; Marcenko, Fishman, & Friedman, 1999; Nock et al., 2006). Persistent ideation with intent increases risk for eventual suicide and has been the focus of the majority of previous studies (Wyman et al., 2009). However, suicidal ideation encompasses a spectrum of suicide-related thoughts (Silverman, Berman, Sanddal, O'Carroll, & Joiner, 2007), and even relatively mild suicidal ideation occurring in early to middle childhood is predictive of persistent suicidal ideation and suicide attempts in adulthood (Herba, Ferdinand, & Verhulst, 2007). Much less research has focused on observing the emerging stages of suicidal ideation (Mayes et al., 2015; Mzur-Mosiewicz et al., 2015), and understanding early predictors for and mechanisms of emerging suicidal ideation is an important step for suicide prevention efforts in children and adolescents. The current study focuses on clarifying how two common features of ADHD: negative affect and executive function impairment contribute to suicidal ideation in children with ADHD, a group at increased risk for suicidality.

Negative Affect

There is growing recognition of the importance of emotional lability and negative affect in explaining functional impairments associated with ADHD (Banaschewski et al., 2012; Karalunas et al., 2014; Shaw, Stringaris, Nigg, & Leibenluft, 2014; Steinberg & Drabick, 2015). At the group level, children with ADHD are more likely to be irritable and have difficulty regulating negative emotions than their typically-developing peers (Martel & Nigg, 2006; Shaw, Stringaris, Nigg, & Leibenluft, 2014). Those with ADHD and problems regulating negative emotions have increased risk for onset of comorbid mood and anxiety disorders as compared to other children with ADHD (Karalunas et al., 2014), suggesting it is a potent early predictor of diverging clinical course in the disorder.

Emotion dysregulation, generally, and poor regulation of negative affect, specifically, are associated with both suicidal behavior (Bradley et al., 2010; Linehan, 1993; Pinto & Whisman, 1996; Selby, Franklin, Carson-Wong, & Shireen, 2013; Stein, Apter, Ratzoni, Har-Even, & Avidan, 1998) and suicidal ideation (Tamas, et al., 2007) in adult psychiatric populations. For adults with ADHD, emotion regulation difficulties have been found to interact with depressive symptoms to predict suicidal ideation (Van Eck et al., 2014). However, the use of only self-report questionnaires for ADHD diagnosis and lack of assessment for diagnostic comorbidity, limit interpretation of these results. Studies have yet to examine how increased negative affect in ADHD may be related to suicidal ideation in younger children, before the emergence of depressive disorders, which will be a key step in defining early risk factors.

Executive Functioning

Executive functioning is a complex construct consisting of multiple sub-abilities, referring at a general level to the ability to use top-down control to overcome stimulus-driven responses in order to pursue goals. Weaker executive function is related to general impairment in ADHD (Biederman et al., 2004; Wählstedt, Thorell, & Bohlin, 2008) and may also be a specific risk factor for suicidal ideation. Across development, impairments in executive function undermine behavioral and emotional regulatory capacities, and may contribute to increased negative affect, difficulty controlling thoughts and actions, and reduced positive coping in response to stress (Barkley, 1997; Bredemeier & Miller, 2015; Ochsner & Gross, 2005; Rothbart, Sheese, Rueda, & Posner, 2011).

Executive function impairments are associated with suicide attempts in a variety of patient populations, even after accounting for severity of depression (Gujral et al., 2014; Keilp et al., 2013; Keilp et al., 2001; Marzuk, Hartwell, Leon, & Portera, 2005). Some prior literature also suggests a tentative link between executive function impairment and suicidal ideation, specifically (Mazur-Mosiewicz et al., 2015). However, findings are mixed as to whether executive function impairment is primarily related to lethality of suicide attempts (Keilp et al., 2001) or is related to suicidal ideation independent of history of attempts (Marzuk, Hartwell, Leon, & Portera, 2005). One problem in disentangling these relationships is that prior research has focused on the effects suicidality has on executive function, rather than the possible roles poor executive function plays in the development of suicidal ideation

(Keilp et al., 2013; Westheide, et al., 2008). Most studies of suicidal ideation and executive function are also in adult samples with complex histories of prior attempts, leaving the relationships between executive function impairment and suicidal ideation earlier in development unclear. Due to the prevalence of executive function impairment in children with ADHD and their increased suicide risk, this population is a critical locus for clarifying these associations.

An additional complication, is that executive function is not a unitary construct (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000;). Here we focus on two components: response inhibition and working memory. Response inhibition is a primary measure of cognitive functioning in studies of suicide and suicidal ideation because it is often considered a type of impulsivity (Conner, Meldrum, Wieczorek, Duberstein, & Welte, 2004; Gvion & Apter, 2011; Hull-Blanks, Kerr, & Kurpius, 2004; LeGris, Links, van Reekum, Tannock, & Toplak, 2012). However, the role of response inhibition in suicide-related thoughts and behaviors is heavily debated (Anestis, Soberay, Gutierrez, Hernandez, & Joiner, 2014; Joiner, 2005; Klonsky & May, 2010; Simon et al., 2002; Smith et al., 2008; Williams et al., 1980; Witte et al., 2008). Some prior work suggests that response inhibition may be related to whether an individual *acts* on suicidal ideation, but not to suicidal ideation itself (Mann, Waternaux, Hass, and Malone 1999; Nock et al., 2008). In ADHD specifically, one study has found that response inhibition mediated suicidal behaviors (Swanson, Owens, & Hinshaw, 2014); however, studies have not directly examined the relationships between response inhibition and suicidal ideation, leaving questions about whether poor impulse control drives earlier risk.

Working memory is another hallmark measure of executive function that is impaired in children with ADHD (Kasper, Alderson, & Hudec, 2012; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt et al., 2005). Part of the function of working memory is to clear distracting information to free up mental space for goal-related action. Thus, impairments in working memory are related to difficulties removing irrelevant negative material from active processing (Joormann & Gotlib, 2008), suggesting one mechanism by which weak working memory may contribute to suicidal ideation. Despite its theoretical importance, in a recent review of executive function and suicidality only 2 of 43 studies included specific measures of working memory (Bredemeier & Miller, 2015). While these studies indicate a relationship between working memory and suicide attempts, the relationship between working memory impairment and suicidal ideation has not been examined (Delaney et al., 2012; Keilp, et al., 2001; Richard-Devantoy, Berlim, & Jollant, 2014).

Relationships between Negative Affect and Executive Functioning

Individuals may have high trait levels of negative affect for many reasons, however, one pathway by which executive function deficits may contribute to suicidal ideation is via poor regulation of negative affect. Within ADHD, co-occurring impairments in executive function and regulation of negative affect are commonly observed (Bridgett, Oddi, Laake, Murdock, & Bachman, 2013; Jarrett, Wolff, Davis, Cowart, & Ollendick, 2016; Suchy, & Kraybill, 2010; Walcott & Landau, 2004; Williams, Schmeichel, Volokhov, & Demaree, 2008),

although whether these are related remains unclear (Banaschewski et al., 2012). Several influential theoretical models suggest that the ability to suppress impulses and clear negative information from working memory are closely related to the ability to regulate negative affect (Hofmann, Schmeichel, & Baddely, 2011; Gyurak et al., 2009; Moran, 2016; Rueda, Posner, & Rothbart, 2005). In typically-developing children, weaker working memory has been shown to mediate increased level of negative affect (Bridgett, Oddi, Laake, Murdock, & Bachman, 2013). Thus, while theory and some data suggest that weak executive function may mediate higher negative affect, which in turn may contribute to suicidal ideation, this important mediational model has not been tested.

Summary

Although children with ADHD have higher rates of suicidal ideation than those without ADHD, the mechanisms of this risk remain unclear. Here, we test whether impairments in working memory or response inhibition in ADHD mediate higher levels of negative affect, as well as how these processes are related to suicidal ideation. We hypothesize that poorer working memory will mediate higher levels of negative affect, and that both working memory and negative affect will mediate the relationship between ADHD and suicidal ideation. We did not expect the same relationships to be present in for response inhibition because of its association with suicidal action rather than ideation.

Method

Participants and Diagnostic Procedures

Participants were 623 community-recruited children ages 7-12 classified as ADHD (n=388) and typically-developing (n=235). The sample included 102 sibling pairs and one sibling trio. Clustering within families was accounted for in analyses as described below. Ethics approval was obtained from the Institutional Review Board at Oregon Health & Science University. A parent/legal guardian provided written informed consent, and children provided written assent for the study. Children were recruited using a community-based recruitment strategy based on public advertising and outreach. After an initial screening phone call, children were identified for the study via a best-estimate confirmation procedure. First, a parent/guardian and teacher completed standardized rating scales, including the Conners' Rating Scales-Revised (CRS-R, Conners, 2003) and the ADHD Rating Scale (ADHD-RS, DuPaul, Power, Anastopoulos, & Reid, 1998). If a child was prescribed stimulant medications, parents and teachers were asked to rate the child's behavior when not taking medication. The parent/guardian also completed a semi-structured clinical interview administered by a Master's-level clinician who had achieved research reliability on the interview (Kiddie Schedule for Affective Disorders and Schizophrenia, K-SADS, Kaufman et al., 1997). Parents rated their child's overall level of impairment in academic, family, and peer relationships using the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 2001). IQ was estimated based on a reliable and valid three-subtest short form of the WISC-IV (Vocabulary, Block Design, and Information, Wechsler, 2003).

In a best estimate procedure, final diagnoses were made by a clinical diagnostic team (a board certified child psychiatrist and licensed clinical child psychologist), who took into

account data from the parent and teacher ratings, parent clinical interview, IQ and achievement testing, and behavioral observations. Blind to one another's ratings and to the subsequent cognitive test scores, they formed a diagnostic opinion based on all available information. Their agreement rate was excellent (ADHD diagnosis kappa=.88). Disagreements were conferenced and consensus reached. Cases where consensus was not readily achieved were excluded. In determining their diagnostic impression, the clinicians used the following rule: If both parent and teacher ratings exceeded T-score ≥ 60 on at least one ADHD scale and both rated at least 3 symptoms as "often" or "very often" on the ADHD rating scale (teachers) and K-SADS (parents), then the "or" algorithm could be employed for counting symptoms towards the final diagnosis. Consistent with DSM criteria, to be in the ADHD group, the "or" algorithm needed to yield at least 6 symptoms of inattention, 6 symptoms of hyperactivity-impulsivity, or both. When informants disagreed (i.e., one of the informants did not have T-score ≥ 60 or did not report more than 3 symptoms), clinicians were asked to judge whether this was explained by successful medication treatment during the school day. If so, they they used all available data to make a diagnostic determination. If the discrepancy was not easily explained by successful medication treatment during the day, then the case was rejected as failing to meet the DSM criteria of substantial symptoms present in more than one setting. In addition to symptom count criteria, children in the ADHD group were required to meet all other DSM criteria including (a) impairment (identified on the KSAD by the clinician as well as on the SDQ impact supplement section for parents and teachers), (b) onset prior to age 7 (current at the time we began enrollment), (c) sustained impairing symptoms > 1 year, and (d) symptoms of ADHD not better accounted for by comorbid conditions, trauma history, or other confounds. For non-ADHD comparison children, total symptoms combining inattention and hyperactivity-impulsivity across raters had to be ≤ 4 .

Children were excluded if they: were prescribed long-acting non-stimulant psychotropic medications; had neurological impairment, seizure history, head injury with loss of consciousness, other major medical conditions, or substance abuse disorder; had prior diagnosis of intellectual disability, autism spectrum disorder, or psychosis; were experiencing a major depressive episode at the time of diagnostic interview; or had estimated IQ < 70 . Children prescribed stimulant medications (42%) were included but were required to be off medication for 24 (for short-acting preparations) to 48 hr (for long-acting preparations) prior to cognitive testing. Comorbidities other than ADHD were allowed in the typically developing sample to increase generalizability (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015).

Measures

Working memory—Working memory was assessed using multiple tasks across verbal and visuospatial domains. Non-verbal working memory maintenance was assessed using two versions (forward span and backward span) of a computerized task based on the Spatial Span subtest from the CANTAB test battery (De Luca et al., 2003). In both versions of the task, children saw a screen containing 10 squares arranged in a fixed position. Individual squares changed color in a fixed sequence. In the forward span task, children were instructed to click on the squares in the order in which they changed color. In the backward span task,

children were instructed to click on the squares in the *reverse* order in which they changed color. For both tasks, number of squares in the sequence began at three and increased to nine, with two trials for each sequence length. The task discontinued when a child got two sequences of the same length incorrect (e.g., after getting both the sequences with 5 items incorrect). The primary outcome variables used were the total number items attempted during the forward and backward trials, which is directly related to span length.

As a measure of verbal working memory maintenance, children completed the digit span task (forward and backward conditions) from the WISC-IV (Wechsler, 2003). Raw accuracy scores were used as primary outcome variables.

Children also completed a computerized N-back test to assess both maintenance and updating functions of working memory with two conditions: 1-back and 2-back. This task captures working memory maintenance, as well as updating aspects of working memory at the higher backwards lags. Children saw a picture of an apple with 4 holes. A worm appeared every 2000ms and stay on the screen for 1000ms. After disappearing, a tone prompted the participant to indicate which hole the worm just came out of one trial prior (1-back) or two trials prior (2-back). Responses were made by pressing a number key that corresponded with the hole (cutouts of an apple shape were placed over the keyboard number pad to facilitate responding). Ten practice trials were given prior to each condition, followed by 45 scored trials per condition. The primary outcome variable was accuracy.

Informed by confirmatory factor analysis (described below), these six measures were used as indicators of a working memory latent variable that was used in all other analyses.

Response inhibition—Response inhibition was evaluated based on a tracking version of the “stop task” originally developed by Logan and colleagues (Logan, Cowan, & Davis, 1984), here modified as in prior studies (Nigg, 1999; Schachar, Mota, Logan, Tannock, & Klim, 2000). For each trial, a central fixation point appeared for 500 ms. An “X” or an “O” then appeared for 1000 ms. On 75% of trials (“go” trials), children were asked to indicate with a key press whether an “X” or an “O” appeared in the center of the screen. Children were given a total of 2000 ms to respond after which the next trial automatically commenced. On 25% of trials (“stop” trials), an auditory tone presented after the stimulus (timing varied adaptively based on participant performance) indicated that the child should not respond. An initial mean reaction time (MRT) was determined based on the practice trials and the auditory stop tone was initially set to occur 250 ms before the MRT. The MRT was then dynamically recalculated after each correct go trial and the delay at which the stop tone was presented was adjusted dynamically in 50 ms increments to maintain an overall ~50 % accuracy rate. After 32 practice trials, children completed 8 blocks of 64 experimental trials. Prior to analysis, the following validity criteria were applied to each block: a) stop accuracy between 30-70%, b) hit accuracy greater than 75%, and c) mean RT for the block between 100-1500ms. Stop signal RT (SSRT), the primary measure of response inhibition, was calculated for each valid block by subtracting the average stop signal delay from average RT (Logan, 1994); SSRTs less than 50ms were considered invalid. Valid SSRTs were averaged to create the final outcome variable. Following convention, the practice trials and the first block of data were excluded from the final average to exclude

warm-up effects. 2.2% of data were excluded because no blocks of data met the validity criteria; these were treated as missing data in analyses.

Negative Affect—Trait negative affect was measured using the well-validated Temperament in Middle Childhood Questionnaire (TMCQ). The 157 TMCQ uses a 5-point Likert-type item scale. The TMCQ items combine into 16 scales and 3 higher-order factors based on prior factor analysis (Simonds and Rothbart, 2004): Activity Level, Affiliation, Anger/Frustration, Assertiveness/Dominance, Attention Focusing, Discomfort, Fantasy/Openness, Fear, High Intensity Pleasure, Impulsivity, Inhibitory Control, Low Intensity Pleasure, Perceptual Sensitivity, Sadness, Shyness, and Soothability/Falling Reactivity. The scales contributing to the negative affect composite include Anger/Frustration, Fear, Sadness, Discomfort, and Soothability/Falling Reactivity. Internal consistency (Cronbach's α) for negative affect scales in our sample are all acceptable and ranged from 0.85 to 0.94

Suicidal Ideation—Suicidal ideation was determined using a combination of parent report on the KSAD and child report on the CDI (Kovacs, 2004). The CDI is a 27-item, self-rated symptom-oriented scale that is suitable for youths ages 7-17 with acceptable levels of reliability and validity. Question 9 on the CDI asks the child to select one of the following answers: “I do not think about killing myself,” “I think about killing myself but I would not do it,” and “I want to kill myself.” Suicidal ideation was coded positive if the child endorsed either “I think about killing myself but I would not do it” or “I want to kill myself” or if parents endorsed child suicidal ideation during KSAD interview, creating a dichotomous present/absent outcome variable. This approach is similar to methods used in prior studies to assess suicidal ideation in children with and without ADHD (Hauser, Galling, & Correll, 2013; Mayes et al., 2015; Mazur-Mosiewicz et al., 2015), including studies that have used similar items in childhood to prospectively predict adult suicide attempts (Herba, Ferdinand, & Verhulst, 2007), suggesting that even this relatively mild early ideation is an important clinical indicator. Note that all of the responses leading to positive coding of suicidal ideation required the child to endorse thinking about killing themselves and not only thinking about death or dying, which may not be a sensitive indicator of suicide risk (Stoep, McCauley, Flynn, & Stone, 2009.)

Analyses

Rates of suicidal ideation, levels of negative affect, and performance on cognitive tasks were compared between groups using standard ANOVA and chi-square tests in SPSS v.23.0. Path models were used to test the directional hypothesis, which for simplicity we refer to as mediation, although these are cross sectional data (Kenny, 1979). These models were implemented in MPLUS v.7.2 using the robust weighted least squares means estimator, which can accommodate non-normal categorical data. Non-independence of observations (i.e., the nesting of children within families) was handled using MPLUS's *cluster* command. Mediation was examined using the *model indirect* command. Primary results focus on the negative affect scale from the TMCQ. Secondary analyses also considered child report of negative mood from the Children's Depressive Inventory (CDI; Kovacs, 2004) as a measure of negative affect; however, to avoid confounding of measures suicidal ideation and negative

affect by using the same measurement instrument, we simply note that none of the results differed when child report of negative affect was used instead of parent report.

Handling of covariates—Analyses were conducted both with and without age, sex, and IQ as covariates. Significance of all direct and indirect pathways remained the same regardless of covariates, and results are presented without these covariates. The sample was community-recruited and excluded children with a *current* major depressive episode at the time of participation, which resulted in low rates of comorbid lifetime mood disorders for both ADHD (7%) and control (1%) children, making it an ideal sample for identifying early risk factors unconfounded by mood disorder. Rates of oppositional defiant disorder (ODD), which is a risk factor for later depression, were consistent with those expected in a community-recruited ADHD sample (19% in ADHD, 1% in control group), and ODD was included as a covariate in mediational models. Results both with and without the covariate are reported.

Handling of Missing Data—Each child in the sample had recorded data for at least one cognitive task (n=623). However, data was not available for all children on all tasks: 10.9% of children had missing data for the response inhibition task and 8.5% were missing one or more working memory tasks. Missing data were due either to computer failure or exclusion because the child did not meet validity criteria for the task, as described above. Children with complete data did not differ reliably from those without complete data in sex, IQ, or ADHD symptoms severity (all $p > .05$). Missing data in the mediation analyses were handled via full information maximum likelihood algorithms in MPLUS v.7.2.

Results

Sample characteristics

Means, standard deviations, and effect sizes for all comparisons are reported in Table 1. As expected, children with ADHD had more negative affect ($p < .001$) and higher rates of ODD ($p < .001$) than typically-developing; Children with ADHD also had poorer performance on all working memory tasks ($p < .001$) and had worse response inhibition ($p < .001$) than the non-ADHD control group. Correlations between measures are presented in Table 2.

Main effect model

Prior to testing the mediation models, a main effects model was examined. Specifically, the current study's measure of suicidal ideation was regressed on child ADHD status. Results indicated that the ADHD group had a higher rate of suicidal ideation than the control group (26.7% v. 15.1%, respectively), $\beta = .20$ (SE = .06), $p < .001$. Rates in the typically-developing sample were consistent with population averages in epidemiological studies (Cash & Bridge, 2009).

Mediation models

Two mediational models were tested: one including response inhibition (SSRT) as the cognitive mediator and one with the working memory latent variable as the cognitive mediator. In both cases, the model predicted that cognitive impairment (response inhibition

or working memory) mediated ADHD-related increases in negative affect, which in turn mediated increased suicidal ideation. A non-serial mediation path through the cognitive measure (response inhibition or working memory) to suicidal ideation that did not include negative affect was also included. Both serial and non-serial paths and their confidence intervals were examined for statistical significance. Figure 1 depicts the model for the working memory cognitive mediator as an example. The coefficients for the direct and indirect paths are listed in Table 3.

Response Inhibition

In a model with response inhibition as the cognitive mediator and ODD included as a covariate, the direct effects of ADHD on suicidal ideation and response inhibition were significant ($p < .01$); however no other effects were reliably different than zero. The parameter estimates for all paths in the model are listed in Table 3. We note that when ODD was not included as a covariate the indirect effect of ADHD on suicidal ideation through negative affect was significant (indirect effect=.11, SE=.05, $p=.03$; 95% CI: .006 to .096).

Working Memory

In the model with working memory as a cognitive mediator and ODD as a covariate, the indirect effect from ADHD to suicidal ideation through negative affect was not significant (indirect effect=.02, SE=.02, $p=.17$; 95% CI: -.010 to .058), but the indirect path from ADHD to suicidal ideation through working memory was significant (indirect effect=.05, SE=.03, $p < .05$; 95% CI: .001 to .096). The indirect effect of ADHD on negative affect through working memory was also significant (indirect effect=.04, SE=.02, $p=.01$; 95% CI: .008 to .072). The serial mediation path in which working memory mediated increased negative affect, which in turn mediated increased SI, was not significant (indirect effect=<.01, SE=<.01, $p=.20$, 95% CI: -.002 to .009). After accounting for indirect effects, the direct effect of ADHD on suicidal ideation was no longer significant (direct effect=.08, SE=.07, $p=.21$; 95% CI: -.05 to .21). Taken together results indicate that working memory impairments mediated both increased negative affect and increased suicidal ideation in ADHD, after accounting for comorbid oppositional defiant disorder. Figure 1 visually depicts these effects. The parameter estimates for all paths in the model are listed in Table 3.

Discussion

Children with ADHD are at increased risk for suicidality compared to their typically-developing peers, but the mechanisms and early predictors of risk remain poorly understood. The present study replicated prior findings (Chronis-Tuscano et al., 2010) with a near doubling of incidence of suicidal ideation in youth with ADHD that was not fully accounted for by comorbid disorders. This is among only a small number of studies to consider executive functioning and negative affect as mediators of ADHD's association with suicidal ideation. There were two key findings. First, weak working memory mediated higher levels of negative affect in children with ADHD. Second, weak working memory also mediated increased likelihood of suicidal ideation, after controlling for comorbid oppositional defiant disorder. Most research on suicidality has focused on adolescents and adults with complex histories of depression and suicide attempts. Here, results demonstrate that working memory

may be a risk indicator independent of the mood dysregulation associated with ODD and before the onset of serious depressive symptoms.

Increased negative affect also mediated increased suicidal ideation in ADHD; however, this path was only significant when not accounting for comorbid oppositional defiant disorder, an indicator of mood dysregulation and risk factor for depressive disorders. Contrary to our hypotheses, although working memory mediated both negative affect and suicidal ideation, the serial mediation of poor working memory to negative affect to increased suicidal ideation was not significant. This may be because the association between negative affect and suicidal ideation was accounted for by comorbid ODD and suggests working memory and negative affect operate partially independently in this context. Findings are consistent with prior work which has found that disruptive behavior and mood disorder symptoms in childhood are risk factors for depression and suicidality in adolescence (Chronis-Tuscano et al., 2010). Dysregulation of negative affect may increase risk for developing comorbid disruptive behavior and mood disorders, which in turn increases risk of suicidality. Alternatively, negative affect may be the underlying feature increasing risk for a multitude of negative outcomes, including both comorbid disorders and suicidality. Regardless, negative affect and comorbid disruptive behavior symptoms appear to provide important but overlapping information about risk for suicidal ideation in ADHD, while working memory plays a distinct role in predicting suicidal ideation. Taken together, results indicate that working memory deficits may be an important early risk factor for both negative affect and suicidal ideation, and a possible target for early prevention and early intervention efforts in addition to reducing negative affect and treating comorbid disruptive behavior disorders.

Although the serial mediation path in which impaired working memory mediates negative affect, which in turn mediates suicidal ideation was not significant, working memory did mediate increased negative affect. This finding is consistent with prior literature that has found strong associations between ADHD, executive functioning, and deficits in regulating negative affect (Bridgett, Oddi, Laake, Murdock, & Bachman, 2013; Jarrett, Wolff, Davis, Cowart, & Ollendick, 2016; Suchy, & Kraybill, 2010; Walcott & Landau, 2004; Williams, Schmeichel, Volokhov, & Demaree, 2008). While these data are cross sectional and cannot test causality, several causal sequences may account for working memory's relationship to negative affect and suicidal ideation. Working memory impairments may operate directly by reducing a child's ability to employ positive coping strategies. In particular, impairments in working memory may prevent an individual from quickly cognitively reappraising emotional experiences or clearing negative emotional information from memory, increasing their likelihood of experiencing negative affect (Hofman et al., 2011; Gross & Thompson, 2007; Bridgett et al., 2013). This would be consistent with a diathesis-stress model in which lower working memory creates increased vulnerability to stress and increases the likelihood that a child will experience suicidal ideation. Alternatively, working memory impairments may contribute to cascading long-term effects (e.g. social difficulties, poor school performance) that contribute to increased negative affect and suicidal ideation over time (Barkley, 1997; Murray-Close et al., 2010).

Response inhibition was not related to negative affect or suicidal ideation in the current study. Although some prior work has found a relationship between response inhibition and

negative affect, it is most strongly associated with the expression (rather than the internal experience) of negative emotions. Thus, less impulsive individuals may only *express* less negative affect but not actually differ in their experiences of negative emotions (Carlson & Wang, 2007). Current results are consistent with prior research, which has not consistently found relationships between response inhibition and suicidality, although prior work has focused primarily on suicidal behavior rather than ideation (Fikke, Melinder, & Landrø, N. I., 2011; Gvion & Apter, 2011; Hull-Blanks, Kerr, & Kurpius, 2004; Maser et al., 2002; Williams, Davidson, & Montgomery, 1980). Although impulsivity may increase an individual's probability that they experience more painful and provocative events, thereby leading to greater capability to attempt a lethal or near lethal attempt, it may not be as important for developing suicidal ideation (Anestis, Soberay, Gutierrez, Hernández, & Joiner, 2014; Van Orden et al., 2010). In addition, although response inhibition as measured here is the most commonly investigated type of impulsivity in relation to suicidality and behaviors it reflects only one type or aspect of impulsivity. While the current work does not challenge suggestions that impulsivity is related to suicidal action, our results are consistent with the suggestion that the type of impulsivity reflected in response inhibition, does not fully explain suicidal behavior (Simon et al., 2002) and is not a core mechanism driving early risk factors, such as suicidal ideation. Follow up in the current sample as they reach adolescence and with additional measures of impulsivity (Dombrovski et al., 2011), may be useful for characterizing predictors of the transition from suicidal ideation to suicidal action. Further research is needed to determine an optimal measure of impulsivity as other constructs and methods may be more related to suicidality than others.

Limitations

These findings should be interpreted within the context of the limitations of the study. First, the cross-sectional nature of the current data limits our ability to make any causal conclusions. Although we offer directional interpretation of our findings based firmly in the scientific process of testing a theoretical claim from the literature (Kenny, 1979), alternative directional relationships are also mathematically equivalent and plausible. For example, although not as well articulated in theory, it could be that increasing negative affect impairs working memory, rather than working memory impairment leading to increases in negative affect. In addition, the lower-bound 95% CI estimates for several of the mediational effects were quite small, and fully explaining increased suicidal ideation in the ADHD population will require consideration of other cognitive and non-cognitive processes as well.

Second, for the current study, suicidal ideation was defined broadly to include both less severe ideation with no suicidal intent and more severe ideation with at least some suicidal intent (Silverman, Berman, Sanddal, O'Carroll, & Joiner, 2007). Both types of ideation are differentiated from more general thoughts about death or dying, which are not strongly related to suicide risk (Stoep, McCauley, Flynn, & Stone, 2009). Although some children who endorsed suicidal ideation will not go on to develop serious ideation or intent, this window of time covering the possible transition between passive ideation into serious ideation with intent, could be a crucial period for preventative efforts that promote resiliency and have long-lasting protective effects. Future studies with detailed assessments of suicidal

ideation severity and intent will be important for fully understanding the development of suicidality in children and adolescents.

The current sample was community-recruited, thereby capturing a full spectrum of ADHD symptom severity and comorbid disorders, which increases the generalizability of results. However, consistent with known gender differences in rates of ADHD diagnosis, this recruitment method also resulted in more boys than girls in the ADHD group. The latest report on suicide deaths found that females ages 10-14 had the greatest increase (200%) of any group over the last fifteen years (CDC, 2016). In the current sample, sex was not related to likelihood of suicidal ideation and models did not differ when sex was included as a covariate. While rates of childhood mood disorders are similar in preadolescents, during adolescence the prevalence of depression in girls becomes double that in boys (Nolen-Hoeksema & Girgus, 1994). As this sample reaches adolescence, additional analyses to address mechanisms contributing to these divergent courses will be informative.

We also excluded children who had a current major depressive episode at baseline, in part, because of the well-documented effects on cognitive task performance that would preclude getting accurate estimates of children's cognitive abilities. This may have resulted in somewhat more severe cases being screened out of the study, but contributes to our ability to draw conclusions about the role of working memory and negative affect independent of other comorbid mood problems.

Several caveats related to our cognitive measures are also important. SSRT, our measure of response inhibition, relies on subtraction methods ($SSRT = MRT - SSD$), which can reduce measurement reliability. While this is a widely-used and well-validated approach (see discussion of multiple considerations by White, Servant, & Logan, 2017) that allows estimation of inhibition separate from speed of processing, other approaches or measures may also be informative. Working memory is viewed differently by different theorists. One model suggests that it has different components, including the ability to hold multiple things in mind at once (maintenance), as well as to mentally manipulating one or more items (updating) (Baddeley, 2012). Other models suggest that there is short term memory and executive attention (Kane, Bleckley, Conway, & Engle, 2001) and more recently that executive attention may comprise the core element of both putative short term and complex working memory tasks (Unsworth & Engle, 2007). Our working memory latent variable includes measures of both maintenance/short-term memory and updating/executive attention working memory functions (Schmiedek, Hildebrandt, Lövdén, Wilhelm, & Lindenberger, 2009), but it more heavily emphasizes maintenance tasks. In addition, while verbal and non-verbal working memory share considerable overlap, they are partially distinct, and our latent variable combines both verbal and non-verbal tasks. In the current context, both verbal working memory and the updating function (or more executive aspects of working memory) may be particularly important. Although we detect mediational effects, it will be important for future work to include additional verbal working memory measures and additional tasks that directly tap updating/central executive processes.

Conclusion

Although increased suicidal ideation and suicide risk are previously documented in ADHD, relatively few studies have focused on the specific mechanisms accounting for this increased risk. The current finding replicates the basic association and highlights the importance of considering working memory as an early marker of risk for negative affect and suicidality. There is growing interest in developing non-pharmacological interventions to improve working memory (Holmes et al., 2010; Melby-Lervåg & Hulme, 2013), as well as clarifying the effects of stimulant medications on both negative affect and working memory performance (Bedard, Jain, Johnson, & Tannock, 2007). The current work suggests that treatments that mitigate working memory impairments in ADHD may have downstream positive effects on negative affect and more serious adverse outcomes including suicidal ideation. Identifying early predictors is critical for prevention and early intervention to reduce suicide risk in ADHD.

Acknowledgments

We thank Elisabeth Nousen and Andrew Bontemps with data collection and preparation. We gratefully acknowledge the participants and their caregivers, as well as the graduate students, staff, and research assistants whose remarkable dedication has made this research possible.

Funding: This work was supported by NIMH R37-59105 (PI: Nigg)

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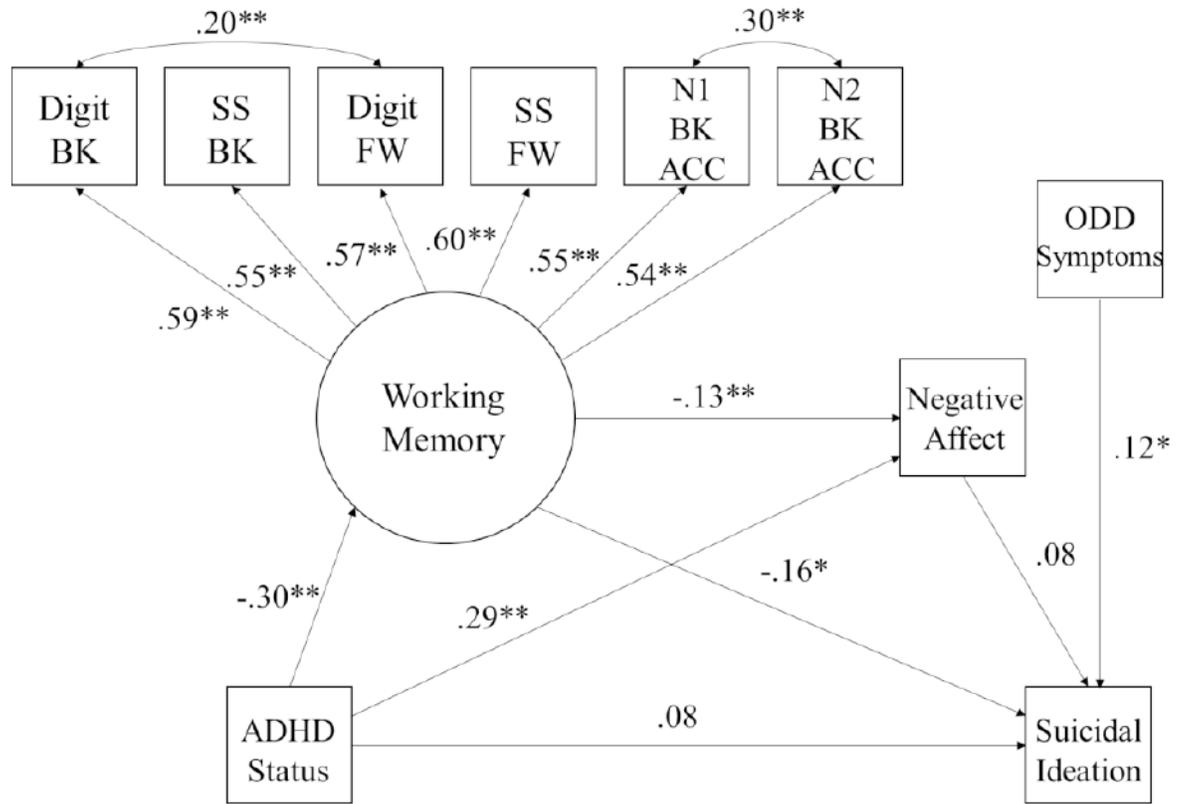


Figure 1. Serial Mediation Model Using Working Memory as Executive Functioning Task depicts the serial mediation model relating ADHD status to suicidal ideation, through working memory and negative affect, controlling for child ODD symptoms, $\chi^2(29) = 81.91$, $p = .00$, CFI = .93, RMSEA = .05. As reported in Table 3, the indirect effect of ADHD status on suicidal ideation through working memory was significant (ADHD→WM→SI), $\beta = .048$, $p = .049$ (95% CI = .001, .096). Additionally, working memory mediates the effect of ADHD on negative affect (ADHD→WM→NA), $\beta = .040$, $p = .013$ (95% CI = .008, .072). After accounting for indirect effects, the direct effect of ADHD on suicidal ideation was not significant, $\beta = .084$, $p = .206$ (in contrast to the significant main effect when these mediators were not included in the model, $\beta = .195$, $p = .001$). ** $p < .01$, * $p < .05$.

Table 1

Sample characteristics.

	<i>Control</i>	<i>ADHD</i>	<i>p-value^a</i>	<i>Effect Size (d)</i>
<i>Basic Demographics</i>				
N	235	388		
(Boys:Girls)	119:116	267:121	<.01	---
Full Scale IQ	115.63 (12.21)	108.32 (14.24)	<.01	0.55
Annual Family Income	< \$100,000	< \$75,000	<.01	0.26
Race (% identifying as Hispanic or Non-White)	13%	18%	.12	---
Age	8.93 (1.47)	9.34 (1.51)	.17	0.28
% on Stimulant Medications	---	42%	<.01	---
Current Mood Disorder (% of group)	0%	1%	.16	---
Anxiety Disorder (% group)	8%	20%	<.01	---
ODD (% of group)	1%	19%	<.01	---
Lifetime Mood Disorder (% of group)	1%	7%	<.01	---
Conduct Disorder	0%	2%	.09	---
Suicidal Thoughts	18%	37%	<.01	---
CDI T-Score	43.6 (6.8)	49.6 (9.6)	<.01	0.72
ADHD-RS T-Score (Parent)	44.2 (6.8)	71.3 (13.0)	<.01	2.62
ADHD-RS T-Score (Teacher)	42.0 (3.0)	57.2 (8.3)	<.01	2.44
Negative Affect (TMCQ)	2.3 (.49)	2.8 (.56)	<.01	0.84
<i>Executive Functioning Tasks</i>				
Working Memory Maintenance Factor Score	.41 (1.2)	-.25 (1.3)	<.01	0.53
Stop Signal Task	243.3 (76.6)	279.3 (110.7)	<.01	0.38
Digit Span Backward Accuracy	6.9 (1.9)	6.3 (1.8)	<.01	0.28
Digit Span Forward Accuracy	8.5 (2.0)	7.7 (2.0)	<.01	0.41
Spatial Span Backward	7.9 (2.5)	7.0 (2.6)	<.01	0.34
Spatial Span Forward	8.9 (2.5)	7.7 (2.4)	<.01	0.46
N-back 1 Accuracy	.77 (.23)	.69 (.26)	<.01	0.33
N-back 2 Accuracy	.47 (.27)	.40 (.24)	<.01	0.27

Note. FSIQ = Full Scale Intelligence Quotient; ADHD-RS = Attention Deficit/Hyperactivity Disorder Rating Scale; CDI = Children Depression Inventory; ODD = Oppositional Defiance Disorder. Median annual income reported.

^a χ^2 test for gender and race, Fisher's Exact Test for disorders, Mann-Whitney U for annual family income, and two-tailed independent sample *t* tests for all others.

Table 2

Correlations for executive functioning variables and negative affect

Variables	1	2	3	4
1 Negative Affect	-			
2 Working Memory Maintenance Factor Score	-.18**	-		
3 Response Inhibition	.03	-.06	-	
4 Suicidal Ideation	.13**	-.12**	-.02	-

Note. Numbers represent Pearson's correlation coefficient;

**
 $p < 0.01$

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Table 3

Path Coefficients from Working Memory and Response Inhibition Serial Meditational Models

Path	Direct Effect		Indirect Effect	
	Standardized	Unstandardized	Standardized	Unstandardized
<i>Working Memory</i>				
ADHD→WM	-.30 ^{***}	-.95 ^{***}		
ADHD→NA	.29 ^{***}	.32 ^{***}		
WM→SI	-.16 [*]	-.11 [*]		
NA→SI	.08	.16		
ADHD→SI	.08	.18		
WM→NA	-.13 ^{**}	-.05 ^{**}		
ODD→SI	.12 [*]	.38 [*]		
ADHD→WM→SI			.05 [*]	.10 [*]
ADHD→NA→SI			.02	.05
ADHD→WM→NA			.04 [*]	.05 [*]
ADHD→WM→NA→SI			.00	.01
<i>Response Inhibition</i>				
ADHD→SSRT	.19 ^{***}	39.2 ^{***}		
ADHD→NA	.33 ^{***}	.38 ^{***}		
SSRT→SI	.01	.00		
NA→SI	.11 ⁺	.20 ⁺		
ADHD→SI	.12 ⁺	.26 ⁺		
SSRT→NA	-.03	.00		
ODD→SI	.12 [*]	.38 [*]		
ADHD→SSRT→SI			.00	.00
ADHD→NA→SI			.07 ⁺	.04 ⁺
ADHD→SSRT→NA→SI			.00	.00

Note.⁺ $p < .08$,^{*} $p < .05$,^{**} $p < .01$,^{***} $p < .001$.

ADHD = attention deficit/hyperactivity disorder; WMM= working memory maintenance; SSRT = stop signal reaction time; NA = negative affect; SI = suicidal ideation; ODD = comorbid oppositional defiant disorder (yes/no). Results reported are for the full model including covariates.