Published in final edited form as:

Am J Psychiatry. 2021 April 01; 178(4): 321–332. doi:10.1176/appi.ajp.2020.20020120.

Multimodal neuroimaging of suicidal thoughts and behaviors in a US population-based sample of school-aged children

Pablo Vidal-Ribas, PhD^{1,2,†}, Delfina Janiri, MD^{3,4,†}, Gaelle E Doucet, PhD^{3,5}, Narun Pornpattananangkul, PhD^{2,6}, Dylan M Nielson, PhD², Sophia Frangou, MD, PhD^{3,7,*}, Argyris Stringaris, MD, PhD, FRCPsych^{2,*}

¹Social and Behavioral Science Branch, National Institute of Child Health and Human Development, Bethesda, USA ²Mood Brain and Development Unit, National Institute of Mental Health, Bethesda, USA ³Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, USA ⁴Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy ⁵Boys Town National Research Hospital, Omaha, USA ⁶Department of Psychology, University of Otago, Dunedin, New Zealand ⁷Centre for Brain Health, University of British Columbia, Vancouver, Canada

Abstract

Objective: Suicide deaths and suicidal thoughts and behaviors are considered a public health emergency, yet their brain underpinnings remain elusive. We aim to examine the classification accuracy of individual, environmental, and clinical characteristics, as well as multimodal brain imaging correlates of suicidal thoughts and behaviors in a US population-based sample of school-aged children.

Methods: Children aged 9–10 years (n=7,994) from a population-based sample from the Adolescent Brain Cognitive Development study were assessed for lifetime suicidal thoughts and behaviors. Following quality control, we examined structural magnetic resonance imaging (sMRI) (n=6,238), resting state functional MRI (rs-fMRI) (n=4,134), and task-based fMRI (range n=4,075 to 4,608). We examined differences with Welch's t-test and Equivalence Tests, with observed effect sizes (Cohen's *d*) and their 90% confidence interval (CI) < |0.15|. Classification accuracy was examined with area under precision-recall curves (AUPRC).

Results: Among the 7,994 unrelated children (3,757 females [47.0%]), those with lifetime suicidal thoughts and behaviors based on children (n=684 [8.6%]), caregiver (n=654 [8.2%]) or concordant reports (n=198 [2.5%]), presented higher levels of social adversity and psychopathology on themselves and their caregivers compared to never-suicidal children (n=6,854 [85.7%]). Only one imaging test survived statistical correction: caregiver-reported suicidal thoughts and behaviors were associated with a thinner left bank of the superior temporal sulcus

Corresponding author: Pablo Vidal-Ribas, PhD, Social and Behavioral Science Branch, National Institute of Child Health and Human Development, National Institutes of Health, 6710 Rockledge Drive, Building 6710B, Room 3153A, Bethesda, MD, 20892, Phone: (301) 555-5555, pablo.vidal-ribasbelil@nih.gov.

[†] these authors made an equal contribution to the manuscript

^{*} these authors made an equal contribution to the manuscript

Declaration of Interest: The authors declare no competing interests.

($d = -0.17$, 95% CI $-0.26, -0.08$, $p_{FDR} = 0.019$). Based on the prespecified bounds of $|0.15|$, ~48% of the group mean differences for child-reported suicidal thoughts and behaviors comparisons and a ~22% for parent-reported suicidal thoughts and behaviors comparisons were considered equivalent. All observed effect sizes were relatively small ($d \leq 0.30$) and both non-imaging and imaging correlates had low classification accuracy (AUPRC ≤ 0.10).

Conclusions: Using commonly applied neuroimaging measures, we were unable to find a discrete brain signature related to suicidal thoughts and behaviors in youth. There is a great need for improved approaches to the neurobiology of suicide.

Introduction

Rates of suicide deaths and suicidal thoughts and behaviors have risen over 50% amongst young people in the last decade (www.who.int/data/gho) (1, 2), making suicide the second-leading cause of death in those aged 10–19 years (1, 3). Whereas individual, environmental and clinical risk factors for suicidal thoughts and behaviors have been well-established (4–13), including in the current sample (14), these have demonstrated low predictive validity (15–17). In response, the number of studies examining neurobiological underpinnings of suicidal thoughts and behaviors has grown exponentially in the last two decades (18). Nevertheless, our understanding and utility of the neural mechanisms underlying suicidal thoughts and behaviors is still poor, especially in young children, for several reasons.

First, it is still unclear whether findings from neuroimaging studies examining suicidal thoughts and behaviors apply to children, since most studies have been conducted in adult samples. Second, results of these studies have been inconsistent. Whereas systematic reviews on the topic suggest that suicidal thoughts and behaviors are associated with abnormalities in regions involved in affective processing and impulsive regulation, the specific regions highlighted in each review differ, and all emphasize the modest sample sizes, heterogeneity, and lack of replicability across studies (18–21). In addition, meta-analyses of structural and functional imaging studies have failed to find differences between suicidal and non-suicidal participants (22–24), and those that found differences were either based on a small number of studies or reported inconsistent findings (24, 25). Third, it is unclear whether the effect sizes of any described neural correlates of suicidal thoughts and behaviors are large enough to have clinical utility. Studies with small sample sizes have limited power to detect differences (19). However, finding no difference does not mean that the difference equals zero; the observed effect size could be considered large enough to be meaningful. On the other hand, studies with large sample sizes are more powered to detect small differences; yet, the observed effect size of such differences might be too small for practical purposes (23). To examine whether an observed effect size is large enough to be considered meaningful one can test for equivalence (26), an approach originally employed in the field of pharmacokinetics (27) with the aim of showing that a new cheaper drug was practically as effective as an existing one.

In the current study, we employed data from a large population-based sample from the Adolescent Brain and Cognitive Development (ABCD) study (<https://abcdstudy.org/>) (28, 29) to examine the correlates of suicidal behaviors using a multi-informant approach. In

children aged 9–10 years, we first examined the classification accuracy (i.e., predicted probability of an observation of belonging to a class, e.g., suicide case vs never-suicidal case) of individual, environmental and clinical correlates of suicidal thoughts and behaviors that have shown to differ in the current sample (14). Next, we sought to identify associations between suicidal thoughts and behaviors and brain morphometry, functional connectivity at rest, and functional measures during three tasks. Specifically, we examine neural correlates of processes that have been implicated with suicidal behavior in clinical and at-risk samples of youth, named reward processing (30–33) with the Monetary Incentive Delay task (34), inhibitory control (35, 36) with the Stop Signal Task (37), and working memory and affective processing (38–41) with an emotional version of the N-back task (42). We tested for differences in these measures using a traditional null hypothesis significance test, and complemented our analyses with Equivalence testing (26) to examine whether observed effect size were large enough to be considered meaningful based on a prespecified benchmark. Finally, we examined the ability of neural correlates to classify suicide cases in our sample and discuss this in relation to non-imaging correlates of suicidal thoughts and behaviors.

Methods

The ABCD study

All the data used here were accessed from the ABCD Study Curated Annual Release 2.1 and are available on request from the NIMH Data Archive (<https://data-archive.nimh.nih.gov/abcd>). The baseline ABCD sample consists of 11,875 children from 22 sites across the United States that match the demographic profile of the American Community Survey (29). The University of California at San Diego Institutional Review Board was responsible for the ethical oversight of the ABCD study. The present study is based on 7,994 unrelated ABCD participants for whom complete self-report *and* caregiver data on childhood suicidal thoughts and behaviors were available. As detailed in the Supplementary eMethods and illustrated in eFigure 1, the neuroimaging analyses involved subsamples based on the availability of high-quality magnetic resonance imaging (MRI) data for each modality.

Determination of childhood suicidal thoughts and behaviors

Suicidal thoughts and behaviors in children were assessed using the child- and caregiver-report of the computerized Kiddie Schedule for Affective Disorders and Schizophrenia for DSM-5 (KSADS-5) (43). A detailed description of the assessment is provided in the eMethods. Based on children and caregiver reports, four suicidal thoughts and behaviors groups were computed: 1) child-reported suicidal thoughts and behaviors 2) caregiver-reported suicidal thoughts and behaviors, 3) concordantly-reported suicidal thoughts and behaviors (i.e., both child and parent endorse at least one item; i.e. the overlap between the first two groups), and 4) never-suicidal (i.e., both child and parent do not endorse any item). Analyses were conducted based on all three groups (i.e., child-reported caregiver-reported, and concordantly-reported suicidal thoughts and behaviors) compared with the never-suicidal children.

In addition, based on previous reports suggesting that some suicidal thoughts and behaviors phenotypes are more likely to be associated with neural correlates (22, 44), we also performed secondary analyses on three further groups of participants: those with lifetime suicide attempts, those with current suicidal thoughts and behaviors (as opposed to lifetime), and those with lifetime suicidal thoughts and behaviors and family history of suicide attempt or death in their parents. Given the small number of participants meeting these criteria in the current sample, we computed these groups by combining child- and caregiver-reports.

Individual and environmental characteristics

We examined the classification accuracy of individual and environmental characteristics, as well as clinical factors of the child and caregivers that have been associated with suicidal thoughts and behaviors in previous studies (4–6, 8–10, 12) and the current sample (14). A detailed description of these factors and instruments employed to assess these variables are provided in Supplementary eTable 1.

Neuroimaging

High-resolution T₁-weighted images as well as resting-state and task-based fMRI data were obtained at each ABCD site using 3T MRI systems. In the current study we examined cortical thickness (n=68 parcellations) and subcortical volumes (n=18 parcellations), functional connectivity at rest (n=306 connectivity indices) and neural activations (n=167 parcellations) evoked by three tasks: a modified Monetary Incentive Delay task (34), Stop Signal Task (37) and Emotional N-back task (42, 45). To preserve statistical power, we analyzed each modality separately rather than selecting only those children that had high-quality data across all three of the imaging modalities (eFigure 1). A detailed description of the acquisition protocols, quality control procedures, imaging processing, and analyses of the ABCD study have been published elsewhere (28, 46) and are summarized in the eMethods.

Statistical analysis

All analyses compared never-suicidal children with those with endorsed suicidal thoughts and behaviors. A detailed rationale and description of the tests can be found in the eMethods.

Analysis of individual and environmental characteristics

Group differences in psychosocial factors were examined with Welch's t-tests (47), to allow for unequal number of observations, and chi-squared tests. Results were considered significant at $p < 0.05$ with False Discovery Rate (FDR) correction for multiple comparisons. We further estimated effect sizes (Cohen's d) of mean and frequency differences, and examined the classification accuracy of the most robust correlates calculating the area under precision-recall curve (AUPRC, see below and eMethods for a further description)

Analysis of differences and equivalence of neuroimaging data

We examined *differences* in neuroimaging measures between groups with Welch's t-tests to account for unequal number of observations. We examined *equivalence* of mean differences

(i.e., whether observed effect sizes of mean differences were meaningful effects) with Equivalence tests (which also included Welch's t-tests to account for unequal number of observations). In equivalence testing, the observed data are statistically compared against *a priori* specified equivalence interval (δ), defined by upper ($+L$) and lower ($-L$) equivalence bounds. The aim of equivalence testing is to reject the null hypothesis that the observed effect size (Cohen's d) is at least as extreme as a pre-specified smallest effect size of interest (SESOI). We used the "two one-sided tests" (TOST) procedure (26, 48) implemented with the *TOSTtwo* function from the library *TOSTER* in R. Given the current sample size and previous results in a large sample (23), the upper ($+L$) and lower ($-L$) equivalence bounds were specified as a conservative $d=0.15$ and $d=-0.15$ (i.e., $SESOI=|0.15|$), which correspond to traditional notions of a "small" effect size (49). That is, effect size with 90% CI within $[-0.15, 0.15]$ were considered statistically equivalence (i.e., not meaningful effects). The threshold for statistical significance for both tests was set at $p < 0.05$ after applying FDR-correction for multiple comparisons.

Analysis of classification accuracy

Classification accuracy of the most robust differences in both non-imaging and imaging data was estimated with the area under precision-recall curves (AUPRC), which provides more accurate information on the performance of a prediction model than the widely used receiver operating-characteristic (ROC) curves in cases where there is an imbalance in the observations between the two classes (50). Precision, or positive predictive value, can be defined as how good a model is at predicting true positive cases. Recall, or sensitivity, can be defined as how good a model is at predicting *all* the true positive cases. A perfect model would have an AUPRC of 1, as in ROC; however, whereas in ROC a random classifier would have an AUC close to 0.50, in PRC that value would be close to the prevalence of positive cases in the population, calculated as $y=P/(P+N)$ (e.g. AUPRC=0.10 if prevalence is 10%) (see eMethods for a further description).

Results

Prevalence of suicidal thoughts and behaviors in the sample

The four groups based on suicidal thoughts and behaviors were composed as follows: child-reported suicidal thoughts and behaviors ($n=684$, 8.6%), caregiver-reported suicidal thoughts and behaviors ($n=654$, 8.2%), concordantly-reported suicidal thoughts and behaviors ($n=198$, 2.5%), and never-suicidal ($n=6,854$, 85.7%). Among participants with endorsed suicidal thoughts and behaviors, either by the child or the caregiver ($n=1,140$, 14.3%), there was an agreement of 17.4% ($n=198$).

Lifetime suicidal ideation without attempts (including passive, active and plans) in the child was endorsed by 577 children (7.2% of the sample, 84.4% of cases) and 615 caregivers (7.7% of the sample, 94% of cases). Lifetime suicide attempts in the child were endorsed by 107 children (1.3% of the sample, 15.6% of cases) and 39 caregivers (0.5% of the sample, 6% of cases). Current suicidal thoughts and behaviors in the child was endorsed by 183 children (2.3% of the sample, 27% of the cases), and 119 caregivers (1.5% of the sample, 18.2% of cases). Cases with lifetime suicidal thoughts and behaviors and family history of

suicide attempt or death were 68 based on child reports (0.9% of the sample, 9.9% of cases) and 90 based on caregiver reports (1.1% of the sample, 13.8% of cases). eTable 2 shows the rate of suicidal behaviors reported by either the children or the caregivers and the rate of positive agreement for each item.

Individual and environmental characteristics

A full report of suicidal thoughts and behaviors correlates in the current sample is published elsewhere (14). eTable 3 in the Supplemental provides a summary of the descriptive statistics and differences of individual, environmental and clinical characteristics between the suicidal thoughts and behaviors groups. We further examined current and lifetime mental health problems in caregivers. Several variables differed at $p_{FDR} < 0.05$ between the three groups with suicidal thoughts and behaviors and the never-suicidal group. For these variables, we estimated effect sizes and classification accuracy with the AUPRC (Table 1). Absolute effect sizes (Cohen's d) of non-imaging correlates of suicidal thoughts and behaviors ranged 0.14 to 0.87 for child report, 0.29 to 1.42 for caregiver report, and 0.33 to 1.47 for concordantly-reported suicidal thoughts and behaviors. Overall, the smallest effect sizes of significant correlates were for sex of the child, economic problems in the last year, and use of mental health services by the father. The largest effect sizes of significant correlates were for child-reported family conflict, child psychopathology (14), and caregiver current and lifetime mental health problems, especially in the mother. General psychopathological symptoms, behavioral disorders (i.e., oppositional defiant disorder and conduct disorder), and PTSD had the largest effect.

However, in terms of classification accuracy, this was either very poor or not better than what would be expected by chance. Specifically, AUPRC ranged 0.04 to 0.20 for child-reported suicidal thoughts and behaviors, 0.03 to 0.30 for caregiver-reported suicidal thoughts and behaviors, and 0.01 to 0.15 for concordantly-reported suicidal thoughts and behaviors.

Differences and equivalence of neuroimaging data

Supplementary eFigure 1 shows the sample size of the groups for each imaging modality analyzed. For each modality, we provide the combined results of applying traditional null-hypothesis Welch's t-tests and Equivalence test, after applying FDR-correction for multiple comparisons. The distribution of results is depicted in Figure 1.

Results at corrected and uncorrected level for all modalities are summarized in Supplementary eTables 4 and 5, along with brain measures, if any, that showed to be statistically different *and* not statistically equivalent across two or more group comparisons.

Brain structural imaging: Among the 86 regions examined, only the left bank of the superior temporal sulcus was found to be significantly thinner in the caregiver-reported suicidal thoughts and behaviors group than in the never-suicidal group after applying FDR-correction ($d = -0.17$, 95% CI $-0.26, -0.08$, $p_{FDR} = 0.019$) (Figures 1–2, Supplementary eTables 6–8). In addition, based on our prespecified bounds of ± 0.15 , this effect was large enough to be considered meaningful. Thickness in the superior temporal sulcus was not

associated with having a parent with history of suicide/attempt ($t(5969)=-0.59$, $p=0.557$); however, it was associated with level of income ($r(5679)=0.05$, $p<0.001$), having economic problems in the last year ($t(6727)=3.11$, $p=0.002$, $d=0.10$), level of caregiver highest education achieved ($r(6227)=0.05$, $p<0.001$), history of mental health hospitalizations in the mother ($t(6016)=2.36$, $p=0.018$, $d=0.14$), and history of depression in either mother or father ($t(5976)=2.13$, $p=0.033$, $d=0.06$). Nevertheless, in a multivariate analysis including caregiver-reported suicidal thoughts and behaviors as predictor, only suicidal thoughts and behaviors remained significantly associated with lower thickness in the superior temporal sulcus ($\beta=-0.04$, $t(5040)=-2.93$, $p=0.003$).

All the remaining regions showed to be not statistically different (all $p_{FDR}>0.05$). Of these, most regions were statistically equivalent (i.e., effect size were practically zero) for the child-reported suicidal thoughts and behaviors comparison (62 regions [72.1%], $d_{range}=-0.07, 0.07$) and for the caregiver-reported suicidal thoughts and behaviors comparison (76 regions [88.4%], $d_{range}=-0.06, 0.07$). In contrast, for the concordantly-reported suicidal thoughts and behaviors comparisons, all regions were found to be not statistically equivalent (i.e., d 90%CI included zero and overlapped with at least one of the $|0.15|$ bounds) with d ranging -0.23 to 0.23 (Figure 1, Supplementary eFigures 2–7).

Resting-state functional imaging: Among the 306 functional connectivity measures, none showed to be statistically different after applying FDR-correction (all $p_{FDR}>0.05$) (Figure 1, Supplementary eTables 9–11). In addition, most functional connectivity measures were statistically equivalent (i.e., effect size were practically zero) for the child-reported suicidal thoughts and behaviors comparison (170 [55.6%], $d_{range}=-0.04, 0.04$). In contrast, for the caregiver- and concordantly-reported suicidal thoughts and behaviors comparisons, all functional connectivity measures were found to be not statistically equivalent (i.e., d 90%CI included zero and overlapped with at least one of the $|0.15|$ bounds) with d ranging -0.18 to 0.20 , and -0.34 to 0.28 , respectively (Supplementary eFigures 8–10).

Task-based functional imaging: Results of Welch's t-test and Equivalence tests for each of the tasks and contrasts examined are shown in Figure 1, Figure 3, Supplementary eTables 12–35, and Supplementary eFigures 11–60. Briefly, among the 167 regions-of-interest mean activations examined for each of the 3 tasks and 8 contrasts, none showed to be statistically different after applying FDR-correction (all $p_{FDR}>0.05$).

Of the regions-of-interest mean activations, the number of statistically equivalent measures ranged between 0–126 (0%–75.4%, $d_{range}=-0.05, 0.05$) for the child report comparison, 0–116 (0%–69.5%, $d_{range}=-0.04, 0.04$) for the caregiver report comparison and were none for the concordantly-reported suicidal thoughts and behaviors comparison (Figure 1, Figure 3, Supplementary eFigure 60). No evidence of equivalence was found for 41–167 (24.6%–100%, $d_{range}=-0.17, 0.16$), 51–167 (30.5%–100%, $d_{range}=-0.17, 0.20$), and 167 (100%, $d_{range}=-0.34, 0.25$) of regions-of-interest mean activations for child-, caregiver-, and concordantly-reported suicidal thoughts and behaviors comparisons, respectively. The Monetary Incentive Delay task showed the higher rates of regions-of-interest activations that were statistically equivalent, followed by the Stop Signal Task, and Emotional N-back (Figure 1, Figure 3, Supplementary eFigure 60).

Classification accuracy of neuroimaging data

Overall, observed effect sizes were small, especially for child- and caregiver-reported suicidal thoughts and behaviors analyses. Maximum effect size for child-, caregiver- and concordant-analyses were |0.17|, |0.20|, and |0.34|, respectively (Supplementary eTable 36). Based on lowest and highest 90%CI bounds, all results would have been statistically equivalent if thresholds were |0.29|, |0.33|, and |0.56| for child-, caregiver, and concordantly-reported suicidal thoughts and behaviors comparisons, respectively.

For child- and caregiver-suicidal thoughts and behaviors comparisons, only 23 tests (0.67%) resulted in an effect size equal or over our smallest effect size of interest (d |0.15|) (Figure 4, Supplementary eTable 37). These included lower thickness of the left bank superior temporal sulcus, aberrant connectivity of the default and cingulo-parietal network with hippocampus and other subcortical areas, and aberrant task-elicited activation of frontal, temporal, and parietooccipital areas, and insula. The AUPRC of these observed effect size ranged 0.07 to 0.10. Based on the prevalence of suicidal thoughts and behaviors on child- and caregiver-reports in our sample (~8.5%), these can be considered random classifiers. The AUPRC of the largest effect size, found in the sensorimotor mouth-visual area connectivity in the concordant group analysis ($d=0.34$, 95%CI -0.55, -0.12) was 0.02.

Neuroimaging correlates of high-risk suicidal thoughts and behaviors groups

eTable 38 provides the sample size of the groups for each imaging modality analyzed, and eTable 39 provides a summary of the findings in high-risk groups in terms of difference and equivalence of means. For cases with current suicidal thoughts and behaviors or lifetime suicidal thoughts and behaviors with family history of suicide attempt/death, all results were not statistically different at and not statistically equivalent after applying FDR-correction (all $p_{FDR}>0.05$). The same was true for cases with lifetime suicide attempt with two exceptions: during the Stop Signal Task, children with lifetime suicide attempt showed higher activation in the left pallidum when failed in inhibiting a response ($d=0.47$, 95%CI 0.20, 0.74, $p_{FDR}=0.028$), and lower activation in the right ventral diencephalon when succeeded in inhibiting a response ($d=0.56$, 95%CI 0.28, 0.84, $p_{FDR}=0.013$). However, the classification accuracy of these two findings was not better than what would be expected by chance, with AUPRCs of 0.02 and 0.01, respectively.

Discussion

In a large US population-based sample of school-aged children we found that endorsement of suicidal thoughts and behaviors was strongly associated with higher levels of psychopathology and social adversity, but these factors had poor classification accuracy. In terms of neural correlates, over the 5,000 tests performed to examine differences in structural MRI and resting-state and task-based fMRI, only one survived correction, in which suicidal thoughts and behaviors were associated with thinner left bank of the superior temporal sulcus. Nevertheless, effect sizes of neural correlates were very small, and their

ability to classify cases with suicidal thoughts and behaviors was not better than what would be expected by chance.

The rate of reported suicidal thoughts and behaviors in our sample was in line with rates found in pre-pubertal and school-aged children (51, 52), which is lower than in community samples of adolescents and young adults (4–7, 53). Child and caregiver reports of suicidal thoughts and behaviors were not consistent, which is a common observation in adolescents and young adults in whom non-disclosure might involve concerns about stigmatization, difficulties in communication and unavailability of social and family support (54).

In the current sample, suicidal thoughts and behaviors was associated with higher psychosocial adversity and clinical correlates, thus replicating a number of studies (14). The effect sizes of these associations ranged from small to large, with the largest effect sizes being linked to clinical characteristics in the child and caregivers, and child-reported family conflict. For example, behavioral disorders such as oppositional defiant disorder and conduct disorder, as well as PTSD had effect sizes over 1. The strongest association of suicidal behaviors with externalizing rather than internalizing behaviors is consistent with reports in pre-pubertal children (10, 11). However, regardless of the effect sizes, the classification accuracy of non-imaging correlates was not better than random selection or extremely poor, in line with previous reports (16).

In terms of neuroimaging correlates, at uncorrected level, we found several regions associated with suicidal thoughts and behaviors not consistently reported in the literature (18); and those regions that we found that have been reported (e.g. aberrant thickness in medial orbitofrontal gyrus, aberrant connectivity in the default mode and salience networks, or aberrant task-elicited activations in temporal lobe and insula) differed in directionality or specific regions involved (18, 40, 41, 55–58). Moreover, after FDR-correction, we only found a thinner left bank of the superior temporal sulcus in the caregiver-reported suicidal thoughts and behaviors analysis. Similar findings in cortical thickness have been found in adults with schizophrenia (59) and, in adolescents with history of suicide attempt, Pan et al. (60) found reduced volume, but not thickness, in this same region. The superior temporal region is part of a neural network involved in inhibitory control and emotion processing in social contexts and has been associated with lethality of attempts and impulsivity (61). Secondary analyses in those with lifetime suicide attempts showed altered activation during inhibitory control in the pallidum and the ventral diencephalon. The latter has been associated with suicidal ideation, but not attempts, in adults with depression (62). No associations were found with current suicidal thoughts and behaviors or lifetime suicidal thoughts and behaviors with family history of suicide attempt or death.

Regardless of differences, and based on our prespecified conservative bound of $|0.15|$, we showed that around half of the group means for child-reported suicidal thoughts and behaviors comparisons ($\sim 48\%$), and a fifth for parent-reported suicidal thoughts and behaviors comparisons ($\sim 22\%$) were equivalent (i.e., not a meaningful effect); these would have been nearly 100% equivalent with a prespecified bound of $|0.30|$, which is still small. In the case of the concordant group and the high-risk groups, all observed effect size of mean differences were not statistically equivalent (i.e., meaningful effects). In these cases, where

there is no difference, but effects are not statistically equivalent, there is insufficient data to draw conclusions. With our conservative SESOI of $|0.15|$ the equivalence bounds became narrower and the concordant and high-risk groups should have had a larger sample size in order to obtain a sufficiently narrow confidence interval to conclude that the observed effect size were statistically equivalent (i.e., not a meaningful effect). Whilst widely employed, the choice of a $d=|0.15|$ for the equivalence tests is, of course, arbitrary and only meant as an indicator of potential clinical meaningfulness. Our power calculations indicated that our sample sizes in this study could be used to detect such differences at a standard statistical significance thresholds and power ($\alpha = 0.05$ and $1-\beta = .80$, see Supplement), at least for sMRI. Obviously, even bigger samples would be required to detect such differences after the application of correction for multiple comparisons. This points to the fact that, much as in the field of genetics, power—and therefore sample size—may be a limitation for the discovery of brain networks significantly contributing to clinical phenotypes, such as suicidality. Equally, our findings indicate that, at least for the phenotypes studied here, brain effects are most likely to be small.

Indeed, in the current study, observed effect sizes were relatively small for all regions and connectivity indices tested ($d < |0.30|$) in line with studies conducted in large samples (23), even within the concordant and high-risk groups (with the only exception of the two significant finding in those with suicide attempt). Small effect size can still be clinically relevant if they can predict clinical outcomes, treatment response, or point to mechanistic pathways of disease (63). We therefore examined the classification accuracy of the largest effect sizes in our sample, as we did with the non-imaging correlates. We found that these were not better at classifying suicidal cases than what one would get by selecting cases randomly from the population. This is important because, ironically, the shift from studying psychosocial risk factors to neurobiological biomarkers of suicidal thoughts and behaviors was partly motivated by the poor sensitivity of the former in predicting suicide (15–17) which we have also shown in the current study. While the pattern of increasing suicide rates in young people does not give signs of stopping, it is yet not clear whether this change in focus of study is providing us with any benefit, especially given the cost of neuroimaging studies. The aim was to improve identification and prevention of suicidal thoughts and behaviors; however, to date, the evidence is still weak for this purpose due to small sample sizes, heterogeneity and inconsistency across studies, and, as further shown in this study, small effects sizes with limited classification accuracy. Non-imaging correlates, albeit also having low classification accuracy, at least have moderate to large effect sizes, especially associated clinical characteristics. Therefore, addressing psychosocial and clinical factors might be our best bet as per today. Nevertheless, there is an urgent need to improve the study of neurobiological biomarkers. Future studies should aim their efforts at using other methodologies such as machine learning (64, 65) and building models based on aggregation of multiple variables, including neuroimaging, psychosocial, clinical, and genetic correlates of suicidal behaviors to increase predictive validity. That said, what our results show is that vulnerability to suicidal thoughts and behaviors does not appear to have a “brain signature” with a strong enough effect in school-age children. However, this does not imply that suicidal thoughts and behaviors does not have brain correlates but indicates that such associations, if any, might not be discernible using common neuroimaging measures at this age.

for different reasons. First, it is possible that what we call “suicidal thoughts and behaviors” in children is different than suicidal thoughts and behaviors in adolescents or adults. Historically, it was believed that prepuberal children could not have suicidal thoughts and behaviors due to their concrete operational thinking, which limits their concept of causality, as well as the concepts of death and finality (66, 67). However, current evidence suggest that even preschoolers can show suicidal behaviors with the intent to cause self-injury or death (66, 68), which is agreed to be the essential quality of suicidal thoughts and behaviors, regardless of their understanding of finality or lethality (67). Second, as brain organization evolves during the adolescent years, also a time when more active suicidal behaviors emerge, it is plausible that neural correlates of suicidal thoughts and behaviors become more evident as the brain matures. In that sense, investigation of the longitudinal data from the ABCD cohort when they become available will likely shed some light to these incongruent findings across samples of different ages. Finally, it is also plausible that we might not find a single correlate of suicidal thoughts and behaviors in those adolescents. Suicide is known to be a complex phenomenon, and based on works from affective neuroscience (69, 70), it is likely that suicidal behaviors are not discrete categories and thus do not have one-to-one brain signatures. Comprehensive reviews on the topic are a good reminder of that heterogeneity (18). Future studies should combine multiple types of correlates and examine interrelated trajectories across factors that might help us to identifying the shift to more active suicidal behaviors at peak ages such as late adolescence and early adulthood.

Our study has some limitations. Since participants were drawn from the community very few had active suicidal thoughts or behaviors - especially the latter - at the time of scanning and therefore were not necessarily comparable to clinical cases. This is important because some studies suggest that suicidal ideation might have distinct clinical, genetic, and imaging correlates than suicidal behaviors (18, 71). We tried to address these limitations by analyzing only those cases at highest risk; yet, this approach reduced considerably the number of participants and limited the power to detect differences. Nevertheless, the majority of effect sizes showed to be small, which suggest that these would be small even when increasing the sample size. Moreover, passive ideation has been shown to be associated with significant psychiatric comorbidity and be similar to active ideation in terms of risk factors (72), as also shown in this study. Whereas using a community-based sample avoids referral biases and might aid the identification of suicidal thoughts and behaviors in non-clinical samples, future waves of ABCD should capture the age-related increase in prevalence of more active suicidal behaviors.

Conclusions

Vulnerability to suicidal thoughts and behaviors in young children does not appear to have a discrete brain signature when considering commonly-used neuroimaging measures. Moreover, observed effect sizes of imaging correlates of suicidal thoughts and behaviors are small with limited classification accuracy. There is a great need for improved approaches to the neurobiology of suicide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:

We thank Dr. Anthony Steven Dick, Associate Professor, Florida International University, for his advice in implementing and interpreting the equivalence tests. We thank Dr. Stephen E. Gilman, Chief of Social and Behavioral Science, National Institute of Child Health and Human Development, for his valuable insight and commentaries on this manuscript.

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (<https://abcdstudy.org>), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9–10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, U24DA041147, U01DA041093, and U01DA041025. A full list of supporters is available at <https://abcdstudy.org/federal-partners.html>. A listing of participating sites and a complete listing of the study investigators can be found at <https://abcdstudy.org/scientists/workgroups/>. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

Funding: This work was supported by the National Institute of Mental Health under grant R01MH113619 and R01 MH116147. This work was also supported by the National Institute of Mental Health Intramural Research Program Project ZIA-MH002957 (to AS). GED was supported by grant R03AG064001. NP was supported by Oakley Mental Health Research Foundation.

References

1. CDC: Web-based Injury Statistics Query and Reporting System (WISQARS). Atlanta, GA, National Center for Injury Prevention and Control; 2019.
2. Plemmons G, Hall M, Doupnik S, Gay J, Brown C, Browning W, Casey R, Freundlich K, Johnson DP, Lind C, Rehm K, Thomas S, Williams D. Hospitalization for Suicide Ideation or Attempt: 2008–2015. *Pediatrics*. 2018;141.
3. Curtin SC, Heron M, Minino AM, Warner M. Recent Increases in Injury Mortality Among Children and Adolescents Aged 10–19 Years in the United States: 1999–2016. *National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System*. 2018;67:1–16.
4. Nock MK, Green JG, Hwang I, McLaughlin KA, Sampson NA, Zaslavsky AM, Kessler RC. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA psychiatry*. 2013;70:300–310. [PubMed: 23303463]
5. Sampasa-Kanyinga H, Dupuis LC, Ray R. Prevalence and correlates of suicidal ideation and attempts among children and adolescents. *International journal of adolescent medicine and health*. 2017;29.
6. Mars B, Heron J, Klonsky ED, Moran P, O'Connor RC, Tilling K, Wilkinson P, Gunnell D. What distinguishes adolescents with suicidal thoughts from those who have attempted suicide? A population-based birth cohort study. *Journal of child psychology and psychiatry, and allied disciplines*. 2019;60:91–99.
7. Barzilay R, Calkins ME, Moore TM, Boyd RC, Jones JD, Benton TD, Oquendo MA, Gur RC, Gur RE. Neurocognitive functioning in community youth with suicidal ideation: gender and pubertal effects. *The British journal of psychiatry: the journal of mental science*. 2019;215:552–558. [PubMed: 30919791]
8. Dervic K, Brent DA, Oquendo MA. Completed suicide in childhood. *The Psychiatric clinics of North America*. 2008;31:271–291. [PubMed: 18439449]

9. Roche AM, Giner L, Zalsman G. Suicide in early childhood: a brief review. *International journal of adolescent medicine and health*. 2005;17:221–224. [PubMed: 16231473]
10. Tishler CL, Reiss NS, Rhodes AR. Suicidal behavior in children younger than twelve: a diagnostic challenge for emergency department personnel. *Academic emergency medicine: official journal of the Society for Academic Emergency Medicine*. 2007;14:810–818. [PubMed: 17726127]
11. Bridge JA, Goldstein TR, Brent DA. Adolescent suicide and suicidal behavior. *Journal of child psychology and psychiatry, and allied disciplines*. 2006;47:372–394.
12. Soole R, Kolves K, De Leo D. Suicide in Children: A Systematic Review. *Archives of suicide research: official journal of the International Academy for Suicide Research*. 2015;19:285–304. [PubMed: 25517290]
13. Turecki G, Brent DA. Suicide and suicidal behaviour. *Lancet (London, England)*. 2016;387:1227–1239. [PubMed: 26385066]
14. Janiri D, Doucet GE, Pompili M, Sani G, Luna B, Brent DA, Frangou S. Risk and protective factors for childhood suicidality: a US population-based study. *The lancet Psychiatry*. 2020;7:317–326. [PubMed: 32171431]
15. Pokorny AD. Prediction of suicide in psychiatric patients. Report of a prospective study. *Archives of general psychiatry*. 1983;40:249–257. [PubMed: 6830404]
16. Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X, Musacchio KM, Jaroszewski AC, Chang BP, Nock MK. Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. *Psychological bulletin*. 2017;143:187–232. [PubMed: 27841450]
17. Belsher BE, Smolenski DJ, Pruitt LD, Bush NE, Beech EH, Workman DE, Morgan RL, Evatt DP, Tucker J, Skopp NA. Prediction Models for Suicide Attempts and Deaths: A Systematic Review and Simulation. *JAMA psychiatry*. 2019;76:642–651. [PubMed: 30865249]
18. Schmaal L, van Harmelen AL, Chatzi V, Lippard ETC, Toenders YJ, Averill LA, Mazure CM, Blumberg HP. Imaging suicidal thoughts and behaviors: a comprehensive review of 2 decades of neuroimaging studies. *Molecular psychiatry*. 2019.
19. Dominguez-Baleon C, Gutierrez-Mondragon LF, Campos-Gonzalez AI, Renteria ME. Neuroimaging Studies of Suicidal Behavior and Non-suicidal Self-Injury in Psychiatric Patients: A Systematic Review. *Frontiers in psychiatry*. 2018;9:500. [PubMed: 30386264]
20. Desmyter S, van Heeringen C, Audenaert K. Structural and functional neuroimaging studies of the suicidal brain. *Progress in neuro-psychopharmacology & biological psychiatry*. 2011;35:796–808. [PubMed: 21216267]
21. Bani-Fatemi A, Tasmim S, Graff-Guerrero A, Gerretsen P, Strauss J, Kolla N, Spalletta G, De Luca V. Structural and functional alterations of the suicidal brain: An updated review of neuroimaging studies. *Psychiatry research Neuroimaging*. 2018;278:77–91. [PubMed: 29929763]
22. Jollant F, Wagner G, Richard-Devantoy S, Köhler S, Bär K-J, Turecki G, Pereira F. Neuroimaging-informed phenotypes of suicidal behavior: a family history of suicide and the use of a violent suicidal means. *Translational psychiatry*. 2018;8:120. [PubMed: 29921964]
23. Rentería ME, Schmaal L, Hibar DP, Couvy-Duchesne B, Strike LT, Mills NT, de Zubicaray GI, McMahon KL, Medland SE, Gillespie NA, Hatton SN, Lagopoulos J, Veltman DJ, van der Wee N, van Erp TGM, Wittfeld K, Grabe HJ, Block A, Hegenscheid K, Völzke H, Veer IM, Walter H, Schnell K, Schramm E, Normann C, Schoepf D, Konrad C, Zurovski B, Godlewska BR, Cowen PJ, Penninx B, Jahanshad N, Thompson PM, Wright MJ, Martin NG, Christensen H, Hickie IB. Subcortical brain structure and suicidal behaviour in major depressive disorder: a meta-analysis from the ENIGMA-MDD working group. *Translational psychiatry*. 2017;7:e1116. [PubMed: 28463239]
24. Huang X, Rootes-Murdy K, Bastidas DM, Nee DE, Franklin JC. Brain Abnormalities Associated with Self-Injurious Thoughts and Behaviors: A Meta-Analysis of Neuroimaging Studies. 2019:526525.
25. van Heeringen K, Bijttebier S, Desmyter S, Vervaeke M, Baeken C. Is there a neuroanatomical basis of the vulnerability to suicidal behavior? A coordinate-based meta-analysis of structural and functional MRI studies. *Frontiers in human neuroscience*. 2014;8:824. [PubMed: 25374525]
26. Lakens D. Equivalence Tests: A Practical Primer for t Tests, Correlations, and Meta-Analyses. *Social psychological and personality science*. 2017;8:355–362. [PubMed: 28736600]

27. Hauck WW, Anderson S. A new statistical procedure for testing equivalence in two-group comparative bioavailability trials. *Journal of pharmacokinetics and biopharmaceutics*. 1984;12:83–91. [PubMed: 6747820]
28. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, Soules ME, Teslovich T, Dellarco DV, Garavan H, Orr CA, Wager TD, Banich MT, Speer NK, Sutherland MT, Riedel MC, Dick AS, Bjork JM, Thomas KM, Chaarani B, Mejia MH, Hagler DJ Jr, Daniela Cornejo M, Sicut CS, Harms MP, Dosenbach NUF, Rosenberg M, Earl E, Bartsch H, Watts R, Polimeni JR, Kuperman JM, Fair DA, Dale AM. The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. *Developmental cognitive neuroscience*. 2018;32:43–54. [PubMed: 29567376]
29. Garavan H, Bartsch H, Conway K, Decastro A, Goldstein RZ, Heeringa S, Jernigan T, Potter A, Thompson W, Zahs D. Recruiting the ABCD sample: Design considerations and procedures. *Developmental cognitive neuroscience*. 2018;32:16–22. [PubMed: 29703560]
30. Pan L, Segreti A, Almeida J, Jollant F, Lawrence N, Brent D, Phillips M. Preserved hippocampal function during learning in the context of risk in adolescent suicide attempt. *Psychiatry research*. 2013;211:112–118. [PubMed: 23158778]
31. Tsypes A, Owens M, Hajcak G, Gibb BE. Neural responses to gains and losses in children of suicide attempters. *Journal of abnormal psychology*. 2017;126:237–243. [PubMed: 27808540]
32. Jollant F, Lawrence NS, Olie E, O'Daly O, Malafosse A, Courtet P, Phillips ML. Decreased activation of lateral orbitofrontal cortex during risky choices under uncertainty is associated with disadvantageous decision-making and suicidal behavior. *NeuroImage*. 2010;51:1275–1281. [PubMed: 20302946]
33. Tsypes A, Owens M, Gibb BE. Blunted Neural Reward Responsiveness in Children With Recent Suicidal Ideation. *Clinical Psychological Science*. 2019;7:958–968. [PubMed: 32042508]
34. Knutson B, Westdorp A, Kaiser E, Hommer D. FMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage*. 2000;12:20–27. [PubMed: 10875899]
35. Pan LA, Batezati-Alves SC, Almeida JR, Segreti A, Akkal D, Hassel S, Lakdawala S, Brent DA, Phillips ML. Dissociable patterns of neural activity during response inhibition in depressed adolescents with and without suicidal behavior. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2011;50:602–611.e603. [PubMed: 21621144]
36. McHugh CM, Chun Lee RS, Hermens DF, Corderoy A, Large M, Hickie IB. Impulsivity in the self-harm and suicidal behavior of young people: A systematic review and meta-analysis. *Journal of psychiatric research*. 2019;116:51–60. [PubMed: 31195164]
37. Logan GD. On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In *Inhibitory processes in attention, memory, and language*. San Diego, CA, US, Academic Press; 1994. pp. 189–239.
38. Bomyea J, Stout DM, Simmons AN. Attenuated prefrontal and temporal neural activity during working memory as a potential biomarker of suicidal ideation in veterans with PTSD. *Journal of affective disorders*. 2019;257:607–614. [PubMed: 31349177]
39. Bauer BW, Gustafsson HC, Nigg J, Karalunas SL. Working memory mediates increased negative affect and suicidal ideation in childhood attention-deficit/hyperactivity disorder. *J Psychopathol Behav Assess*. 2018;40:180–193. [PubMed: 30386005]
40. Pan LA, Hassel S, Segreti AM, Nau SA, Brent DA, Phillips ML. Differential patterns of activity and functional connectivity in emotion processing neural circuitry to angry and happy faces in adolescents with and without suicide attempt. *Psychological medicine*. 2013;43:2129–2142. [PubMed: 23298821]
41. Johnston JAY, Wang F, Liu J, Blond BN, Wallace A, Liu J, Spencer L, Cox Lippard ET, Purves KL, Landeros-Weisenberger A, Hermes E, Pittman B, Zhang S, King R, Martin A, Oquendo MA, Blumberg HP. Multimodal Neuroimaging of Frontolimbic Structure and Function Associated With Suicide Attempts in Adolescents and Young Adults With Bipolar Disorder. *The American journal of psychiatry*. 2017;174:667–675. [PubMed: 28135845]
42. Cohen AO, Breiner K, Steinberg L, Bonnie RJ, Scott ES, Taylor-Thompson K, Rudolph MD, Chein J, Richeson JA, Heller AS, Silverman MR, Dellarco DV, Fair DA, Galván A, Casey BJ. When Is an Adolescent an Adult? Assessing Cognitive Control in Emotional and Nonemotional Contexts. 2016;27:549–562.

43. Kobak K, Kratochvil C, Stanger C, Kaufman J: Computerized screening of comorbidity in adolescents with substance or psychiatric disorders. in Poster presented at the 33rd annual anxiety disorders and depression conference, La Jolla, CA Retrieved from http://www.telepsychology.net/resources/KSADS_ADAAPosterv4pdf2013.
44. Lieb R, Bronisch T, Hofler M, Schreier A, Wittchen HU. Maternal suicidality and risk of suicidality in offspring: findings from a community study. *The American journal of psychiatry*. 2005;162:1665–1671. [PubMed: 16135626]
45. Cohen A, Conley M, Dellarco D, Casey BJPotSfNSD CA. 11. The impact of emotional cues on short-term and long-term memory during adolescence. 2016.
46. Hagler DJ Jr, Hatton S, Cornejo MD, Makowski C, Fair DA, Dick AS, Sutherland MT, Casey BJ, Barch DM, Harms MP, Watts R, Bjork JM, Garavan HP, Hilmer L, Pung CJ, Sicat CS, Kuperman J, Bartsch H, Xue F, Heitzeg MM, Laird AR, Trinh TT, Gonzalez R, Tapert SF, Riedel MC, Squeglia LM, Hyde LW, Rosenberg MD, Earl EA, Howlett KD, Baker FC, Soules M, Diaz J, de Leon OR, Thompson WK, Neale MC, Herting M, Sowell ER, Alvarez RP, Hawes SW, Sanchez M, Bodurka J, Breslin FJ, Morris AS, Paulus MP, Simmons WK, Polimeni JR, van der Kouwe A, Nencka AS, Gray KM, Pierpaoli C, Matochik JA, Noronha A, Aklin WM, Conway K, Glantz M, Hoffman E, Little R, Lopez M, Pariyadath V, Weiss SR, Wolff-Hughes DL, DelCarmen-Wiggins R, Feldstein Ewing SW, Miranda-Dominguez O, Nagel BJ, Perrone AJ, Sturgeon DT, Goldstone A, Pfefferbaum A, Pohl KM, Prouty D, Uban K, Bookheimer SY, Dapretto M, Galvan A, Bagot K, Giedd J, Infante MA, Jacobus J, Patrick K, Shilling PD, Desikan R, Li Y, Sugrue L, Banich MT, Friedman N, Hewitt JK, Hopfer C, Sakai J, Tanabe J, Cottler LB, Nixon SJ, Chang L, Cloak C, Ernst T, Reeves G, Kennedy DN, Heeringa S, Peltier S, Schulenberg J, Sripada C, Zucker RA, Iacono WG, Luciana M, Calabro FJ, Clark DB, Lewis DA, Luna B, Schirda C, Brima T, Foxe JJ, Freedman EG, Mruzek DW, Mason MJ, Huber R, McGlade E, Prescott A, Renshaw PF, Yurgelun-Todd DA, Allgaier NA, Dumas JA, Ivanova M, Potter A, Florsheim P, Larson C, Lisdahl K, Charness ME, Fuemmeler B, Hettema JM, Maes HH, Steinberg J, Anokhin AP, Glaser P, Heath AC, Madden PA, Baskin-Sommers A, Constable RT, Grant SJ, Dowling GJ, Brown SA, Jernigan TL, Dale AM. Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *NeuroImage*. 2019;116091. [PubMed: 31415884]
47. Welch BL. The generalisation of student's problems when several different population variances are involved. *Biometrika*. 1947;34:28–35. [PubMed: 20287819]
48. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of pharmacokinetics and biopharmaceutics*. 1987;15:657–680. [PubMed: 3450848]
49. Cohen J: Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ, Erlbaum; 1988.
50. Saito T, Rehmsmeier M. The precision-recall plot is more informative than the ROC plot when evaluating binary classifiers on imbalanced datasets. *PloS one*. 2015;10:e0118432. [PubMed: 25738806]
51. Pfeffer CR, Zuckerman S, Plutchik R, Mizruchi MS. Suicidal behavior in normal school children: a comparison with child psychiatric inpatients. *Journal of the American Academy of Child Psychiatry*. 1984;23:416–423. [PubMed: 6747147]
52. Gould MS, King R, Greenwald S, Fisher P, Schwab-Stone M, Kramer R, Flisher AJ, Goodman S, Canino G, Shaffer D. Psychopathology associated with suicidal ideation and attempts among children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1998;37:915–923. [PubMed: 9735611]
53. Mars B, Heron J, Klonsky ED, Moran P, O'Connor RC, Tilling K, Wilkinson P, Gunnell D. Predictors of future suicide attempt among adolescents with suicidal thoughts or non-suicidal self-harm: a population-based birth cohort study. *The lancet Psychiatry*. 2019;6:327–337. [PubMed: 30879972]
54. Levi-Belz Y, Gavish-Marom T, Barzilay S, Apter A, Carli V, Hoven C, Sarchiapone M, Wasserman D. Psychosocial Factors Correlated with Undisclosed Suicide Attempts to Significant Others: Findings from the Adolescence SEYLE Study. *Suicide & life-threatening behavior*. 2019;49:759–773. [PubMed: 29851140]

55. Miller AB, McLaughlin KA, Busso DS, Brueck S, Peverill M, Sheridan MA. Neural Correlates of Emotion Regulation and Adolescent Suicidal Ideation. *Biological psychiatry: cognitive neuroscience and neuroimaging*. 2018;3:125–132. [PubMed: 29529407]
56. Ordaz SJ, Goyer MS, Ho TC, Singh MK, Gotlib IH. Network basis of suicidal ideation in depressed adolescents. *Journal of affective disorders*. 2018;226:92–99. [PubMed: 28968564]
57. Schwartz J, Ordaz SJ, Ho TC, Gotlib IH. Longitudinal decreases in suicidal ideation are associated with increases in salience network coherence in depressed adolescents. *Journal of affective disorders*. 2019;245:545–552. [PubMed: 30439679]
58. Marchand WR, Lee JN, Johnson S, Thatcher J, Gale P, Wood N, Jeong EK. Striatal and cortical midline circuits in major depression: implications for suicide and symptom expression. *Progress in neuro-psychopharmacology & biological psychiatry*. 2012;36:290–299. [PubMed: 22079109]
59. Besteher B, Wagner G, Koch K, Schachtzabel C, Reichenbach JR, Schlosser R, Sauer H, Schultz CC. Pronounced prefronto-temporal cortical thinning in schizophrenia: Neuroanatomical correlate of suicidal behavior? *Schizophrenia research*. 2016;176:151–157. [PubMed: 27567290]
60. Pan LA, Ramos L, Segreti A, Brent DA, Phillips ML. Right superior temporal gyrus volume in adolescents with a history of suicide attempt. *The British journal of psychiatry: the journal of mental science*. 2015;206:339–340. [PubMed: 25497300]
61. Soloff P, White R, Diwadkar VA. Impulsivity, aggression and brain structure in high and low lethality suicide attempters with borderline personality disorder. *Psychiatry research*. 2014;222:131–139. [PubMed: 24656768]
62. Richard-Devantoy S, Ding Y, Lepage M, Turecki G, Jollant F. Cognitive inhibition in depression and suicidal behavior: a neuroimaging study. *Psychological medicine*. 2016;46:933–944. [PubMed: 26670261]
63. Funder DC, Ozer DJ. Evaluating Effect Size in Psychological Research: Sense and Nonsense. 2019;2:156–168.
64. Fazel S, O'Reilly L. Machine Learning for Suicide Research-Can It Improve Risk Factor Identification? *JAMA psychiatry*. 2019.
65. Just MA, Pan L, Cherkassky VL, McMakin DL, Cha C, Nock MK, Brent D. Machine learning of neural representations of suicide and emotion concepts identifies suicidal youth. *Nature human behaviour*. 2017;1:911–919.
66. Connolly L. Suicidal behaviour – does it exist in pre-school aged children? *Irish Journal of Psychological Medicine*. 1999;16:72–74.
67. Pfeffer CR. Childhood suicidal behavior. A developmental perspective. *The Psychiatric clinics of North America*. 1997;20:551–562. [PubMed: 9323312]
68. Sheftall AH, Asti L, Horowitz LM, Felts A, Fontanella CA, Campo JV, Bridge JA. Suicide in Elementary School-Aged Children and Early Adolescents. *Pediatrics*. 2016;138. [PubMed: 27544347]
69. Wilson-Mendenhall CD, Barrett LF, Barsalou LW. Variety in emotional life: within-category typicality of emotional experiences is associated with neural activity in large-scale brain networks. *Social cognitive and affective neuroscience*. 2015;10:62–71. [PubMed: 24563528]
70. Lindquist KA, Wager TD, Kober H, Bliss-Moreau E, Barrett LF. The brain basis of emotion: a meta-analytic review. *The Behavioral and brain sciences*. 2012;35:121–143. [PubMed: 22617651]
71. Campos AI, Verweij KJH, Statham DJ, Madden PAF, Maciejewski DF, Davis KAS, John A, Hotopf M, Heath AC, Martin NG, Rentería ME. Genetic aetiology of self-harm ideation and behaviour. *Scientific reports*. 2020;10:9713. [PubMed: 32546850]
72. Liu RT, Bettis AH, Burke TA. Characterizing the phenomenology of passive suicidal ideation: a systematic review and meta-analysis of its prevalence, psychiatric comorbidity, correlates, and comparisons with active suicidal ideation. *Psychological medicine*. 2020:1–17.

Figure 1. Percentage of outcomes of the Welch's t-test and Equivalence test for each imaging modality by suicidal thoughts and behaviors group comparison.

For each informant, structural MRI examined 86 regions, resting-state fMRI examined 306 connectivity indices, and task-based fMRI examined activations in 167 regions. No evidence of difference (Welch's t-test, $p_{FDR} > 0.05$, 95% confidence interval (CI) includes zero), Evidence of difference (Welch's t-test, $p_{FDR} < 0.05$, 95% CI does not include zero). Evidence of equivalence (Equivalence test, $p_{FDR} < 0.05$, 90% CI does not overlap with bounds); No evidence of equivalence (Equivalence test, $p_{FDR} > 0.05$, 90% CI overlaps with bound/s). sMRI, structural MRI. rs-fMRI, resting-state fMRI.

Figure 2. Equivalence testing for mean differences in brain cortical thickness and subcortical volumes relating to suicidal thoughts and behaviors.

Distribution of t-values from Equivalence tests comparing the regional means between the never-suicidal group (n=5,381) and the child-reported suicidal thoughts and behaviors group (n=525) (Panel A) and the caregiver-reported suicidal thoughts and behaviors group (n=482) (Panel B); Higher t-values (i.e., darker green) suggest equivalence between groups. *Only the left bank of the temporal sulcus in the caregiver-reported suicidal thoughts and behaviors analysis showed to be statistically different and not statistically equivalent after FDR-correction.

Figure 3. Equivalence testing for mean differences in functional activation during the Monetary Incentive Delay task, the Stop Signal Task and Emotional N-back task relating to suicidal thoughts and behaviors.

Distribution of absolute t-values from Equivalence tests comparing the regional means between the never-suicidal group and the child-reported suicidal thoughts and behaviors group (Panel A) and the caregiver-reported suicidal thoughts and behaviors group (Panel B); Higher t-values (i.e., darker green) suggest equivalence between groups. No statistical differences were found after applying FDR-correction for multiple comparisons. The remaining contrasts are depicted in Supplementary eFigure 60.

Figure 4. Observed effect sizes of mean differences for each imaging modality by suicidal thoughts and behaviors group comparison.

For each informant, structural MRI examined 86 regions, resting-state fMRI examined 306 connectivity indices, and task-based fMRI examined activations in 167 regions. Blue individual lines represent effect size of group mean differences for a region or connectivity index. Shaded area represents effect size lower than the prespecified smallest effect size of interest (SESOI) of $d \in [0.15]$. sMRI, structural MRI. rs-fMRI, resting-state fMRI.

Table 1.

Effect sizes and predictive value of the most consistent differences in individual, environmental and clinical characteristics between suicidal thoughts and behaviors groups by informant

	Child-reported suicidal thoughts and behaviors n=684		Caregiver-reported suicidal thoughts and behaviors n=654		Concordantly-reported suicidal thoughts and behaviors n=198	
Percentage of positive cases	9.1%		8.7%		2.8%	
	d	AUPRC	d	AUPRC	d	AUPRI
Individual characteristics						
Sex (% male)	0.17	0.04	0.29	0.03	0.33	0.0
Exposure to stressful events (%)	0.18	0.06	0.36	0.05	0.35	0.0
Environmental, family and school characteristics						
Economic problems in the last year (%)	0.22	0.07	0.31	0.07	0.33	0.0
Family conflict (Caregiver report), mean (sd)	0.18	0.11	0.49	0.14	0.44	0.0
Family conflict (Child report), mean (sd)	0.52	0.15	0.40	0.13	0.64	0.0
Positive school environment, mean (sd)	0.44	0.07	0.36	0.07	0.61	0.0
Individual clinical characteristics						
General psychopathology (CBCL), mean (sd) T-scores	0.62	0.18	1.16	0.30	1.33	0.1
Current Psychiatric disorders (Caregiver report) (%)						
Any disorder	0.37	0.07	0.78	0.06	0.87	0.0
Any depressive disorder	0.38	0.12	0.60	0.13	0.72	0.0
Any anxiety disorder	0.35	0.10	0.62	0.10	0.77	0.0
ADHD	0.37	0.10	0.71	0.11	0.77	0.0
Oppositional defiant disorder	0.52	0.13	0.91	0.16	0.97	0.0
Conduct disorder	0.59	0.15	1.07	0.20	1.05	0.0
PTSD	0.87	0.20	1.42	0.30	1.47	0.1
Family clinical characteristics						
General psychopathology (ASR), mean (sd) T-scores	0.35	0.13	0.66	0.17	0.74	0.0
Maternal mental health service use (%)	0.25	0.06	0.51	0.05	0.64	0.0
Paternal mental health service use (%)	0.14	0.07	0.31	0.07	0.37	0.0
Maternal mental health hospitalization (%)	0.40	0.12	0.63	0.13	0.77	0.0
Paternal mental health hospitalization (%)	0.31	0.11	0.44	0.11	0.57	0.0
Maternal history of depression (%)	0.27	0.07	0.53	0.07	0.67	0.0
Paternal history of depression (%)	0.30	0.09	0.45	0.09	0.58	0.0
Maternal history of suicide attempt/death (%)	0.50	0.13	0.73	0.15	0.81	0.0
Paternal history of suicide attempt/death (%)	0.48	0.13	0.58	0.14	0.83	0.0

Maternal alcohol/substance use during pregnancy (%)	0.29	0.10	0.31	0.10	0.34	0.0
---	------	------	------	------	------	-----

Effect sizes are Cohen’s *d* presented in absolute values, all $p_{FDR}<0.05$.

ADHD, Attention deficit hyperactivity disorder; ASR, Adult Self-Report; AUPRC, Area under precision-recall curve; CBCL, Child Behavior Checklist.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript