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Behavioral Activation Sensitivity and Default Mode Network-Subgenual Cingulate Cortex Connectivity in Youth

Allesandra S. Iadipaolo^a, Hilary A. Marusak^a, Kelsey Sala-Hamrick^b, Laura M. Crespo^b, Moriah E. Thomason^{c,d,e}, and Christine A. Rabinak^{a,f,g,h}

^aDepartment of Pharmacy Practice, Wayne State University, Detroit, Michigan

^bDepartment of Psychology, Wayne State University, Detroit, Michigan

^cDepartment of Pediatrics, Wayne State University, Detroit, Michigan

^dDepartment of Merrill Palmer Skillman Institute, Wayne State University, Detroit, Michigan

^ePerinatology Research Branch, National Institutes of Health

^fDepartment of Pharmaceutical Sciences, Wayne State University, Detroit, Michigan

^gDepartment of Psychiatry & Behavioral Neurosciences, Wayne State University, Detroit, Michigan

^hDepartment of Translational Neuroscience Program, Wayne State University, Detroit, Michigan

Abstract

Increased resting-state functional connectivity (rsFC) between the default mode network (DMN) and subgenual anterior cingulate cortex (sgACC) is consistently reported in adults and youth with psychopathologies related to affect dysregulation (e.g. depression, posttraumatic stress disorder). This pattern of increased rsFC is thought to underlie ruminative thought patterns through integration of negative affect (via sgACC) into self-referential operations supported by the DMN. Neurobiological studies in adults show that behavioral activation system (BAS) sensitivity is a potential protective factor against the development of psychopathology, particularly in the context of stress and trauma exposure. However, whether BAS sensitivity is associated with variation in DMN-sgACC stress-vulnerability circuitry in youth, particularly those at risk for affect dysregulation, has not yet been studied. This association was tested in a sample of ninety-eight children and adolescents (ages 6–17) at high sociodemographic risk for psychopathology (i.e., urban, lower income, high frequency of violence and abuse exposure). Participants underwent a six-minute resting-state functional magnetic resonance imaging scan. Using a targeted, small-volume corrected approach, we found that youth with higher BAS sensitivity demonstrated lower DMN-sgACC rsFC, suggesting a potential link between the purported protective effects of BAS

Corresponding Author: Christine A. Rabinak, PhD, Assistant Professor, Pharmacy Practice, Pharmaceutical Sciences, Psychiatry & Behavioral Neurosciences, Translational Neuroscience Graduate Program, Wayne State University, 259 Mack Avenue, Detroit, MI 48201, (313) 577-9875, rabinak@wayne.edu.

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sensitivity and stress-vulnerability circuitry. This work suggests that interventions that augment BAS sensitivity, such as behavioral activation therapy, may protect against the development of stress-related psychopathology by modifying a critical rumination circuitry in the brain. Such interventions may be especially important for bolstering resiliency in at-risk urban youth, who are disproportionately burdened by early stress and associated psychopathology.

Keywords

fMRI; resting-state; early stress; adolescents; children; resiliency

1. Introduction

Roughly one out of five children and adolescents [youth] in the U.S. are living below the poverty line [1] and over half of all youth report being exposed to one or more types of violence or abuse [2]. These negative early experiences constitute a significant risk factor for the development of psychopathologies related to affect dysregulation [e.g., mood disorders; 3, 4]. Fortunately, not every youth who experiences early stressful life events will go on to develop psychopathology [5]. In fact, only as many as 44% and 32% with a history of early stress exposure have been reported to develop childhood-onset and later-onset psychopathology, respectively [6–8]. Why is it, then, that some youth develop psychopathology while others maintain psychological well-being into adulthood, even when both have similar exposure histories? This particular question has motivated the fields of developmental neuroscience and biological psychiatry to identify potential factors that may increase a child's risk for, as well as protect against, the development of psychopathology following exposure to early stress [9–11].

Rumination is a well-established risk factor for emotional psychopathology in adults and in youth [12–14]. Rumination is the tendency to repetitively think about the causes and consequences of one's distressing symptoms, as opposed to its solutions [15] and is a symptom frequently observed in individuals suffering from depressive disorders [16, 17]. Exposure to stressful life events during development has been associated with higher levels of rumination and was recently reported to mediate the longitudinal association between early stress exposure and increases in depressive and anxious symptomology among adolescents and adults [18]. In line with these findings, neuroimaging studies have identified functional alterations in the neural circuitry underlying rumination in adults and youth with depressive disorders [19–21]. In particular, patients with depressive disorders have increased resting-state functional connectivity (rsFC) between the default mode network (DMN) and subgenual anterior cingulate cortex [sgACC; 22, 23]. This pattern of rsFC may reflect ruminative thought patterns through integration of negative affect (via sgACC) into self-referential operations supported by the DMN [22]. Prior research suggests that sgACC-DMN rsFC increases from childhood to young adulthood [24, 25] and heightened DMN-sgACC rsFC is associated with depressive disorder severity as well increased levels of rumination from adolescence to adulthood [26, 27]. Further, heightened DMN-sgACC rsFC is predictive of treatment response [28], highlighting the relevance of this system for clinical and preventive interventions.

Like rumination, sensitivity of the behavioral activation system (BAS), which regulates motivated and approach behavior, reward-seeking, and positive affect [29], has also been associated with depressive disorders, but, unlike rumination, may be protective against psychopathology [30]. For instance, onset and severity of depressive symptoms following early stress are often predicted by low BAS sensitivity [31], whereas higher BAS sensitivity in youth has been associated with decreased risk for psychopathology following stressful life events [32–36]. Youth with increased BAS sensitivity report less negative affect and depressive symptoms [37], which may reflect a better ability to disengage from negative mood states and ruminative thought [18, 38].

Given that the neural circuitry underlying rumination (i.e., DMN-sgACC) is altered in individuals with depressive disorders and higher BAS sensitivity is associated with lower rumination [39], a key unanswered question is whether higher BAS sensitivity is associated with lower (i.e., more normalized) DMN-sgACC rsFC. The purported protective effects of BAS sensitivity against the development of mood disorders may be associated with alterations in this circuitry. A possible link between DMN-sgACC circuitry and BAS sensitivity in youth, in particular, is critical given that affective disorders frequently begin during childhood and adolescence [40]. Identification of early potential neurobiological protective factors may provide novel mechanistic targets for interventions capable of circumventing the onset of psychopathology in at-risk youth.

Here, we tested whether BAS sensitivity affects DMN-sgACC rsFC. Importantly, we tested this prediction in a sample of youth at high risk (i.e., lower income, high incidence of violence and abuse exposure) for the development of stress-related affective disorders [3, 4]. Based on prior studies showing heightened DMN-sgACC rsFC [22, 23] and reduced BAS sensitivity [31, 41] in individuals with depressive/affective disorders, we predicted that higher BAS sensitivity would correspond with *lower* DMN-sgACC rsFC. We tested for specificity of effects to BAS sensitivity by also evaluating effects of anxiety and depressive symptomology, and environmental risk factors (i.e., violence/abuse exposure, community distress, and household income) on DMN-sgACC circuitry.

2. Materials and Methods

2.1 Participants

This study reports on ninety-eight youth (aged 6–17 years, 90% right-handed via parent report) recruited from Detroit, Michigan and the surrounding metro area. Participant demographics and characteristics are provided in Table 1. Parent-child dyads were recruited via community advertisements and local mental health clinics. Families were compensated for their time. All procedures were approved by the Wayne State University Institutional Review Board. All parent and youth participants completed informed consent and/or assent, respectively.

A relatively wide age range was included to examine neural correlates of BAS sensitivity prior to and during adolescence, a critical developmental period that is considered to be high risk for the development of depressive symptomology [40]. Thus, we additionally tested for

effects of age on neural correlates of BAS sensitivity, which may shed new light on developmental changes in protective factors and/or periods of sensitivity for intervention.

Given inherent differences in comprehension ability across the wide age range, participants were assisted by research staff in completing all self-report measures. Specifically, research staff read questions aloud to the participants, provided explanation and clarification when necessary, and made sure younger children understood the questions.

2.2 Inclusion/exclusion criteria

Eligible participants were native English speakers and free of magnetic resonance imaging (MRI) contraindications. Youth with past or present pervasive developmental, neurological, or physical disorder which could affect brain functioning were excluded. Youth were not excluded on the basis of medication use, but medication use was noted and tested as a potential confounding factor. Six participants reported taking psychotropic medications: amphetamine ($n = 2$), atomoxetine ($n = 1$), somatropin injection ($n = 1$), diazepam ($n = 1$), melatonin ($n = 1$), selective serotonin reuptake inhibitor ($n = 2$), and levothyroxine ($n = 1$). Follow-up analyses excluding these six participants yielded no changes to results.

2.3 Pubertal maturation and intelligence

In addition to reporting their age, participants also provided self-reports of pubertal maturation using the Tanner Scale [42]. The Tanner Scale measures physical development based on reported appearance of primary and secondary sex characteristics. In this sample, 53.7% of participants were characterized as ‘early-to-mid’ pubertal (Tanner stages 1 or 2), and 46.3% were ‘mid-to-late’ pubertal (Tanner stages 3, 4, or 5).

Intelligence quotient (IQ) was estimated using the Kaufman Brief Intelligence Test [KBIT-2; 43]. Overall, the sample had an ‘average’ IQ (see Table 1).

2.4 Behavioral activation system sensitivity

BAS sensitivity was assessed using the Behavioral Inhibition and Activation Scales [BIS/BAS; 44], which has been validated and widely used in youth as young as 6 years old [37, 45–47]. Following prior work, BAS sensitivity was computed as the total sum score of BAS items (Cronbach’s α 0.79), covering a range of reward and motivated behaviors, e.g., drive, fun seeking, reward responsiveness [48, 49]. Participants rated each statement on a 1–4 scale (1= very false for me, 4= very true for me). Sample items include: *When good things happen to me, it affects me strongly; when I’m doing well at something, I love to keep at it; when I get something I want, I feel excited and energized*. Higher scores indicate higher BAS sensitivity. In our sample, the average of the three BAS sub-scales ($M=13.41$, $SD=1.71$) was similar to previous findings in a sample of 284 children between the ages of 8 and 12 [$M=16.85$, $SD= 6.39$, 50].

2.5 Anxiety and depressive symptomology

Anxiety and depressive symptomology was measured using the self-report 41-item Screen for Child Anxiety Related Emotional Disorders [SCR-Child; 51] and the 10-item Children’s Depression Inventory Short Form [CDI-S; 52], respectively. Of note, this version of the CDI

captures symptoms of depression related to negative affect, rather than positive affect (e.g., anhedonia, reward sensitivity).

2.6 Trauma exposure

Based on parent and/or child endorsements, participants who experienced at least one trauma indicated on the Children's Trauma Assessment Center Screen Checklist were classified as "trauma-exposed" ($n=43$; see Table 1). "Trauma" was defined here as threats to safety (e.g., abuse, violence exposure) and deprivation (e.g., neglect), distinct but central trauma types [8]. Three checklist items were excluded to narrow trauma to these types: (i) exposure to drug activity, (ii) parental/caregiver drug use/substance abuse, and (iii) frequent and multiple moves or homelessness. Of the trauma-exposed participants (44%), nearly 56% endorsed exposure to more than one trauma type (see Table 1).

2.7 Imaging data acquisition

MRI data were acquired using a 3.0 T Siemens MAGNETOM Verio scanner (MRI Research Facility, Wayne State University School of Medicine). After having completed all questionnaires, participants completed a 6-minute resting-state scan, during which they were instructed to lay awake with their eyes closed. For most participants (64%), the resting-state scan occurred mid-way through (13–23 minutes after start) the total scan time (<60 minutes), following non-emotional reversal learning and response inhibition tasks. For the remaining participants (36%), the resting-state scan occurred at the very end of the fMRI session. Foam padding was used to minimize motion. Data were combined across two functional magnetic resonance imaging (fMRI) sequences to achieve a larger sample size. Seventy-five participants underwent the following fMRI sequence: 180 volumes, repetition time [TR] = 2000 ms; echo time [TE] = 25 ms; flip angle = 90° ; voxel size = $3.44 \times 3.44 \times 4$ mm; matrix = 220×220 and 29 slices. The remaining 23 participants underwent the following fMRI sequence: 240 volumes, repetition time [TR] = 1500 ms; echo time [TE] = 31 ms; flip angle = 83° ; voxel size = $2.9 \times 2.9 \times 2.9$ mm; matrix = 186×186 and 51 slices. To correct for potential influence of sequence differences, parameters (i.e., repetition time [TR]) were accounted for when computing functional connectivity values, and sequence was included as a nuisance variable in group level analyses. In an additional assessment, BAS sensitivity did not differ by sequence, $t(96) = 0.070$, $p = 0.944$ and no effects of sequence on DMN-sgACC connectivity were detected, $t(96) = 0.485$, $p = 0.630$. A high-resolution T1-weighted image was obtained for anatomical reference within the same imaging session.

2.8 Imaging data preprocessing

Image preprocessing was performed using SPM8 (Statistical Parametric Mapping; <http://www.fil.ion.ucl.ac.uk/spm/>). Images were slice-time corrected, realigned, spatially normalized to the Montreal Neurological Institute (MNI) template, and smoothed using a 6-mm Gaussian kernel. Maximum and mean framewise displacement (FD) across the scan were computed as measures of participant motion.

2.9 Resting-state functional connectivity analysis

Connectivity analyses were performed using the CONN fMRI functional connectivity toolbox (version 15.h; <http://www.nitrc.org/projects/conn>). Following prior studies of rsFC of the DMN in children [e.g., 53], resting-state fMRI volumes were submitted to seed-based connectivity analyses to assess connectivity of the DMN. First, seed time series data were extracted from a DMN mask comprised of three spheres (six mm radii) centered at Montreal Neurological Institute (MNI) coordinates of peak-valued loci (see Fig. 1, left). These coordinates were determined by group averaged independent components analysis of intrinsic functional networks identified in an independent N= 65 pediatric sample [ages 6–17; 54]: Brodmann Area (BA) 29 (retrosplenial cortex; $x = 5, y = -53, z = 13$), BA 10 (anterior prefrontal cortex; $x = -2, y = 57, z = -18$), and BA 39 (angular gyrus; $x = 52, y = -63, z = 26$). Second, time series from this DMN mask was extracted for each participant, connectivity between the mask and the rest of the brain was computed using Pearson's r correlation. Third, r values were then transformed to Z -scores using Fisher's Z -transformation. The resulting DMN connectivity map for each participant was subsequently used for group-level analysis.

2.10 Mitigation of potential motion-related artifact

Several complementary approaches were implemented to decrease effects of motion on rsFC estimates: (1) functional image volumes were realigned to the mean, (2) realignment parameters were removed using covariate regression analysis before rsFC was computed, (3) signals from white matter and cerebral spinal fluid were removed using anatomical component correction [aCompCor; 55]. (4) Separate follow-up group analyses were repeated with the addition of maximum and mean FD as nuisance covariates. Results were consistent with main findings, and presented in the results section. (5) Of note, motion was relatively low across the sample (< 0.5 mm FD; see Table 1), and motion parameters were not associated with our variable of interest, BAS sensitivity, $r^2s < 0.11$, $p^2s > 0.29$.

2.11 Statistical analysis

Individual participant maps of DMN connectivity were then submitted to group-level regression analyses, to evaluate the association between BAS sensitivity and DMN connectivity with sgACC. In particular, we performed a regression analysis on individual participant DMN connectivity values in SPM8, with BAS sensitivity as the regressor of interest. In addition, BIS sensitivity, depressive symptoms, and anxiety were each entered as regressors of interest in separate analyses. Age and sequence were entered as nuisance regressors. Results were masked within non-overlapping left (604 voxels) and right (443 voxels) sgACC regions of interest (see Fig. 1, right), anatomically-defined via cytoarchitectonic probabilistic maps of BA 25 provided in the SPM Anatomy toolbox [56]. A small-volume family-wise error (FWE) corrected threshold of $pFWE < 0.05$ was applied. Results of complementary whole brain analyses are also examined, using a combined voxelwise threshold of $p < 0.001$ and a cluster threshold of > 407 voxels, determined by computing the spatial autocorrelation of the data via AFNI's 3dFWHMx and subsequently performing Monte Carlo simulations (10,000 iterations) using 3dClustSim (compile date July 22, 2016; https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). This

corrected whole brain threshold was also used to display DMN connectivity across the sample. All coordinates provided in this report are given in MNI convention.

3. Results

3.1 Demographic and self-report measures

Given that a majority of the participants resided in low-income households and in high-distress communities, the sample is considered to be high sociodemographic risk (see Table 1). Although diagnostic testing was not performed, 37% of participants exceeded thresholds suggested for detecting pathological anxiety [SCR > 22; 57], and 39% for depression [CDI-S 3; 58; see Table 1]. Additionally, 44% of participants reported experiencing one or more traumatic events (Table 1) and thus are considered at increased risk for depression and other psychopathology. We did not further dissociate trauma types here, given their high co-occurrence and that no participants endorsed experiencing only neglect. Supporting a link between early stress and psychopathology, trauma-exposed youth reported higher depressive symptoms than their unexposed counterparts, $t(96) = 2.26$, $p = 0.026$. BAS sensitivity was not related to anxiety or depressive symptoms, trauma exposure, community distress, or income, p 's > 0.2, suggesting unique distribution of BAS sensitivity. In addition, BAS sensitivity was not linearly or nonlinearly associated with age, p 's > 0.3, and did not differ between boys and girls, $t(96) = 0.93$, $p = 0.35$.

3.2 DMN connectivity across the sample

DMN connectivity across the sample was observed across regions of the medial prefrontal cortex, posterior cingulate cortex, precuneus, and lateral parietal cortex (see Fig. 2). This spatial network topology is consistent with prior research [24, 54].

3.3 Effects of BAS sensitivity on DMN-sgACC connectivity

Controlling, for age, youth reporting higher levels of BAS sensitivity demonstrated lower DMN connectivity with right sgACC ($x = 2$, $y = 8$, $z = -14$; $Z = 2.83$, 13 voxels, $pFWE = 0.033$; Fig. 3). Controlling for pubertal status in place of age, this result remained significant ($p = .012$). This effect also remained significant when additionally controlling for mean FD, $pFWE = 0.032$, and maximum FD, $pFWE = 0.031$. There was a similar effect of reduced DMN connectivity with left sgACC in youth with higher BAS sensitivity, but this effect did not reach significance ($x = -2$, $y = 10$, $z = -16$; $Z = 2.68$, 27 voxels, $pFWE = 0.054$). The effect on left sgACC became significant, $pFWE = 0.048$, or marginally significant, $pFWE = 0.05$, when controlling for mean FD, and maximum FD, respectively. DMN-sgACC connectivity was not related to depressive symptoms, anxiety symptoms, trauma exposure, community distress, or income, p 's > 0.1, suggesting unique effects of BAS sensitivity on this circuitry. Age was not associated with DMN connectivity with left, $t(98) = -0.029$, $p = 0.78$, or right sgACC, $t(98) = 0.034$, $p = 0.74$. Boys and girls did not differ in DMN connectivity with left, $t(96) = 0.33$, $p = 0.74$, or right sgACC, $t(96) = 0.27$, $p = 0.79$. Of note, BIS sensitivity, depressive, or anxiety measures had a significant effect on DMN-sgACC FC.

3.4 Whole-brain results

No results were significant at the corrected whole-brain threshold.

4. Discussion

In this study we tested the association of BAS sensitivity, a potential protective factor, on the integrity of a well-established stress vulnerability circuit of the brain (i.e., DMN-sgACC). Importantly, we tested this in a sociodemographic at-risk sample of youth, with a large number of low resource families living in high-distress communities, 57% reporting high levels of anxiety and/or depressive symptoms, and nearly half reporting violence and/or abuse exposure (see Table 1). We found that youth reporting higher BAS sensitivity demonstrated lower DMN-sgACC connectivity. This is consistent with studies in adults and emerging data in youth showing that *higher* DMN-sgACC connectivity is associated with depressive disorders and other conditions related to negative affect [22, 23]. In this sample, DMN-sgACC connectivity was not related to negative affect-related depressive symptoms, anxiety symptoms, trauma exposure, or socioeconomic factors, suggesting unique effects of BAS sensitivity on this circuitry. Our findings suggest that the purported protective role of BAS sensitivity against deleterious effects of early stress [32] may be due to its effects on this key stress-susceptibility circuitry in the brain.

Increased DMN-sgACC FC is implicated in stress-vulnerability as it is thought to be a neural substrate of depressive rumination [22]. This model predicts the integration of processes related to self-reference (DMN), negative affect, and behavioral withdrawal/inhibition (sgACC). Here, we found that higher BAS sensitivity was associated with *lower* DMN-sgACC rsFC in youth. Anxiety or negative-affect related depressive symptoms were not associated with DMN-sgACC circuitry here, which may suggest a relation to positive-affect related disruptions (i.e., BAS) rather than negative affect (e.g., depressed mood, sadness) in this at-risk sample. Although we did not measure ruminative thought here, BAS sensitivity may interfere with behavioral withdrawal or "turning inward," and thus protect against the onset of psychopathology. Indeed, prior research suggests that individuals who are more actively engaged with their environment (i.e., have higher BAS sensitivity) are less susceptible to rumination, which can be thought of as a loss of contact with the immediate environment [59]. These behavioral and psychological effects will be important to test in future research.

Recent conceptual models propose that BAS sensitivity mediates the link between stress and the development of psychopathology [32]. Our results build on these important models by suggesting that BAS sensitivity may influence DMN-sgACC stress vulnerability and rumination circuitry (see Fig. 4). BAS sensitivity may protect against abnormal increases in DMN-sgACC connectivity, thus reducing risk for the development of psychopathology, particularly in the context of stress. While we observed a link between trauma exposure and increased symptoms of depression in this cross-sectional study, BAS sensitivity was not related to stress exposure (i.e., income, community distress, trauma) or to symptomology. Links among BAS sensitivity, stress exposure, and onset of psychopathology are established in prior prospective studies [60], suggesting that potential mediating effects of BAS sensitivity, and/or associated DMN-sgACC rsFC may emerge over time, or later in life. For example, early stress may sensitize individuals to stress experienced in adulthood [61–63]. Additionally, these results may reflect more dynamic and active processes related to resiliency that may not be adequately captured by level of symptomology [64]. Nonetheless,

our results suggest a novel link between a protective factor (BAS sensitivity) and known stress-vulnerability circuitry (DMN-sgACC) in at-risk youth. These results generate at least two novel and testable predictions. First, youth showing lower BAS sensitivity and/or increased DMN-sgACC rsFC should demonstrate longitudinal increases in depressive symptomology. The second prediction is that preventive interventions focused on enhancing BAS sensitivity in youth, such as behavioral activation [65], should lead to reductions in DMN-sgACC rsFC. Other behavioral therapies thought to interfere with habitual depressive rumination might also be associated with changes in DMN-sgACC circuitry, for e.g., mindfulness-based interventions [66].

Limitations of this study warrant discussion. For instance, the use of a cross-sectional design precludes investigation into causation, for example, whether BAS sensitivity is protective against the development of psychopathology following early stress. In addition to a longitudinal design, future research may benefit from the addition of objective measures of BAS sensitivity, such as brain or behavioral response to reward, and evaluation of DMN-sgACC circuitry in the context of a rumination task. However, self-reported BAS sensitivity has been shown to correspond with changes in neural response to rewards over time in adolescence [67], and patterns observed in the resting-state predict individual differences during various tasks [68]. Next, dimensional models of early stress propose that threat (i.e., violence, abuse) and deprivation (i.e., neglect) have different effects on brain development [8]. We did not dissociate trauma types here; given their high co-occurrence and that no participants endorsed experiencing only neglect. Future studies including more discrete experiences of neglect [e.g., institutionalization; 69] should be better able to dissociate these.

5. Conclusion

These data provide new evidence that BAS sensitivity in youth may protect against the development of stress-related psychopathology by interfering with a key stress vulnerability circuitry in the brain [i.e., DMN-sgACC; 22]. The link between BAS sensitivity and DMN-sgACC rsFC is worth further investigating as a psychobiological mechanism of resiliency in the context of early stress. Our work also suggests a potential role for interventions that bolster BAS sensitivity, such as behavioral activation therapy, in protecting against the development of psychopathology by modifying DMN-sgACC circuitry. Although this remains to be tested in youth, research on other interventions in adults show initial promise. For example, transcranial magnetic stimulation (TMS) of the dorsolateral prefrontal cortex attenuates increased DMN-sgACC connectivity in depressed adults [28]. In this work, the degree of DMN-sgACC connectivity at baseline was predictive of subsequent clinical improvement after TMS, suggesting that this circuitry may not only approximate risk but also predict treatment response. Advances in prevention and intervention strategies may be particularly critical for urban, socioeconomically disadvantaged youth, who are disproportionately burdened by stress and negative mental health outcomes [4, 70].

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References

1. DeNavas-Walt, C., Proctor, BD. Income and Poverty in the United States: 2014. Washington, DC: US Census Bureau; 2015. Current Population Reports P60-252
2. Finkelhor D, Turner HA, Shattuck A, Hamby SL. Violence, crime, and abuse exposure in a national sample of children and youth: An update. *JAMA Pediatrics*. 2013; 167(7):614–621. [PubMed: 23700186]
3. Kaufman J, Plotsky PM, Nemeroff CB, Charney DS. Effects of early adverse experiences on brain structure and function: clinical implications. *Biological Psychiatry*. 2000; 48(8):778–790. [PubMed: 11063974]
4. Cutrona CE, Wallace G, Wesner KA. Neighborhood Characteristics and Depression: An Examination of Stress Processes. *Current Directions in Psychological Science*. 2006; 15(4):188–192. [PubMed: 18185846]
5. Merikangas KR, Nakamura EF, Kessler RC. Epidemiology of mental disorders in children and adolescents. *Dialogues in Clinical Neuroscience*. 2009; 11(1):7–20. [PubMed: 19432384]
6. Green J, McLaughlin KA, Berglund PA, et al. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication i: Associations with first onset of dsm-iv disorders. *Archives of General Psychiatry*. 2010; 67(2):113–123. [PubMed: 20124111]
7. Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Aguilar-Gaxiola S, Alhamzawi AO, Alonso J, Angermeyer M, Benjet C, Bromet E, Chatterji S, Girolamo Gde, Demyttenaere K, Fayyad J, Florescu S, Gal G, Gureje O, Haro JM, Hu C-y, Karam EG, Kawakami N, Lee S, Lépine J-P, Ormel J, Posada-Villa J, Sagar R, Tsang A, Üstün TB, Vassilev S, Viana MC, Williams DR. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *The British Journal of Psychiatry*. 2010; 197(5):378. [PubMed: 21037215]
8. McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood adversities and first onset of psychiatric disorders in a national sample of adolescents. *Archives of general psychiatry*. 2012; 69(11):1151–1160. [PubMed: 23117636]
9. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry*. 2001; 49(12):1023–1039. [PubMed: 11430844]
10. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience & Biobehavioral Reviews*. 2003; 27(1–2):33–44. [PubMed: 12732221]
11. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. 2009; 10(6):434–445. [PubMed: 19401723]
12. Broderick PC, Korteland C. A Prospective Study of Rumination and Depression in Early Adolescence. *Clinical Child Psychology and Psychiatry*. 2004; 9(3):383–394.
13. Abela JRZ. Rumination as a vulnerability factor to depression during the transition from early to middle adolescence: A multiwave longitudinal study. *Journal of abnormal psychology*. 2011; 120(2):259–271. 1965. [PubMed: 21553940]
14. Bijttebier P, Raes F, Vasey MW, Feldman GC. Responses to Positive Affect Predict Mood Symptoms in Children Under Conditions of Stress: A Prospective Study. *Journal of Abnormal Child Psychology*. 2012; 40(3):381–9. [PubMed: 21984180]
15. Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking rumination. *Perspectives on psychological science*. 2008; 3(5):400–424. [PubMed: 26158958]

16. Kuehner C, Weber I. Responses to depression in unipolar depressed patients: An investigation of Nolen-Hoeksema's response styles theory. *Psychological medicine*. 1999; 29(06):1323–1333. [PubMed: 10616938]
17. Joormann J, Gotlib IH. Emotion regulation in depression: Relation to cognitive inhibition. *Cognition and Emotion*. 2010; 24(2):281–298. [PubMed: 20300538]
18. Michl LC, McLaughlin KA, Shepherd K, Nolen-Hoeksema S. Rumination as a mechanism linking stressful life events to symptoms of depression and anxiety: Longitudinal evidence in early adolescents and adults. *Journal of Abnormal Psychology*. 2013; 122(2):339–352. [PubMed: 23713497]
19. de Kwaasteniet BP, Rive MM, Ruhé HG, Schene AH, Veltman DJ, Fellerling L, van Wingen GA, Denys D. Decreased Resting-State Connectivity between Neurocognitive Networks in Treatment Resistant Depression. *Frontiers in Psychiatry*. 2015; 6:28. [PubMed: 25784881]
20. Ho TC, Connolly CG, Henje Blom E, LeWinn KZ, Strigo IA, Paulus MP, Frank G, Max JE, Wu J, Chan M, Tapert SF, Simmons AN, Yang TT. Emotion-Dependent Functional Connectivity of the Default Mode Network in Adolescent Depression. *Biological Psychiatry*. 2015; 78(9):635–646. [PubMed: 25483399]
21. Patriat R, Birn RM, Keding TJ, Herringa RJ. Default-Mode Network Abnormalities in Pediatric Posttraumatic Stress Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2016; 55(4):319–327. [PubMed: 27015723]
22. Hamilton JP, Farmer M, Fogelman P, Gotlib IH. Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. *Biological Psychiatry*. 2015; 78(4):224–230. [PubMed: 25861700]
23. Connolly CG, Wu J, Ho TC, Hoeft F, Wolkowitz O, Eisendrath S, Frank G, Hendren R, Max JE, Paulus MP, Tapert SF, Banerjee D, Simmons AN, Yang TT. Resting-State Functional Connectivity of Subgenual Anterior Cingulate Cortex in Depressed Adolescents. *Biological psychiatry*. 2013; 74(12):898–907. [PubMed: 23910949]
24. Supekar K, Uddin LQ, Prater K, Amin H, Greicius MD, Menon V. Development of functional and structural connectivity within the default mode network in young children. *NeuroImage*. 2010; 52(1):290–301. [PubMed: 20385244]
25. Kelly AC, Di Martino A, Uddin LQ, Shehzad Z, Gee DG, Reiss PT, Margulies DS, Castellanos FX, Milham MP. Development of anterior cingulate functional connectivity from late childhood to early adulthood. *Cerebral cortex*. 2009; 19(3):640–657. [PubMed: 18653667]
26. Davey C, Harrison B, Yücel M, Allen N. Regionally specific alterations in functional connectivity of the anterior cingulate cortex in major depressive disorder. *Psychological medicine*. 2012; 42(10):2071–2081. [PubMed: 22954259]
27. Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J. Depression, rumination and the default network. *Social cognitive and affective neuroscience*. 2010:nsq080.
28. Liston C, Chen AC, Zebly BD, Drysdale AT, Gordon R, Leuchter B, Voss HU, Casey BJ, Etkin A, Dubin MJ. Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression. *Biological Psychiatry*. 2014; 76(7):517–526. [PubMed: 24629537]
29. Gray, JA. *The psychology of fear and stress*, CUP Archive. 1987.
30. Martell, CR., Addis, ME., Jacobson, NS. *Depression in context: Strategies for guided action*. WW Norton & Co; 2001.
31. McFarland BR, Shankman SA, Tenke CE, Bruder GE, Klein DN. Behavioral activation system deficits predict the six-month course of depression. *Journal of Affective Disorders*. 2006; 91(2–3): 229–234. [PubMed: 16487598]
32. Auerbach RP, Admon R, Pizzagalli DA. Adolescent Depression: Stress and Reward Dysfunction. *Harvard review of psychiatry*. 2014; 22(3):139–148. [PubMed: 24704785]
33. Kasch KL. Behavioral activation and inhibition systems and the severity and course of depression. *Journal of abnormal psychology*. 2002; 111(4):589–597. 1965. [PubMed: 12428772]
34. Heponiemi T, Keltikangas-Järvinen L, Puttonen S, Ravaja N. BIS/BAS sensitivity and self-rated affects during experimentally induced stress. *Personality and Individual Differences*. 2003; 34(6): 943–957.

35. Campbell-Sills L, Liverant GI, Brown TA. Psychometric evaluation of the behavioral inhibition/behavioral activation scales in a large sample of outpatients with anxiety and mood disorders. *Psychol Assess.* 2004; 16(3):244–54. [PubMed: 15456380]
36. Telzer EH. Dopaminergic reward sensitivity can promote adolescent health: A new perspective on the mechanism of ventral striatum activation. *Developmental Cognitive Neuroscience.* 2016; 17:57–67. [PubMed: 26708774]
37. Coplan RJ, Wilson J, Frohlick SL, Zelenski J. A person-oriented analysis of behavioral inhibition and behavioral activation in children. *Personality and Individual Differences.* 2006; 41(5):917–927.
38. Gable SL. Behavioral activation and inhibition in everyday life. *Journal of personality and social psychology.* 2000; 78(6):1135–1149. [PubMed: 10870914]
39. McIndoo CC, File AA, Preddy T, Clark CG, Hopko DR. Mindfulness-based therapy and behavioral activation: A randomized controlled trial with depressed college students. *Behaviour Research and Therapy.* 2016; 77:118–128. [PubMed: 26745622]
40. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB. Age of onset of mental disorders: A review of recent literature. *Current opinion in psychiatry.* 2007; 20(4):359–364. [PubMed: 17551351]
41. Hundt NE, Nelson-Gray RO, Kimbrel NA, Mitchell JT, Kwapil TR. The interaction of reinforcement sensitivity and life events in the prediction of anhedonic depression and mixed anxiety-depression symptoms. *Personality and Individual Differences.* 2007; 43(5):1001–1012.
42. Marshall W, Tanner J. Growth and physiological development during adolescence. *Annual review of medicine.* 1968; 19(1):283–300.
43. Kaufmann, A. Kaufmann Brief Intelligence Scale, (KBIT-II). Los Angeles, CA: 2004.
44. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. *Journal of personality and social psychology.* 1994; 67(2):319.
45. Hamill SK, Scott WD, Dearing E, Pepper CM. Affective style and depressive symptoms in youth of a North American Plains tribe: The moderating roles of cultural identity, grade level, and behavioral inhibition. *Personality and Individual Differences.* 2009; 47(2):110–115.
46. Mellick W, Sharp C, Alfano C. The role of BIS/BAS in the vulnerability for depression in adolescent girls. *Personality and Individual Differences.* 2014; 69:17–21.
47. Yu R, Branje SJ, Keijsers L, Meeus WH. Psychometric characteristics of Carver and White's BIS/BAS scales in Dutch adolescents and their mothers. *Journal of personality. assessment.* 2011; 93(5):500–507.
48. Meyer B, Johnson SL, Winters R. Responsiveness to Threat and Incentive in Bipolar Disorder: Relations of the BIS/BAS Scales with Symptoms. *Journal of Psychopathology and Behavioral Assessment.* 2001; 23(3):133–143. [PubMed: 21765592]
49. Dunn EC, Nishimi K, Powers A, Bradley B. Is developmental timing of trauma exposure associated with depressive and post-traumatic stress disorder symptoms in adulthood? *Journal of Psychiatric Research.* 2017; 84:119–127. [PubMed: 27728852]
50. Muris P, Meesters C, de Kanter E, Timmerman PE. Behavioural inhibition and behavioural activation system scales for children: relationships with Eysenck's personality traits and psychopathological symptoms. *Personality and Individual Differences.* 2005; 38(4):831–841.
51. Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, Neer SM. The screen for child anxiety related emotional disorders (SCARED): scale construction and psychometric characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry.* 1997; 36(4):545–553. [PubMed: 9100430]
52. Kovacs, M., Preiss, M., CDI. Children's Depression Inventory Multi-Health Systems. New York: 1992.
53. Marusak HA, Etkin A, Thomason ME. Disrupted insula-based neural circuit organization and conflict interference in trauma-exposed youth. *NeuroImage Clinical.* 8(2015):516–25. [PubMed: 26199869]

54. Thomason ME, Dennis EL, Joshi AA, Joshi SH, Dinov ID, Chang C, Henry ML, Johnson RF, Thompson PM, Toga AW. Resting-state fMRI can reliably map neural networks in children. *Neuroimage*. 2011; 55(1):165–175. [PubMed: 21134471]
55. Behzadi Y, Restom K, Liao J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage*. 2007; 37(1):90–101. [PubMed: 17560126]
56. Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage*. 2005; 25(4):1325–1335. [PubMed: 15850749]
57. Desousa DA, Salum GA, Isolan LR, Manfro GG. Sensitivity and specificity of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a community-based study. *Child Psychiatry Hum Dev*. 2013; 44(3):391–9. [PubMed: 22961135]
58. Allgaier A-K, Frühe B, Pietsch K, Saravo B, Baethmann M, Schulte-Körne G. Is the Children's Depression Inventory Short version a valid screening tool in pediatric care? A comparison to its full-length version. *Journal of Psychosomatic Research*. 2012; 73(5):369–374. [PubMed: 23062811]
59. Buyck D. Depression in Context: Strategies for Guided Action. Primary care companion to the *Journal of clinical psychiatry*. 2002; 4(5):201.
60. Admon R, Lubin G, Rosenblatt JD, Stern O, Kahn I, Assaf M, Hendler T. Imbalanced neural responsivity to risk and reward indicates stress vulnerability in humans. *Cerebral cortex*. 2012:bhr369.
61. Hammen C. Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of consulting and clinical psychology*. 2000; 68(5):782–787. [PubMed: 11068964]
62. Dougherty LR. A Growth Curve Analysis of the Course of Dysthymic Disorder: The Effects of Chronic Stress and Moderation by Adverse Parent-Child Relationships and Family History. *Journal of consulting and clinical psychology*. 2004; 72(6):1012–1021. [PubMed: 15612848]
63. Kendler KS. Childhood sexual abuse, stressful life events and risk for major depression in women. *Psychological medicine*. 34(08):1475.
64. Charney DS. Psychobiological Mechanisms of Resilience and Vulnerability. *FOCUS*. 2004; 2(3): 368–391.
65. McCauley E, Schloedt K, Gudmundsen G, Martell C, Dimidjian S. Expanding behavioral activation to depressed adolescents: lessons learned in treatment development. *Cognitive and Behavioral Practice*. 2011; 18(3):371–383.
66. Segal, ZV., Williams, JMG., Teasdale, JD. *Mindfulness-based cognitive therapy for depression*. Guilford Press; 2012.
67. Braams BR, van Duijvenvoorde AC, Peper JS, Crone EA. Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. *Journal of Neuroscience*. 2015; 35(18):7226–7238. [PubMed: 25948271]
68. Tavor I, Jones OP, Mars R, Smith S, Behrens T, Jbabdi S. Task-free MRI predicts individual differences in brain activity during task performance. *Science*. 2016; 352(6282):216–220. [PubMed: 27124457]
69. Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, Casey BJ. Elevated amygdala response to faces following early deprivation. *Dev Sci*. 2011; 14(2):190–204. [PubMed: 21399712]
70. Deardorff J, Gonzales NA, Sandler IN. Control Beliefs as a Mediator of the Relation Between Stress and Depressive Symptoms Among Inner-City Adolescents. *Journal of Abnormal Child Psychology*. 2003; 31(2):205–217. [PubMed: 12735403]

Highlights

- Increased DMN-sgACC connectivity is consistently linked to affect dysregulation
- BAS sensitivity may protect against affective disorders in at-risk youth
- We found that BAS sensitivity predicts lower DMN-sgACC connectivity in youth
- Changes in DMN-sgACC circuitry may underlie protective effects of BAS sensitivity

Fig 1. DMN mask and sgACC region of interest

The DMN mask comprised of three seed regions that represent core nodes of the DMN identified in an independent sample of children pediatric sample [54]. The sgACC region of interest was defined using probabilistic cytoarchitectonic maps of Brodmann Area 25 (SPM Anatomy Toolbox). Abbreviations: DMN, default mode network; sgACC, subgenual anterior cingulate cortex; PFC, prefrontal cortex.

Fig 2. DMN connectivity across the sample

Displayed at the corrected whole brain threshold of $p < 0.001$, 407 voxels. Abbreviations: DMN, default mode network.

Fig 3. Effects of BAS sensitivity on DMN connectivity

Results significant using a small-volume family-wise error-corrected threshold within anatomically-defined sgACC, $p_{FWE} < 0.05$. Abbreviations: default mode network, DMN; behavioral activation system, BAS; subgenual anterior cingulate cortex, sgACC.

Fig 4. BAS sensitivity mediates the link between stress and psychopathology, [modified from ref 32]

Black lines: Prior research indicates increased DMN-sgACC connectivity in stress-related pathology [22], and that BAS mediates the link between stress exposure and development of psychopathology [32]. *Dashed lines:* These relationships are likely bidirectional, but have not been tested. BAS sensitivity may have an indirect effect on psychopathology by modifying how early stress impacts behavior. We add to this model (green and orange lines) by showing that BAS may protect against detrimental effects of stress (i.e. development of psychopathology) via its link to DMN-sgACC rumination circuitry in childhood and adolescence.

Table 1

Participant demographics and characteristics

	(N=98)	
	<i>M</i>	<i>SD</i>
Age (years)	11.27	2.73
Tanner Stage	2.83	1.36
KBIT-2 Score (IQ)	101.51	16.45
Movement during scan		
– Maximum FD	4.47	6.46
– Mean FD	0.48	0.66
BAS Sensitivity (sum score)	40.22	5.13
SCR total score	21.91	16.07
CDI-S score	2.62	3.1
	<i>N</i>	<i>%</i>
Gender (female)	61	62.2
Ethnicity (Hispanic/Latino)	2	2.0
Race		
– African American	31	31.6
– Caucasian	23	23.5
– More than one race	6	6.1
– Not reported	36	36.7
Household annual income		
– \$40,000 or less	49	50.0
– Above \$40,000	43	43.9
– Not reported		
Trauma type endorsed		
– Exposure to domestic violence	35	81.4
– Exposure to other violence	15	34.9
– Neglect	11	25.6
– Sexual abuse	10	23.3
– Physical abuse	4	9.3
– Emotional abuse	1	2.3
– More than one type	24	55.8
Community distress score		
– 0–20	26	26.5
– 20–40	8	8.2
– 40–60	16	16.3
– 60–80	8	8.2
– 80–100	40	40.8
SCR total score above threshold for detecting pathological anxiety	36	36.7
CDI-S score above threshold for detecting pathological depression	39	39.8

KBIT-2, Kaufman Brief Intelligence Test; IQ, Intelligence Quotient; FD, framewise displacement; BAS, Behavioral Activation System; SCR, Screen for Child Anxiety Related Emotional Disorders; CDI-S, Children's Depression Inventory Short Form; Tanner scale measures self-reported pubertal maturation [42]. The mean score (2.83) corresponds to the 'early-mid' pubertal stage. Community distress scores were derived from the Distressed Communities Index (<http://eig.org/dci>). Ranging from 0–100, high scores represent high economic distress.

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