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Correlates and Predictors of the Severity of Suicidal Ideation in Adolescence: An Examination of Brain Connectomics and Psychosocial Characteristics

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Abstract

Background: Suicidal ideation (SI) typically emerges during adolescence but is challenging to predict. Given the potentially lethal consequences of SI, it is important to identify neurobiological and psychosocial variables explaining severity of SI in adolescents.

Methods: In 106 participants (59 female) recruited from the community, we assessed psychosocial characteristics and obtained resting-state fMRI data in early adolescence (baseline: ages 9-13 years). Across 250 brain regions, we assessed local graph-theory based properties of interconnectedness: local efficiency, eigenvector centrality, nodal degree, within-module z-score, and participation coefficient. Four years later (follow-up: ages 13-19 years), participants self-reported their SI severity. We used least absolute shrinkage and selection operator (LASSO) regressions to identify a linear combination of psychosocial and brain-based variables that best explain severity of SI symptoms at follow-up. Nested-cross-validation yielded model performance statistics for all LASSO models.

Results: A combination of psychosocial and brain-based variables explained subsequent severity of SI (R^2=0.55); the strongest were internalizing and externalizing symptom severity at follow-up. Follow-up LASSO regressions of psychosocial-only and brain-based-only variables indicated that psychosocial-only variables explained 55% of the variance in SI severity; in contrast, brain-based-only variables performed worse than the null model.

Conclusions: A linear combination of baseline and follow-up psychosocial variables best explained severity of SI. Follow-up analyses indicated that graph-theory resting-state metrics did not increase the prediction of severity of SI in adolescents. Attending to internalizing and

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Supporting information

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

externalizing symptoms is important in early adolescence; resting-state connectivity properties other than local graph-theory metrics might yield a stronger prediction of the severity of SI.

Keywords

suicidal ideation; internalizing and externalizing symptoms; resting-state fMRI; graph theory; adolescence

Introduction

Suicide is the second-leading cause of death in adolescents, resulting in approximately 5,000 adolescent deaths annually in the United States (CDC, 2017). Further, rates of suicide among individuals ages 10-19 years have increased dramatically over the past decade in the United States (Ruch et al., 2019). Unfortunately, suicidal thoughts and behaviors (STBs) are difficult to characterize and predict (Miller & Prinstein, 2019). In individuals with psychiatric symptoms, prior STBs, depression, anxiety, and history of abuse are relatively weak predictors of suicidal ideation (SI) when considered in isolation, but, in combination, may explain significant variation in SI (Franklin et al., 2017). Certainly, it is important to study individuals who already have clinically relevant risk factors, such as mood disorders (Eisenlohr-Moul et al., 2018; Su et al., 2020); however, SI is also prevalent in nonclinical and subclinical samples of community youth. Because many community youth do not seek help for their suicidal thoughts due to stigma or ambivalence about intent to die (Prinstein, 2008), SI can go undetected (Hawton, Saunders, & O'Connor, 2012). Given that SI is often a precursor to suicidal behaviors (Klonsky, May, & Saffer, 2016; Turecki & Brent, 2016), it is critical that we identify factors that predict the severity of SI in order to reduce the risk of transitioning to suicidal behaviors, such as suicide attempts (SA). Examining biological characteristics may increase our prediction of SI in youth who may not yet have observable symptoms. Although the literature examining neural correlates of SI in adolescents is growing, it is still much sparser than is the literature with adults (Auerbach et al., 2020; Gifuni et al., 2020). Nevertheless, several investigators have used resting-state functional magnetic imaging (rs-fMRI) data to identify functional networks typically including the default mode network (DMN) – regions related to self-referential processing, including rumination (Menon, 2011) – associated with SI in youth. These researchers have found that depressed adolescents with a history of SI had lower within-network connectivity of the ventral DMN than did depressed adolescents without SI and healthy controls (Ho et al., 2021). Lower within-network connectivity of the DMN, the executive control network – regions associated with inhibitory control and decision-making (Cao et al., 2020; Menon, 2011; Uddin, 2015), and the salience network – regions that respond to emotionally salient stimuli (Seeley et al., 2007) – has been found to be associated with greater lifetime SI (Ordaz et al., 2018). Collectively, these findings suggest that disruptions in functional connections related to SI are widely distributed across the brain.

A different approach to examining rs-fMRI connectivity patterns involves the use of graph theoretical methods, in which the brain is represented as a network (i.e., graph) composed of nodes (brain regions) and edges (connections) (Bullmore & Sporns, 2009). Using this framework, researchers are able to characterize the functional and structural organization

of the whole brain on both global (network-wide) and local (nodal) levels (Rubinov & Sporns, 2010). Graph theory allows investigators to measure functional relations between nodes, even if they do not share direct anatomical projections (Honey et al., 2009). This approach allows researchers to quantify the organizational properties of specific regions in the context of the overall brain network, which may be informative for simultaneously identifying large-scale and local disruptions in network functioning that are associated with psychopathology (Bassett et al., 2008).

Several researchers have now used these methods to examine SI in adults. These studies have typically focused on differences between depressed adults with and without histories of SA (Stumps et al., 2020; Weng et al., 2019), and among ideating individuals with and without previous attempts and non-ideating individuals with depression (Kim et al., 2017). In relation to SI, these studies have found that connections of the thalamus and SFG with the rest of the brain are associated with severity of SI. In a study that aimed to differentiate SA from depression, Wagner et al. (2019) reported evidence of a possible association between SA and weaker connections among nodes across the brain and by reduced functional connectivity (FC) of the ventral and dorsal prefrontal cortex (PFC) (Wagner et al., 2019).

While these studies provide insight concerning neural organization in adults who are already engaging in harmful thoughts and behaviors, it is not clear whether similar rs-fMRI-based patterns of connectivity assessed in young adolescents without a history of attempt or SI can predict the severity of suicide-related difficulties years later. Moreover, few studies have examined the utility of combining these measures with psychological, environmental, and sociodemographic variables to predict SI. Addressing this gap in our knowledge is especially relevant for young adolescents. Given some research conceptualizes neurobiological factors and alterations in FC as “intermediate risk factors” along the spectrum of distal to proximal risk factors for psychological problems, including SI (Lengvenyte, Conejero, Courtet, & Olié, 2019; Miller & Prinstein, 2019; Auerbach et al., 2020) it is possible that brain-based factors strengthen the prediction of SI during a developmental period in which evidence of clinical disorders is not yet manifested at a behavioral level.

The primary goal of this study was to use graph theoretical methods to identify whether, and which, local properties of functional brain organization in combination with psychological, environmental, and sociodemographic characteristics in early adolescence (ages 9-13) are associated with the severity of self-reported SI in later adolescence (approximately 4 years later; ages 13-19). Importantly, we examined these associations in a sample recruited from the community, unselected for psychiatric disorders or suicidal history, and with no history of STBs in early adolescence. We used rs-fMRI data to compute graphic theoretical measures of the functional interconnectedness of brain regions, including efficiency, eigenvector centrality, nodal degree, within-module degree, and participation coefficient. Each of these metrics yields unique information about a region’s functional interconnectedness with the rest of the brain.

Even though psychological, environmental, and sociodemographic variables on their own are not strong predictors of SI, it is clear from previous research that SI is associated, separately, with the severity of internalizing symptoms (including symptoms

of depression and anxiety), externalizing symptoms (including impulsivity) (Hawton et al., 2012), environmental factors (history of adversity) (Duprey, Oshri, & Liu, 2020), and sociodemographic variables (e.g., sex, pubertal stage, race/ethnicity – particularly marginalized groups) (Baiden, LaBrenz, Asiedua-Baiden, & Muehlenkamp, 2020; Ortin & Miranda, 2020). Far fewer studies have identified neurobiological predictors of SI; thus, it is important that we examine the integrated contribution of neurobiological and psychosocial variables in predicting SI. To examine how psychological, environmental, sociodemographic variables, and exploratory brain-based variables (graph metrics computed across the whole brain) operate in concert to predict the subsequent severity of SI we used machine learning (ML) methods. While there are challenges in understanding the clinical utility of predictors identified using ML (Cox, Moscardini, Cohen, & Tucker, 2020) a key advantage of ML is that it can optimize model performance across a wide range of variables. Therefore, using a data-driven approach with selected variables that have a strong theoretical foundation in combination with exploratory predictors may increase power and precision in characterizing variability in psychopathology (Bzdok & Meyer-Lindenberg, 2018). In addition, a multimodal approach, where we use a combination of neurobiological and psychosocial variables, may maximize the utility and clinical impact of using ML methods (Hedderich & Eickhoff, 2020). Further, by using penalization methods in ML, the model complexity is reduced, leading to greater potential for generalizability of a model that parsimoniously explains the severity of future SI, which may help guide hypothesis-driven research.

Methods and Materials

Participant Recruitment

We recruited 225 participants (132 female) ages 9-13 years (M=11.41, SD=1.00) from the San Francisco Bay Area to participate in a longitudinal study assessing the effects of ELS on neurobiological development over puberty. Because participants were matched on pubertal status, boys were older than girls by an average of 8.31 months. Participants were recruited through print and online advertisements and were unselected for psychiatric disorders or suicidal history. Exclusion criteria included contraindications for MRI scan (e.g., metal implants, braces), history of major neurological disorder, intellectual delay, and non-fluent English speakers. For the current study, participants were excluded if they did not complete a functional resting-state or anatomical scan at baseline or withdrew from the study (N=24), or if their functional scan data included excessive signal dropout or banding (N=2) or movement defined by the following criteria: mean framewise displacement (FD)>2 SD above the mean FD or 20% of volumes>.25mm in FD (N=22), resulting in 177 participants. Two participants' data failed successful preprocessing, resulting in a final sample of 175 participants (104 females). At a follow-up session 3-5 years post-baseline (M=4.08 years), 159 participants were assessed for severity of SI, 31 of whom did not have usable scan data from baseline, 6 of whom had missing data on the SI measure, 7 of whom we excluded from this analysis based on parent and child-reported history of STBs at baseline, 2 of whom had missing parent and child reported history of STBs at baseline, and 7 of whom we excluded for missing data on whether they felt sleepy throughout the scan, resulting in a final sample of 106 participants (see Table 1 for participant characteristics and Table S1 for table of

medications taken at baseline). In accordance with the Declaration of Helsinki, participants and their parents provided informed written assent and consent, respectively. This study was approved by the Stanford University Institutional Review Board and all participants were compensated for their participation.

Psychological Characteristics

K-SADS-PL.—The Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL) is a semi-structured interview used to establish the presence of DSM-IV diagnoses (Kaufman et al., 1997). We asked three questions about STBs, involving recurrent thoughts about death, thoughts about ending their lives, and attempting to end their lives. These symptoms were rated as "not present," "subthreshold," or "threshold." Trained interviewers administered the K-SADS-PL to children and their parents at both timepoints. For the current study we examined child- and parent-reported information of lifetime and current substance/alcohol use and STBs given that these are risk factors for future STBs (King et al., 2019). As we reported above, we excluded 7 participants who had self-reported or informant-reported threshold levels of STBs at baseline. As expected, no participant endorsed substance or alcohol use at baseline.

Internalizing and Externalizing Symptom Severity.—Participants completed the Youth Self Report (YSR; Earls, Brooks-Gunn, Raudenbush, & Sampson, 2007) to assess internalizing and externalizing symptoms. The YSR was administered at baseline and follow-up had high internal consistency at baseline and follow-up for both internalizing and externalizing subscales (αs=.86-.90).

Suicidal Ideation.—To assess severity of SI, participants completed the Suicidal Ideation Questionnaire – Junior Form (SIQ-JR; Reynolds, 1988), a 15-item self-report measure of suicidal thoughts during the past month. We assessed SI severity at follow-up, when we expected SI to develop (Nock et al., 2013). Scores can range from 0-90, with higher scores indicating greater severity. The SIQ was administered had high internal consistency (Cronbach's α=.98).

Environmental and Sociodemographic Characteristics

ELS.—To assess history of ELS, adolescents were interviewed at baseline about exposure to different types of stressful experiences using a modified version of the Traumatic Events Screening Inventory for Children (Ribbe, 1996). We calculated an cumulative objective stress severity score by summing the maximum objective severity scores for each type of stressor endorsed by each adolescent; this method ensured that frequent but less severe events would not be overly weighted (King et al., 2017). We also calculated a stress sensitivity score that represents participants' cumulative subjective stress severity accounting for cumulative objective stress severity (Ho et al., 2017). See the Supporting Information Appendix S1-*"Early Life Stress Interview"* for information about the coding system.

Pubertal Status.—To assess pubertal status, participants rated their developmental stage using the Tanner Staging questionnaire (Marshall & Tanner, 1969, 1970; Morris & Udry, 1980) at baseline and follow-up. This questionnaire measures developmental status based on

schematic drawings of secondary sex characteristics (pubic hair and breast development for females, pubic hair and testicular development for males) on a scale from 1 (no pubertal development) to 5 (adult level of pubertal development). Within each time point, we averaged the two ratings of the secondary sex characteristics to yield a composite measure of the participants' pubertal status. Self-reported Tanner staging is correlated with physicians' physical examinations of pubertal development (Coleman & Coleman, 2002; Shirtcliff, Dahl, & Pollak, 2009), and with pubertal hormones in this sample (King et al., 2020). No participant endorsed taking hormonal contraception at baseline.

Parent Education.—As an index of socioeconomic status (SES), we assessed parental education at baseline. The parent accompanying the child indicated whether they received No GED / No High School Diploma, GED / High School Diploma, Some College, a 2-year College Degree, a 4-year College Degree, a Master's Degree, a Professional Degree (MD, JD, DDS, etc…), or a Doctorate. This was rated from 1 (No GED)–8 (Doctorate).

Brain-Based Characteristics

Sleepiness.—Because we instructed participants in the scanner to keep eyes closed but remain awake, it is possible that sleepiness could occur. At the end of the scan, participants reported whether they experienced sleepiness during the scan. Most (N=71) reported experiencing some feelings of sleepiness during the scan. Therefore, we examined sleepiness as a binary dummy-coded variable.

Global Signal.—We did not use the mean global signal from our resting-state data as a confound in our nuisance regression during postprocessing because we expected this would result in an inflation of negative FC values in our graph analysis. We did, however, include mean global signal as a variable in our regression analyses.

fMRI Acquisition and Preprocessing

MRI scans were conducted on a GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) equipped with a 32-channel head coil (Nova Medical). We collected spoiled gradient echo (SPGR) T1-weighted sagittal anatomical images (repetition time [TR]=6.24ms; echo time [TE]=2.34 ms; flip angle=12°; FOV=230 mm; voxel size=0.8984 x 0.8984 x 0.9000 mm; scan time=5:15). Resting-state BOLD fMRI data were acquired using aT2*-weighted echo planar imaging sequence with 37 axial slices (180 volumes, repetition time [TR]= 2.0 s; echo time [TE]=30 ms; flip angle=77°; FOV=224 mm; voxel size=3.2 mm^3, total scan time=6:00). Participants were instructed to keep their eyes closed but remain awake. The raw functional images were quality checked prior to preprocessing by JSK and RC. The rs-fMRI data we used to compute graph metrics are derived from preprocessing performed using *fMRIPrep* 20.2.1 (Esteban et al., 2019). Fieldmaps were applied if acquired and usable (rated by JSK and SMC). After quality-checking the difference in signal distortion between fieldmap application within participants (JSK and SMC), we repeated the analysis ignoring fieldmaps (see the Supporting Information Appendix S1-*"fMRI Acquisition, fMRI Preprocessing" for complete details*).

Network Construction

Parcellation.—To ensure sufficient spatial resolution (Craddock et al., 2012; Hallquist & Hillary, 2018), we used the Brainnetome Atlas (Fan et al., 2016) to parcellate each participant's preprocessed structural data into 246 ROIs, plus 4 additional subregions of the basal ganglia (Keuken & Forstmann, 2015). We computed and standardized (via Fisher-z transform) the Pearson's correlation coefficients of time-series of all pairs of regions to define the edges of the brain network, yielding a 250x250 fully connected, undirected, and weighted graph for each participant.

Defining edges.—All negative weights in participants' correlation matrices were set to zero to aid interpretation (Lydon-Staley et al., 2018). One challenge in conducting graph theoretical studies is deciding on a threshold to determine what constitutes a meaningful "connection" from a continuous measure of FC (Hallquist & Hillary, 2018). There is no consensus about how to threshold FC values, and most recommendations to date apply to case-control studies (Hallquist & Hillary, 2018). Consequently, we calculated graph metrics over a range of relative density thresholds (Matthews & Fair, 2015) from .10 to .20 in steps of .02. For each graph metric for each of the 250 ROIs, we summed the averages across each pair of thresholds to yield a composite threshold value (van den Heuvel et al., 2017; Hosseini, Hoeft, & Kesler, 2012; Wagner et al., 2019). See the Supporting Information Appendix S1-*"Defining Edges"* for more details.

Computation of graph metrics.—All graph metrics were calculated based on each participant's weighted correlation matrices using *GraphVar version 2.02* (Kruschwitz, List, Waller, Rubinov, & Walter, 2015), which uses functions from the *Brain Connectivity Toolbox* (BCT; Rubinov & Sporns, 2010). We calculated five local graph metrics per node, yielding 1250 graph-based predictors: local efficiency, eigenvector centrality, nodal degree, within-module z-score, and participation coefficient. Each of these metrics of functional brain organization captures different aspects of a node's centrality and membership relative to other neighboring nodes, yielding unique information about a region's interconnectedness with the rest of the brain (see Table S2 for definitions). We used *R version 3.6.2* (R Core Team, 2019) for all subsequent statistical analyses. See JSK-github for code availability.

Relating rs-fMRI graph-based metrics and psychosocial variables to severity of SI

SI Data Distribution and Predictors of SI—At follow-up, participants scored between 0-90 on the SIQ (M=10.95, SD=16.31), with an expected modal response of 2 (10.38% endorsed zero symptoms). Based on clinical cut-off criteria of the SIQ (Herres et al., 2019; Horowitz et al., 2012), 5% reported clinically significant SI in the past month (≥31), 10% reported elevated levels of SI (≥20 and ≤30), and 85% reported normative levels of SI (≤19). Given the positive skew of our continuous SIQ distribution, we log-transformed the data (see Figure S1). To examine whether the combination of whole-brain based graph metrics of resting-state data and psychosocial variables explained severity of SI, we first created a matrix of possible predictors of SIQ that included 1250 brain-based graph metrics obtained at baseline plus psychological (internalizing and externalizing symptom severity at both timepoints), environmental (objective ELS severity, subjective ELS sensitivity), sociodemographic (age, Tanner score, BMI, parent education, sex, and race), and other

MRI-related participant characteristics (interval between baseline scan and follow-up, mean FD, mean global signal, and self-reported sleepiness during scan). Sex, race/ethnicity (white and person-of-color), fieldmap application, and self-reported sleepiness during scan were dummy-coded. For psychosocial variables with missing values (see Table S3) we used the Multivariate Imputation by Chained Equations (mice) package (Buuren & Groothuis-Oudshoorn, 2011) in R. This method uses the information from the other variables to predict and impute missing values. Then, we included these 1270 possible predictors (all continuous variables standardized) into a least absolute shrinkage and selection operator (LASSO) regression, referred here as the 'Psychosocial and Brain-based' model, using nested leave-one-out cross-validation (LOOCV). Details regarding the LASSO and nested-LOOCV are described below under "Primary Regularized LASSO Regressions."

Given that sex, race, and dimensions of ELS have been found to be associated with SI (Adrian, Miller, McCauley, & Stoep, 2016; LaVome Robinson, Droege, Hipwell, Stepp, & Keenan, 2016), and because the effects of other variables in the 'Psychosocial and Brain-based' model may go undetected due to high penalization, we conducted two additional LASSO regressions with nested-LOOCV separating out psychosocial and brain-based variables. Our 'Psychosocial-only' model included psychosocial variables (sex, race, age, BMI, Tanner score, internalizing symptom severity, the interval between the time points, objective ELS severity, subjective ELS sensitivity, parental education). Our 'Brain-based only' model included the 1250 brain-based graph metrics, mean FD, mean global signal, and sleepiness during scan.

Primary Regularized LASSO Regressions—Because we had more predictors than observations and expected collinearity among many of these predictors, we conducted a regularized regression analysis, specifically a LASSO regression, to identify the combination of brain-based (variables collected via fMRI) and psychosocial (psychological, environmental, and sociodemographic) variables that best explain SI in later adolescence (Zou & Hastie, 2005). We used the *glmnet* package (Friedman, Hastie, & Tibshirani, 2010) in R to perform the regularized LASSO regression using a full L1 penalty (i.e., $\alpha=1$) and an expected gaussian distribution. The L1 penalty "shrinks" coefficient estimates of redundant variables to zero in order to identify the features that in combination yield the most predictive model (Tibshirani, 1996). We performed LOOCV using the *cv.glmnet* function to determine the largest λ (i.e., hyperparameter, regularization value) associated with the smallest mean-squared error (MSE) (i.e., "lambda.min"), which yields a sparse matrix of non-zero coefficients. The linear combination of the variables with non-zero coefficient values yields the model that best explains severity of subsequent SI in this sample.

In smaller sample sizes, concerns of overfitting make LOOCV a more appropriate approach than other cross-validation techniques (e.g., validation set approaches) for identifying the optimal λ value, because in LOOCV each iteration is composed of a different training and test set, and the training set consists of almost the full dataset (James et al., 2013). Thus, LOOCV produces less bias in the test error than do other cross-validation approaches (James et al., 2013). Then, to obtain unbiased performance measures (MSE and R^2 values of this procedure) due to concerns of overfitting in the absence of external validation sets, we performed nested-LOOCV where the inner-loop performs LOO on N-1 training sets to

fit the hyperparameter, λ, and the outer-loop is used as the "validation" set (i.e., the full dataset) (Bates, Hastie, & Tibshirani, 2021; Cawley & Talbot, 2010; Hosseini et al., 2020). To aid interpretation of the coefficient estimates, we computed zero-order correlations between each non-zero variable and severity of SI. In addition, we computed supplementary correlations between all non-graph theory-based variables (psychosocial variables, mean FD, mean global signal, and sleepiness during scan) and severity of SI (Table S4).

Analyses using Internalizing Severity as an Outcome—To assess whether we captured predictors of SI specifically or internalizing symptoms more broadly, we repeated the analyses replacing SIQ with the follow-up internalizing subscale of the YSR. In these analyses we followed the same procedure as in our SIQ analysis where we conducted a LASSO regression with all possible variables ('Psychosocial and Brain-based') and then the two follow-up LASSO regressions (one with Brain-based variables only and one with Psychosocial variables only). All LASSO regressions used nested-LOOCV for model performance metrics.

Results

At baseline, participants were in early stages of puberty (Mean Tanner stage=1.96±0.79) and, as expected, males were older than females (on average, 8.31 months; $p<0.001$). At the follow-up assessment four years later when the participants were in later adolescence and more advanced in puberty (Mean Tanner stage=4.23±0.74), males remained slightly but significantly older than females ($p=0.001$). We present results of our nested-LOOCV models: (i) Psychosocial and Brain-based model (Tables 2, S5 with supplementary analysis ignoring fieldmaps presented in Supporting Information Appendix S2, Table S6); (ii) Psychosocial-only model (Table 3); and (iii) Brain-based model for explaining severity of SI (Table S7) and internalizing symptoms (Tables 4,5, S8) at follow-up, respectively. All zero-order correlations were consistent with the direction of associations across the correlations and in the LASSO results.

Psychosocial and Brain-Based Model of Severity of SI

The LOOCV of the LASSO regression used to predict severity of SI yielded 13 variables with non-zero coefficients in which the nested-LOOCV model MSE=0.46 and $R^2=0.55$. The two strongest explanatory variables were severity of follow-up internalizing (β=0.492) and externalizing symptoms (β=0.120). The brain-based variables were distributed across frontal, temporal, parietal, and insular gyri (see Table 2). Overall, 98.98% of the potential predictors of SI had their coefficients reduced to zero.

Psychosocial-Only Model of Severity of SI

In the LASSO regression of psychosocial-only variables, a combination of baseline and follow-up variables was associated with higher severity of SI. Severity of baseline (β=0.07) and follow-up internalizing (β=0.53) symptoms, follow-up externalizing symptoms (β=0.23), and baseline age (β=−0.06) were most strongly associated with a higher severity of SI. The nested-LOOCV MSE=0.46 and $R^2=0.55$ (see Table 3).

Brain-Based Only Model of Severity of SI

The LASSO regression of brain-based variables (1250 graph-based metrics in addition to MRI-related variables including mean FD, mean global signal, fieldmap application, and sleepiness during scan) yielded 22 predictors of SI severity. Six of these predictors were consistent with results of the 'Psychosocial and Brain-Based' Model explaining SI severity (see Table S7). The nested-LOOCV MSE=1.18. Because the MSE (total sum of residuals) is greater than the total sum of squares (1.01), the model fit is worse than the null model, yielding an $R^2 = -0.17$; therefore, we did not interpret the beta coefficients from this model.

Psychosocial and Brain-based Model of Severity of Internalizing Symptoms

The LOOCV of the LASSO regression used to predict severity of internalizing symptoms at follow-up yielded 9 variables with non-zero coefficients, where the nested-LOOCV model MSE=0.58 and $R^2=0.42$. The two strongest explanatory variables were severity of SI (β=0.50) and externalizing symptoms (β=0.07) at follow-up. The brain-based variables were distributed across the temporal lobe, occipital, and cingulate cortices (see Table 4). Overall, 99.29% of the potential predictors of internalizing severity had their coefficients reduced to zero.

Psychosocial-Only Model of Severity of Internalizing Symptoms

The LASSO regression of psychosocial variables indicated that a combination baseline and follow-up variables predicted severity of internalizing symptoms. The strongest predictors were severity of SI at follow-up (β=0.55), sex (β=0.27), and severity of externalizing symptoms at follow-up (β=0.19). Shared explanatory variables with the psychosocial results of follow-up severity of SI were severity of externalizing symptoms at follow-up (β=0.19), severity of internalizing symptoms at baseline (β=0.02), and age at baseline (β=−0.05). The nested-LOOCV MSE=0.45 and $R^2=0.55$ (see Table 5).

Brain-Based Only Model of Severity of Internalizing Symptoms

The LASSO regression of brain-based variables yielded 22 predictors of severity of internalizing symptoms (Table S8). Six of these predictors were the same brain-based predictors in the 'Psychosocial and Brain-based' model explaining severity of internalizing symptoms presented in Table 4. The nested-LOOCV MSE=1.14. Because the MSE (total sum of residuals) is greater than the total sum of squares (1.01), the model fit is worse than the null model, yielding an $R^2 = -0.13$.

Discussion

This study was designed to identify the combination of brain graph-theory metrics and psychosocial characteristics in a community sample of early adolescents that best explained the subsequent severity of SI four years later. At that follow-up, our sample had a skewed distribution of SI, with 5% endorsing clinically significant levels of SI in the past month. We also examined whether these predictors of SI were the same as those that explain severity of internalizing symptoms at follow-up. We found that psychosocial variables explained most of the variance in the severity of SI at follow-up.

Identification of Brain-based Variables in relation to Subsequent Severity of SI

Although there was some convergence of our Brain-based results with results of previous studies that detected effects in the frontal gyrus (Cao et al., 2015; Kim et al., 2017; Schmaal et al., 2020), insula (Li, Chen, Gong, & Jia, 2020; Pan et al., 2013), and middle temporal lobe (Stumps et al., 2020), our data suggest that, even when considered collectively, resting-state brain-based variables do not provide a strong enough signal to predict the severity of SI. This conclusion is consistent with larger-scale reports of neuroimaging correlates of STBs in community-recruited adolescents, in which after correction for multiple comparisons, no resting-state or task-based functional neuroimaging variable was identified in relation to STBs (Vidal-Ribas et al., 2021). Given that our sample was also recruited from the community and that we excluded youth who had STBs at baseline, it may not be surprising that brain-based variables do not predict severity of SI. Additionally, given the uncertainty regarding the timescale reflected by spontaneous fluctuations of fMRI-related activity (e.g., mental processes over the last several days, weeks, etc.) (Laumann & Snyder, 2021), it is also possible that signal coming from the functional organization of the brain is detectable more proximally to the emergence of SI. Our findings suggest that a combination of psychosocial data explain far more variance than do the brain-based variables. Although it is difficult to draw meaningful conclusions about the brain-based variables given their poor performance, we provide a brief presentation of brain-based factors that overlapped our ‘Psychosocial and Brain-based’ and ‘Brain-based only’ models in relation to the severity of subsequent SI in the context of the current literature (presented in the Supporting Information Appendix S3 under Table S7).

Contribution of Psychosocial Variables to the Subsequent Severity of SI

We conducted a separate regression using nested-LOOCV to determine which baseline and follow-up psychosocial variables are associated with the severity of SI. Consistent with our ‘Psychosocial and Brain-based’ model, we found that severity of internalizing and externalizing symptoms at follow-up (concurrent with severity of SI) were the strongest correlates of the severity of SI. It is well established that internalizing symptoms, such as self-reported depression severity and depression disorder diagnoses are risk factors for suicide related behaviors in adolescents (Janiri et al., 2020; Kang et al., 2021; Zelazny et al., 2021). In fact, online programs targeting interpersonal factors related to depression (e.g., pessimism) can moderately reduce SI in adolescents (Dickter et al., 2019). Externalizing symptom severity has also been consistently associated with SI in community samples of adolescents (Adrian et al., 2016; Johnson, McLennan, Heron, & Colman, 2020). In our study ELS was not associated with severity of SI. It is well documented that exposure to stressful life events is a potent risk factor for the development of STBs in adolescents (Dykxhoorn, Hatcher, Roy-Gagnon, & Colman, 2017; Miller & Prinstein, 2019), and in particular lifetime sexual/physical abuse, perceived physical safety at school, and parental support are important indicators of SI in pre-adolescents (Walsh, Sheehan, & Liu, 2021). It is possible that participants in our sample did not experience sufficiently high levels of stress to detect an effect in our analyses.

Severity of Internalizing Symptoms: Shared and Distinct Variables from Severity of SI

It is important to recognize that predictors and correlates of the severity of SI are not necessarily shared with those of the severity of internalizing symptoms, even if these two forms of psychopathology often co-occur. Researchers have found specific variables predict SI and SA above and beyond depressive severity, including impulsivity and hopelessness (O'Connor & Nock, 2014). Here, we found that whereas some psychosocial variables were associated with both severity SI and internalizing symptoms, others were differentially associated with severity of SI and internalizing symptoms. Across models ('Psychosocial and Brain-based', and 'Psychosocial-only'), severity of externalizing symptoms at follow-up explained variance in severity of both SI and internalizing symptoms. Across 'Psychosocial-only' models, higher baseline internalizing symptom severity and younger age at baseline was associated with higher levels of SI and greater severity of internalizing symptoms at follow-up. Recent research on suicide risk screening has reported that younger patients who present with externalizing symptoms (two characteristics consistent with our findings) and hallucinations, but not with SI or attempts, screened positive for suicide risk, suggesting that screening for suicide risk can be beneficial for children as young as 8 or 9 years of age (Cwik et al., 2021). In the models of Psychosocial-only variables, sex, race/ethnicity (people of color compared to White participants), the interval between timepoints, and tanner stage (pubertal stage) at follow-up were associated with increased severity of internalizing severity, but not with increased severity of SI.

Although there are robust findings of a higher prevalence of ideation and attempts in girls than in boys (Fox, Millner, Mukerji, & Nock, 2018), sex was not a significant predictor of severity of SI in our study; however, sex did emerge as a variable that contributed to the severity of internalizing symptoms in the 'Psychosocial-only' model: girls showed higher levels of internalizing symptoms than did boys. Sex differences in the severity of internalizing symptoms during adolescence, particularly after puberty (Thapar, Collishaw, Pine, & Thapar, 2012) could explain why we found that sex contributes to the prediction of future severity of internalizing symptoms. Pubertal stage at follow-up was associated with the severity of internalizing symptoms, but not with the severity of SI. Certain dimensions of puberty (e.g., pubertal onset), however, have been found to predict severity of SI (Patton & Viner, 2007). Because we recruited girls and boys matched on pubertal status and not on age, which led us to exclude girls who started puberty early relative to their peers, we cannot draw strong conclusions about pubertal onset in our sample.

Further, because we recruited a sample that was representative of the local demographic composition of the Bay Area, we were not powered to examine different races/ethnicities; thus, for statistical reasons we created a binary variable identifying people-of-color (POC) and White participants. Although we did not find that race/ethnicity was a predictor of SI, previous studies have reported differences in SI and attempts across different races and ethnicities (Ivey-Stephenson, 2020). We found that this binary variable of race and ethnicity emerged in the 'Psychosocial-only' model of internalizing symptoms at follow-up: POC had higher severity of internalizing symptoms than did White participants. Researchers have reported differing levels of depression by race, such that White individuals have a higher lifetime prevalence of depression; however, Black individuals or African

Americans typically have higher rates of chronicity compared to White individuals (Bailey, Mokonogho, & Kumar, 2019), and in adolescence, Hispanic females tend to have higher levels of depression than do White and Black individuals (McLaughlin, Hilt, & Nolen-Hoeksema, 2007). Such differences may be due to socioeconomic inequality associated with race and ethnicity that creates environmental risk factors for minoritized individuals (Hollingsworth et al., 2017). It will be important for future research to interrogate trends of SI and examine how suicidal thoughts may transition to suicidal behaviors differently across races/ethnicities during adolescence (Meza & Bath, 2021).

With respect to neurobiological factors, we did not find regions or patterns of interconnectedness that were shared across models of severity of SI and of internalizing symptoms. Recent work consistent with this finding has shown that specific FC metrics are differentially associated with depression and SI severity (Chase et al., 2021; Qiu et al., 2020). It is difficult to draw meaningful conclusions about the brain-based variables resulting from our 'Brain-based only' model given their poor performance. However, we provide a brief discussion of differences across 'Psychosocial and Brain-based' and 'Brain-based only' models in relation to the severity of subsequent SI and internalizing symptoms in the context of the current literature (presented in the Supporting Information Appendix S4 under Table S8).

Conclusions

We should note four limitations of this study. First, it is possible that limited variability in SI in our sample limited our power to detect effects. That is, a larger number of participants with more severe SIQ scores might have provided greater signal to detect effects in some of the psychosocial and brain-based metrics. Second, we did not obtain information about family history of STBs. Given previous findings of a significant genetic component predicting suicide attempts (Ruderfer et al., 2019) and neurocognitive differences between youth with a first-degree biological relative with a history of suicide attempt and matched controls (Jones et al., 2021), obtaining family history of STBs may have yielded important information about subsequent severity of SI. As a related point, recent findings from the Adolescent Brain Cognitive Development Study indicate that high family conflict and low parental monitoring are associated with SI (DeVille et al., 2020). In the future, researchers should incorporate this information into their studies. Third, although we used nested-LOOCV to reduce overfitting our models, our findings should be replicated using independent samples, especially because our approach was exploratory. Finally, our resting-state scan was 6 minutes long. Longer scan times can improve the reliability of FC estimates (Birn et al., 2013; Termenon et al., 2016), although estimates have been found to be reliable in scans as short as 5 minutes (Andellini et al., 2015; Van Dijk et al., 2010).

Despite these limitations, the present study highlights the importance of examining early adolescence as a period during which psychosocial variables converge to explain the severity of SI in later adolescence, when suicidal thoughts increase dramatically (Nock et al., 2013). A strength of our investigation is that we recruited a sample of adolescents with minimal psychiatric histories and were able to use psychological, environmental, sociodemographic, and neurobiological factors to test which combination of factors explain the subsequent

severity of SI. Our findings may help guide future research focused on understanding how different fMRI-based metrics play a role in individuals' vulnerability to SI before the emergence of more severe suicidal behaviors. Finally, although we focused in this study on risk for suicidal thoughts, it will be important for researchers to gain a more comprehensive understanding of the factors involved in the transition from suicidal thoughts to behaviors (Kleiman, Glenn, & Liu, 2019).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Suicidal ideation (SI) typically emerges during adolescence and is prevalent in nonclinical and subclinical samples of community youth, but is challenging to predict.
- Using machine learning we tested whether a combination of brain-based and psychosocial variables in a sample with no history of suicidal thoughts and behaviors in early adolescence can explain the subsequent severity of SI.
- We found that psychosocial variables explained most of the variance in the subsequent severity of SI. Brain-based variables did not aid in explaining severity of SI.
- Similar patterns were found when predicting severity of internalizing symptoms.
- Our findings may guide hypothesis-driven research into the neural and psychosocial factors explaining the emergence of SI.

Table 1.

Participant Characteristics (N = 106)

Variable	Mean (SD)	Range
Female (%)	56	
Age baseline (years)	11.41 (1.00)	
Age females	11.05 (1.00)	9.17-13.94
Age males	11.85 (0.79)	
Age follow-up (years)	15.51 (1.14)	
Age females	15.20 (1.17)	13.10-19.23
Age males	15.89 (0.97)	
Interval between baseline and later assessment (years)	4.10 (0.57)	2.69-5.78
Tanner baseline	1.96 (0.79)	1-4.5
Tanner follow-up	4.23 (0.74)	1.5-5
BMI baseline (kg/m2)	18.52 (3.87)	10.85-30.78
BMI follow-up (kg/m2)	21.42 (5.02)	14.09-43.59
Parental Education (mode)	5	1-8
Race/Ethnicity (%)		
White	49	
Black/African American	8	
Latinx/Hispanic	3	
Asian	14	
biracial/multiracial	19	
other	7	
TESI-C based Stress Severity (objective)	6.15 (4.90)	0-22
TESI-C based Subjective Stress Sensitivity	−0.08 (0.51)	−3.82
YSR Internalizing Subscale baseline	11.66 (8.75)	0-39
YSR Externalizing Subscale baseline	9.37 (6.65)	0-39
YSR Internalizing Subscale follow-up	14.09 (9.23)	0-40
YSR Externalizing Subscale follow-up	10.82 (6.74)	1-30
SIQ (raw scores)	10.95 (16.31)	0-90
Head Motion (FD)	0.10 (0.04)	0.04-0.24

Note. 5 on Parental Education = "4-year college degree"; TESI-C = Traumatic Events Screening Inventory for Children; YSR = Youth Self Report; SIQ = Suicidal Ideation Questionnaire; FD = Framewise Displacement (mean FD across all frames acquired per subject in mm)

BMI baseline Missing (N=4)

BMI Follow-up Missing (N=8)

Tanner follow-up Missing (N=5)

Parental Education (N=7)

TESI-C based Subjective Stress Sensitivity (N=2)

YSR Baseline Missing (N=3)

YSR Follow-up Missing (N=4)

Table 2.

Psychosocial and Brain-based Predictors and Correlates of Suicidal Ideation Severity (N=106)

ROI/Variable	x	y	z	Graph Property	Coefficient Estimate (β)	Zero-order correlations (*r*, *p*-value)	Participant Characteristic / Brain Region
Internalizing severity at follow-up					0.492	0.73, < 0.001	Participant Characteristic
Externalizing severity at follow-up					0.120	0.55, < 0.001	Participant Characteristic
Lateral superior frontal gyrus (L)	−11	49	40	Within-module degree	0.131	0.36, < 0.001	Frontal Lobe
Rostral middle temporal lobe (R)	51	6	−32	Participation coefficient	0.063	0.33, 0.001	Temporal Lobe
Postcentral superior parietal lobe (R)	23	−43	67	Participation coefficient	−0.041	−0.28, 0.004	Parietal Lobe
Opercular area of inferior frontal gyrus (R)	42	22	3	Participation coefficient	−0.041	−0.31, 0.001	Frontal Lobe
Caudal middle temporal lobe (L)	−65	−30	−12	Degree	0.034	0.28, 0.003	Temporal Lobe
Medial superior temporal gyrus (R)	31	15	−34	Participation coefficient	0.033	0.27, 0.006	Temporal Lobe
Orbital area 12/47 (L)	−36	33	−16	Within-module degree	0.015	0.26, 0.006	Frontal Lobe
Ventral granular insular gyrus (L)	−38	−4	−9	Local efficiency	−0.011	−0.34, < 0.001	Insular Lobe
Lateral superior frontal gyrus (L)	−11	49	40	Degree	0.012	0.34, < 0.001	Frontal Lobe
Medial paraphippocampal gyrus (R)	19	−36	−11	Degree	0.001	0.13, 0.17	Temporal Lobe
Nucleus accumbens (L)	−17	3	−9	Eigenvector centrality	0.001	0.08, 0.41	Basal Ganglia

Note. Table of significant predictors and correlates of severity of suicidal ideation obtained from a LASSO regression that included the graph metrics (Degree/Within-Module degree/Eigenvector centrality/Participation Coefficient) from 250 ROIs, MRI related variables (mean framewise displacement, mean global signal, fieldmap application, sleepiness during scan) and psychosocial variables (age, sex, race, pubertal status, Body Mass Index, parent education, internalizing and externalizing symptom severity, early life stress severity and sensitivity, interval between scan and follow-up assessment). Leave-One-Out-Cross-Validation determined $\lambda = 0.13$. Nested Leave-One-Cross-Validation model R^2 of 0.55 and mean square error = 0.46. Variables are listed in order of the magnitude of their coefficient estimates. ROI = region of interest; LASSO = least absolute shrinkage and selection operator

Table 3.

Psychosocial Predictors and Correlates of Suicidal Ideation Severity (N=106)

Variable	Coefficient Estimate (β)	Zero-order correlations (*r*, *p*-value)	Measured at Baseline or Follow-up Timepoint
Internalizing Severity	**0.53**	**0.73, < 0.001**	**Follow-up**
Externalizing Severity	**0.23**	**0.55, <0.001**	**Follow-up**
Internalizing Severity	0.07	0.32, 0.001	Baseline
Age	−0.06	−0.25, 0.011	Baseline
Parent Education	0.03	0.05, 0.642	Baseline
BMI	−0.04	0.02, 0.870	Follow-up

Note. Table of significant correlates and predictors of suicidal ideation severity (log-transformed SIQ scores) obtained from a LASSO regression that included psychosocial variables (age, sex, race, pubertal status, Body Mass Index, parent education, internalizing and externalizing symptom severity, early life stress severity and sensitivity, interval between scan and follow-up assessment). Leave-One-Out-Cross-Validation determined $\lambda = 0.05$. Nested Leave-One-Cross-Validation model $R^2 = 0.55$ and mean square error = 0.46. Variables are listed in order of the magnitude of their coefficient estimates. LASSO = least absolute shrinkage and selection operator. Bolded rows indicate shared variables with those in the 'Psychosocial and Brain-based' model of SI.

Table 4.

Psychosocial and Brain-Based Predictors and Correlates of Internalizing Severity (N=106)

ROI/Variable	x	y	z	Graph Property	Coefficient Estimate (β)	Zero-order correlations (*r*, *p*-value)	Participant Characteristic / Brain Region
Suicidal Ideation severity at follow-up					0.50	0.73, < 0.001	Participant Characteristic
Externalizing severity at follow-up					**0.07**	**0.53, < 0.001**	**Participant Characteristic**
Temporal agranular insular parahippocampal gyrus (L)	−23	2	−32	Degree	0.06	0.30, 0.002	Temporal Lobe
Occipital polar cortex (R)	22	−97	4	Within module degree	−0.06	−0.27, 0.005	Occipital Cortex
Subgenual cingulate cortex (R)	5	41	6	Degree	0.05	0.28, 0.003	Cingulate Cortex
Rostral superior temporal gyrus (R)	56	−12	−5	Eigenvector Centrality	0.05	0.38, < 0.001	Temporal Lobe
Intermediate ventral inferior temporal gyrus (R)	46	−14	−33	Within module degree	0.04	0.36, < 0.001	Temporal Lobe
Rostral medioventral occipital cortex (R)	7	−76	11	Participation coefficient	−0.02	−0.21, 0.028	Occipital Cortex
Rostral superior temporal gyrus (L)	−55	−3	−10	Degree	0.01	0.29, 0.002	Temporal Lobe

Note. Table of significant predictors and correlates of internalizing severity obtained from a LASSO regression that included the graph metrics (Degree/Within-Module degree/Eigenvector centrality/Participation Coefficient) from 250 ROIs, MRI related variables (mean framewise displacement, mean global signal, fieldmap application, sleepiness during scan) and psychosocial variables (age, sex, race, pubertal status, Body Mass Index, parent education, internalizing and externalizing symptom severity, early life stress severity and sensitivity, interval between scan and follow-up assessment, and suicidal ideation severity). Leave-One-Out-Cross-Validation determined $\lambda = 0.15$. Nested Leave-One-Cross-Validation model R^2 of 0.42 and mean square error = 0.58. Variables are listed in order of the magnitude of their coefficient estimates. ROI = region of interest; LASSO = least absolute shrinkage and selection operator. Bolded rows indicate shared variables with the variables in the 'Psychosocial and Brain-based' model of SI severity.

Table 5.

Psychosocial Predictors and Correlates of Internalizing Severity (N=106)

Variable	Coefficient Estimate (β)	Zero-order correlations (*r*, *p*-value)	Measured at Baseline or Follow-up Timepoint
Suicidal Ideation Severity	*0.55*	*0.73, < 0.001*	*Follow-up*
Sex	0.27	0.59, 0.002	Baseline
Externalizing Severity	***0.19***	***0.53, < 0.001***	***Follow-up***
Ethnicity/Race	−0.14	−0.32, 0.097	Baseline
Age	−0.05	0.28, 0.004	Baseline
Interval between baseline and follow-up measurements	0.02	0.17, 0.085	Between Baseline and Follow-up
Internalizing Severity	0.02	0.30, 0.002	Baseline
Tanner Stage	0.01	0.17, 0.079	Follow-up

Note. Table of significant predictors of internalizing severity obtained from a LASSO regression that included psychosocial variables (age, sex, race, pubertal status, Body Mass Index, parent education, internalizing symptom severity, suicidal ideation severity, early life stress severity and sensitivity, interval between scan and follow-up assessment). Leave-One-Out-Cross-Validation determined $\lambda = 0.04$. Nested Leave-One-Cross-Validation model $R^2 = 0.55$ and mean square error = 0.45. Predictors are listed in order of the magnitude of their coefficient estimates. LASSO = least absolute shrinkage and selection operator. Bolded rows indicate shared variables with the variables in the 'Psychosocial and Brain-based' model explaining severity of SI. Italicized rows indicate shared variables with those in the 'Psychosocial and Brain-based' model explaining severity of internalizing symptoms.