Review

Biological Psychiatry

Neural Correlates Associated With Suicide and Nonsuicidal Self-injury in Youth

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ABSTRACT

There is no definitive neural marker of suicidal thoughts and behaviors (STBs) or nonsuicidal self-injury (NSSI), and relative to adults, research in youth is more limited. This comprehensive review focuses on magnetic resonance imaging studies reporting structural and functional neural correlates of STBs and NSSI in youth to 1) elucidate shared and independent neural alternations, 2) clarify how developmental processes may interact with neural alterations to confer risk, and 3) provide recommendations based on convergence across studies. Forty-seven articles were reviewed (STBs = 27; NSSI = 20), and notably, 63% of STB articles and 45% of NSSI articles were published in the previous 3 years. Structural magnetic resonance imaging research suggests reduced volume in the ventral prefrontal and orbitofrontal cortices among youth reporting STBs, and there is reduced anterior cingulate cortex volume related to STBs and NSSI. With regard to functional alterations, blunted striatal activation may characterize STB and NSSI youth, and there is reduced frontolimbic task-based connectivity in suicide ideators and attempters. Resting-state functional connectivity findings highlight reduced positive connectivity between the default mode network and salience network in attempters and show that self-injurers exhibit frontolimbic alterations. Together, suicidal and nonsuicidal behaviors are related to top-down and bottom-up neural alterations, which may compromise approach, avoidance, and regulatory systems. Future longitudinal research with larger and well-characterized samples, especially those integrating ambulatory stress assessments, will be well positioned to identify novel targets that may improve early identification and treatment for youth with STBs and NSSI.

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Suicidal thoughts and behaviors (STBs) and nonsuicidal self-injury (NSSI) in youth are major public health concerns. Although STBs and NSSI often co-occur (1), their etiologies are complex and only partially overlap, suggesting both shared and unique vulnerability factors that potentiate STBs and NSSI (2,3). Recent data show that 12.1% of adolescents think about suicide and 4.1% have made an attempt (4). This is concerning, as upwards of 70% of completers are first-time attempters, with suicide deaths markedly higher among males (5). By comparison, 15% to 20% of adolescents report lifetime NSSI engagement (6), disproportionately affecting females (7). These sex differences are important to consider, particularly as NSSI is often a precursor to suicidal behaviors in females, but many males attempting suicide report little or no NSSI history (8,9). Critically, the motivation for engaging in suicidal [e.g., intolerance of psychological pain (10); perceived burdensomeness (11)] versus nonsuicidal [e.g., self-punishment (12); social signaling (13)] behaviors also may differ, perhaps influencing why NSSI often desists in adulthood (14), whereas STBs may persist (15,16). Taken together, contemporary models underscore the importance of elucidating interactive, and potentially transactional, processes that may differentially shape the trajectories of STBs and NSSI during the transition from adolescence to adulthood and, accordingly, focus on identifying biological (e.g., neural correlates) and environmental (e.g., child abuse) factors in the STB and NSSI pathways (2,3,13,17–20).

The diathesis–stress model provides a framework to understand vulnerability to self-injurious behaviors. Neural alterations are biological diatheses that may be a necessary but not sufficient predisposition to engage in self-injurious behaviors. Coupled with specific environmental exposures—particularly acute stress (e.g., peer victimization, interpersonal loss)—the likelihood of suicidal (21–23) and nonsuicidal (24–26) behaviors may increase. Childhood and adolescence represent a unique developmental phase to unpack neural diatheses and stressors that may be separable from those in adults. From a neurodevelopmental perspective, this is a period characterized by asynchronicity between limbic and prefrontal systems (27). Although normative, this has a direct effect on motivated behavior, particularly as it relates to the neural circuitry of approach, avoidance, and regulatory systems. Within the triadic model of motivated behavior, the approach system is guided by the ventral striatum, the avoidance system is largely controlled by the amygdala, and the regulatory system—generally managed by the prefrontal cortex (PFC)—is

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believed to balance approach and avoidance behaviors (28). Indeed, Casey *et al.* (29) have long advanced that risky behaviors in youth stem from earlier maturation of subcortical regions relative to immature prefrontal systems. By contrast, STBs and NSSI may manifest not when there is asynchronicity between limbic and prefrontal systems, but perhaps instead owing to deficiencies at each level—across approach, avoidance, and regulatory systems. Although failure with any one system may result in the emergence of debilitating symptoms or risky behaviors [e.g., (30,31)], when each system is compromised, it undermines the capacity to engage in compensatory strategies (e.g., future-oriented thinking, cognitive flexibility) that would otherwise limit the tendency to engage in suicidal and nonsuicidal behaviors. This is consistent with a recent model summarizing extant STB findings (32), showing that alterations within the extended ventral PFC (VPFC) system may potentiate suicidal thinking, given prominent roles in negative self-referential thinking and rumination (33,34). Suicidal thinking may then be exacerbated by dorsolateral PFC (DLPFC), inferior frontal gyrus (IFG), rostral PFC, and dorsal anterior cingulate cortex (ACC) alterations, as this directly bears on effective cognitive control, flexibility, and decision making (35). Perturbations in bottom-up and top-down connections between these extended systems may, for some, facilitate the transition from suicidal ideation to behavior. It remains unknown, however, whether this relates to STBs in youth, and if this model is applicable to NSSI.

Neural alterations do not operate in isolation. Rather, they interact dynamically with stress (2,3,36,37), a point underscored by the fact that stress is prominently featured in many leading STB (11,20,38) and NSSI (25,39) theories. Childhood and adolescence reflect a unique developmental period whereby there is a progressive shift toward autonomy from parents and greater reliance on peers (40). Interpersonal stressors occur in great abundance during this life stage (23)—a byproduct of navigating puberty (41), fostering close friendships (42), exploring romantic relationships (43), and increasingly, using social media (44). Acute interpersonal stress may serve as proximal triggers that interact with neural diatheses, which, we maintain in this review, may facilitate the transition from ideation to action for both suicidal and nonsuicidal behaviors.

Presently, there are no definitive neural markers of STBs or NSSI. Several prior reviews have highlighted brain regions implicated in suicidal (32,45–49) and nonsuicidal (39,50) behaviors. This review focuses on extant magnetic resonance imaging (MRI) studies reporting structural and functional neural correlates of STBs and NSSI in youth with the aim of 1) elucidating shared and unique neural alternations, 2) clarifying how developmental processes may interact with neural alterations to confer risk, and 3) providing recommendations based on convergence across studies.

METHODS

A PubMed and Google Scholar literature search through January 15, 2020, was conducted to identify original research using the following search terms: *MRI*, *magnetic resonance imaging*, *structural MRI*, *fMRI*, *functional MRI*, *functional magnetic resonance imaging*, *functional connectivity*, *resting state fMRI*, *resting state connectivity* in combination with *suicide*, *suicide attempt*, *suicidal ideation*, *suicidal behavior*, *non-suicidal self-injury*, *parasuicidal behaviors*, and *self-harm*. Articles were selected if they 1) were published in an English-language peer-reviewed journal, 2) included participants under 26 years of age, 3) included participants with lifetime STBs and/or NSSI, and 4) focused on structural, functional, or resting-state MRI. There were no inclusion requirements based on STB or NSSI assessments (see Tables S1–S3 for clinical measures) or MRI scanners. Several reviewed publications assess neural correlates of STBs among youth with lifetime NSSI, and conversely, NSSI studies include STB youth (see Tables S1–S3 for sample overlap). Extant research is summarized, but a pooled meta-analytic estimate of effects is not provided.

RESULTS

Forty-seven articles satisfied inclusion criteria (STBs = 27; NSSI = 20) (Figure 1). The majority of participants in these studies reported lifetime major depressive disorder (MDD), bipolar disorder (BD), and/or borderline personality disorder (BPD) (see Tables 1–3 for sample characteristics). There is enormous heterogeneity in methodological approaches. Most STB studies compared suicide attempters with a psychiatric or healthy comparison group. Few studies compared attempters with ideators. NSSI samples were typically compared with either youth with psychiatric conditions or healthy youth, with some research testing correlates among NSSI youth only. The vast majority of research is cross-sectional.

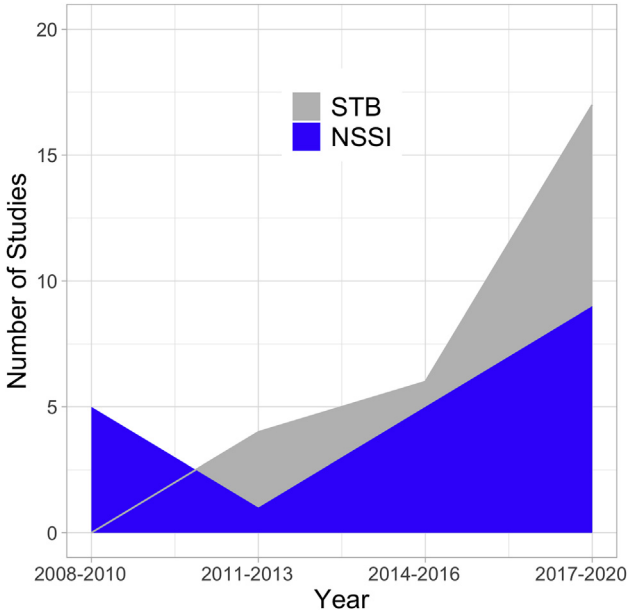

Figure 1. Suicidal thoughts and behaviors (STBs) (gray) and nonsuicidal self-injury (NSSI) (blue) neuroimaging studies included in this comprehensive review. Publications are divided into 3-year bins and calculated separately for STBs and NSSI.

Table 1. Structural Alterations Associated With Suicidal Thoughts and Behaviors and Nonsuicidal Self-injury

Publication	Sample	Age, Years	Method	Select Findings
Suicidal Thoughts and Behaviors				
Fan *et al.*, 2019 (54)[a]	BD+SA = 21 BD = 25 MDD+SA = 19 MDD = 18	14–25	Whole brain, SPM8, GMV	BD+SA, MDD+SA > BD, MDD ↓ left VPFC (BA 11); MDD+SA > MDD, BD+SA, BD ↑ left VPFC (BA 47)[b,c]
Fradkin *et al.*, 2017 (57)	MDD+SA = 29 HC = 29	12–19	Whole brain, FreeSurfer/ Qdec, cortical thickness, surface area	MDD+SA ↓ VMPFC cortical thickness ↑ motor impulsivity; MDD+SA ↑ right paracentral lobule cortical thickness ↑ nonplanning impulsivity[b,d]
Goodman *et al.*, 2011 (59)	BPD+MDD = 13 HC = 13	13–17	ROI (cingulate, PFC), GMV/WMV	↑ SA ↓ BA 24 volume, ↑ BA 23 WMV[b,d]
Ho *et al.*, 2018 (58)	Community sample = 152[e]	9–13	ROI (caudate, NAcc, putamen), FreeSurfer, GMV	↓ Bilateral putamen predicts ↑ implicit SI[b,d]
Huber *et al.*, 2019 (55)[a]	BD+SA = 15 BD = 18 HC = 25	13–21	ROI (OFC), FreeSurfer, thickness/volume	BD+SA > HC ↓ Left OFC volume, ↓ bilateral OFC thickness; BD+SA > BD ↓ right OFC thickness; ↑ SA lethality ↓ bilateral OFC volume; ↑ SI ↓ left OFC volume[b,d]
Johnston *et al.*, 2017 (53)[a,f]	BD+SA = 26 BD = 42 HC = 45	14–25	Whole brain, SPM5, GMV	BD+SA > BD ↓ right OFC, right hippocampus, bilateral cerebellum GMV; BD+SA > HC ↓ right hippocampus GMV[b,c]
Lippard *et al.*, 2019 (56)	Future SA = 17 No future SA = 29	13–25	Whole brain, SPM12, GMV	Future SA > no future SA ↓ VPFC GMV (left BA 11, right ventral BA 10, right BA 47), ↓ left DRPFC (BA 10)[b,d]
McLellan *et al.*, 2018 (60)	MDD+SA = 14 MDD = 14 HC = 17	12–21	ROI (rSTG, frontal, temporal regions), FreeSurfer, cortical thickness/volume	MDD+SA > HC ↓ rSTG volume[b,d]
Pan *et al.*, 2015 (61)	MDD+SA = 28 MDD = 31 HC = 41	12–17	Whole brain, FreeSurfer/ Qdec, cortical thickness/ GMV/WMV	MDD+SA > HC ↓ rSTG GMV[b,d]
Nonsuicidal Self-injury				
Ando *et al.*, 2018 (64)[a]	NSSI+SA = 16[e] NSSI = 13[e] HC = 21	NSSI = 15.9 ± 1.3[g,h] HC = 15.8 ± 1.1[g]	ROI (PFC, ACC, insula, thalamus, hippocampus, amygdala), FreeSurfer, GMV	All NSSI > HC ↓ insula GMV, ↓ ACC GMV; NSSI+SA> NSSI, HC ↓ ACC GMV[b,i]
Beauchaine *et al.*, 2019 (62)[a]	NSSI = 20[e] No NSSI = 20[e]	13–19	Whole brain, SPM12, GMV	NSSI > no NSSI ↓ bilateral insular GMV, ↓ right IFG[b,i]
Chanen *et al.*, 2008 (66)[j]	BPD = 20 HC = 20	BPD = 17.3 ± 1.1[g] HC = 19.0 ± 2.2[g]	ROI (OFC, amygdala, hippocampus), hand tracing, GMV	No association between OFC GMV and number of episodes[b,c]; no association between amygdala or hippocampal GMV and number of episodes[b,i] Sex: BPD males > BPD females, HC ↓ amygdala GMV
Takahashi *et al.*, 2009 (65)[j]	BPD = 20 HC = 20	BPD = 17.3 ± 1.1[g] HC = 19.0 ± 2.2[g]	ROI (insula), hand tracing, GMV	No association between insula GMV and number of episodes[d,k]; null findings between BPD with and without episodes in the past 6 mo
Takahashi *et al.*, 2009 (67)[j]	BPD = 20 HC = 20	BPD = 17.3 ± 1.1[g] HC = 19.0 ± 2.2[g]	ROI (AI, CSP), hand tracing, length	No association between AI or CSP length and number of episodes[b,c]
Takahashi *et al.*, 2010 (68)[j]	BPD = 20 HC = 20	BPD = 17.3 ± 1.1[g] HC = 19.0 ± 2.2[g]	ROI (STG), hand tracing, volume	No association between STG volume and number of episodes; null findings between BPD with and without episodes in the past 6 mo[b,d]

Table 1. Continued

Publication	Sample	Age, Years	Method	Select Findings
Whittle *et al.*, 2009 (69)[j]	BPD = 15 HC = 15	BPD = 17.4 ± 1.15[g] HC = 19.7 ± 2.18[g]	ROI (ACC), hand tracing, GMV	↓ Left ACC GMV ↑ number of episodes[b,i]

In the age column, values are range or mean ± SD.

ACC, anterior cingulate cortex; AI, adhesio interthalamica; BA, Brodmann area; BD, bipolar disorder; BPD, borderline personality disorder; CSP, cavum septum pellucidum; DRPFC, dorsal rostral prefrontal cortex; future SA, participant made a suicide attempt between baseline and follow-up; GMV, gray matter volume; HC, healthy control; IFG, inferior frontal gyrus; MDD, major depressive disorder; NAcc, nucleus accumbens; no future SA, participant did not make a suicide attempt between baseline and follow-up; NSSI, nonsuicidal self-injury; OFC, orbitofrontal cortex; PFC, prefrontal cortex; ROI, region of interest; rSTG, right superior temporal gyrus; SA, suicide attempt; SI, suicidal ideation; VMPFC, ventral medial prefrontal cortex; VPFC, ventral prefrontal cortex; WMV, white matter volume.

[a]Indicates strong methodological approach (i.e., clinical-control comparison, interview assessment of STBs/NSSI, data analysis); [b]Age effects not reported; [c]Sex effects null; [d]Sex effects not reported; [e]Comorbid disorders (see Table S1 for inclusion and exclusion criteria); [f]Also includes functional magnetic resonance imaging (Table 2); [g]Age range not reported; [h]Age range for all NSSI participants including the NSSI+SA group; [i]Female-only sample; [j]Same sample; [k]Age effects null.

STRUCTURAL ALTERATIONS

The reviewed STB and NSSI research probing structural differences employed a wide range of methodologies, including region-based and whole-brain (voxelwise or vertexwise) assessments of structural properties. Several studies relied on hand tracing, though the majority used automated methods (e.g., FreeSurfer) to quantify subcortical volumes as well as cortical thickness and surface area. Other studies used voxel-based morphometry toolboxes (e.g., SPM) to quantify gray matter volume (GMV). Sample characteristics, structural method, and select findings (including age and sex effects) are summarized in Table 1.

Suicidal Thoughts and Behaviors

Structural alterations within the VPFC and orbitofrontal cortex (OFC), which are key to emotion inhibition, decision making, and self-control [e.g., (51,52)], are implicated. Among adolescents with MDD and BD (53,54), suicide attempters showed reduced VPFC and OFC GMV relative to MDD and BD nonattempters, respectively. There is evidence of reduced OFC thickness among BD suicide attempters, and reduced OFC volume negatively correlated with suicidal ideation severity and attempt lethality (55). In a prospective study, reduced ventral and rostral prefrontal GMV at baseline differentiated adolescents and young adults with mood disorders who later attempted suicide (56). Studies on PFC differences, however, are complicated by inconsistent laterality effects [left (54,55) vs. right (53)]. It also is unclear whether results reflect attempts specifically or the underlying mental disorders more broadly. Suicide attempters with MDD exhibited increased OFC GMV (left Brodmann area 47) relative to nonattempters with MDD as well as attempters and nonattempters with BD (54). However, there was a negative correlation between ventromedial PFC thickness and impulsivity among suicide attempters with MDD (57).

Outside of the PFC, suicide attempters with BD have reduced hippocampal (53,54) and bilateral cerebellum (53) GMV compared with BD nonattempters. Additionally, putamen volume was prospectively associated with implicit, but not explicit, suicidal ideation (58). Research also implicates the cingulate cortex, as the number of suicide attempts in adolescents with comorbid MDD and BPD correlated with smaller averaged GMV and white matter volume in the ventral ACC, as well as greater white matter volume in the ventral posterior cingulate cortex (PCC) (59). Yet, it is not clear if this is driven by suicide attempts or overall mental disorder severity. There also is partial evidence linking temporal lobe structure to STBs. MDD attempters have reduced right superior temporal gyrus GMV relative to healthy adolescents but not compared with MDD nonattempters (60,61).

Nonsuicidal Self-injury

Fewer studies examined structural alterations in youth exhibiting NSSI, and this work often 1) assessed youth reporting parasuicidal behaviors (a term no longer commonly used, as it conflates suicidal self-injury and NSSI)[1] and 2) compared NSSI youth with healthy control subjects (as opposed to psychiatric samples without NSSI).

There is limited work probing prefrontal differences related to NSSI. One study reported reduced GMV in the right IFG among NSSI adolescents compared with nondepressed individuals (62). Several studies examined the insula, which may modulate subjective emotional experience (63). In comparison with healthy control subjects, self-injurers showed reduced insula GMV (62,64), but this was not substantiated in youth with BPD reporting parasuicidal behaviors (65). Other research found no relationship with the OFC (66), midline structures (67), or superior temporal gyrus (68).

Several studies point to ACC alterations. Among adolescents with BPD, a greater number of lifetime parasuicidal behaviors in the past 6 months associated with smaller left ACC volume (69), consistent with findings comparing past-year self-injurers and healthy youth (64). Regarding this latter finding, most NSSI participants (55.2%) reported a lifetime suicide attempt, and given prior work linking anterior ACC volume to suicidal behaviors (59), we cannot determine whether effects are specific to NSSI.

FUNCTIONAL NEUROIMAGING

Across the STB and NSSI literature, investigators used a range of experimental paradigms (see Table S4 for task descriptions). Several studies tested task connectivity with

[1]For studies assessing parasuicidal behaviors, we use this term to be consistent with findings reported in the published work.

Table 2. Functional Neural Markers Related to Suicidal Thoughts and Behaviors and Nonsuicidal Self-injury

Publication	Sample	Age, Years	Method	Select Findings
Suicidal Thoughts and Behaviors				
Alarcón *et al.*, 2019 (75)[a,b]	DEP+SA = 24 DEP+High SI = 27 DEP+Low SI = 31 HC = 38	11–18	PPI (amygdala seed) Emotional Self-Other Morph-Query Task *Contrast*: self vs. other for happy, neutral, or sad	DEP+SA, DEP+High SI > DEP+Low SI ↑ PPI to DLPFC/dACC, DMPFC, precuneus; DEP+High SI > DEP+SA, DEP+Low SI ↑ PPI to IPL; DEP+SA ↑ left PPI to ACC; DEP+High SI ↑ right PPI to ACC[c,d]
Chase *et al.*, 2019 (84)	MDD+SA = 19 MDD = 22 HC = 23	MDD+SA = 15.6 ± 1.5[e] MDD = 16.0 ± 1.4[e] HC = 14.7 ± 1.8[e]	Whole brain Dynamic Faces Task *Contrast:* face vs. shape for angry, fearful, happy, and sad	Null findings between MDD+SA and MDD[c,d]
Harms *et al.*, 2019 (82)[b]	3 group analyses: DEP+High SI = 45 DEP+Low SI = 42 HC = 39 4 group analyses: DEP+SA = 26 DEP+High SI = 28 DEP+Low SI = 33 HC = 39	11–18	Whole brain Cyberball Task *Contrast*: exclusion or inclusion vs. practice	DEP+High SI (including SA) > DEP+Low SI, HC ↓ insula, putamen across conditions; DEP+SA > DEP+High SI, DEP+Low SI ↑ ACC, SFG, MFG across conditions[c,f]
Johnston *et al.*, 2017 (53)[a,g]	BD+SA = 26 BD = 42 HC = 45	14–25	Bilateral amygdala seed connectivity Emotional Face Processing Paradigm *Contrast*: emotion vs. fixation for fearful, happy, or neutral	BD+SA> BD ↓ PPI to left ventral PFC connectivity across neutral and happy conditions (fearful did not survive AlphaSim spatial extent thresholding) and ↓ PPI to right rostral PFC for neutral emotion; Among BD+SA ↑ SI ↓ amygdala-right rostral PFC and ↑ attempt lethality ↓ amygdala-left VPFC[c,f]
Just *et al.*, 2017 (86)[a]	SI = 17 HC = 17	SI = 22.9 ± 3.6[e] HC = 22.1 ± 2.8[e]	Whole brain, multivoxel analysis Emotional Semantics Task Machine learning	Left inferior parietal region and left IFG predict SI group membership; Gaussian naïve Bayes classifier correctly discriminated ideators from control subjects as well as attempters (subset of ideators) from ideators with high (85%–94%) accuracy[c,d]
Miller *et al.*, 2018 (85)	SI = 14 No SI = 35	13–20	Whole brain Emotional Regulation Task *Contrast*: reappraisal negative vs. view negative; view negative vs. view neutral	SI > no SI ↑ right DLPFC during cognitive reappraisal; SI > No-SI ↓ right thalamus, left cerebellum/lateral occipital region, right DLPFC, right TPJ (only when controlling for depression symptoms) when viewing negative stimuli[c,d]
Oppenheimer *et al.*, 2020 (80)	ANX = 36	11–16	Whole brain, ROI (AI and dACC) Chatroom Interact Task *Contrast*: rejection vs. acceptance	Peer victimization moderated right AI activation and SI[f,h]
Pan *et al.*, 2011 (78)[i]	MDD+SA = 15 MDD = 15 HC = 14	13–17	Whole brain Go/no-go task	MDD+SA > MDD ↓ right anterior cingulate gyrus during response inhibition blocks[f,h]
Pan *et al.*, 2013 (83)[i]	MDD+SA = 14 MDD = 15 HC = 15	MDD+SA = 16.2 ± 0.8[e] MDD = 15.9 ± 1.6[e] HC = 15.3 ± 1.4[e]	Whole brain, PPI (right anterior cingulate seed) Facial Emotion Processing Task *Contrast:* angry 50% intensity vs. fixation	MDD+SA > MDD ↑ attentional control circuitry (right anterior cingulate gyrus, left DLPFC), primary sensory cortex, right MTG; MDD+SA > MDD, HC ↓ PPI to bilateral insula connectivity[f,h]

Table 2. Continued

Publication	Sample	Age, Years	Method	Select Findings
Pan *et al.*, 2013 (77)[i]	MDD+SA = 15 MDD = 14 HC = 13	12–17	Whole brain Iowa Gambling Task	MDD > MDD+SA, HC ↑ left hippocampus during low-risk decisions (MDD > MDD+SA does not survive post hoc correction for multiple comparisons)[f,h]
Quevedo *et al.*, 2016 (74)[b]	DEP+HS = 43 DEP+LS = 39 HC = 37	11–18	Whole brain Emotional Self-Other Morph-Query Task *Contrast*: self or other vs. baseline for happy, neutral, or sad	DEP+HS > DEP+LS, HC ↑ bilateral cuneus, MOG; DEP+HS, DEP+LS > HC ↑ right DLPFC across all conditions[c,f]
Nonsuicidal Self-injury				
Bonenberger *et al.*, 2015 (99)	NSSI = 14[j] HC = 16	22.4 ± 3.4[e]	Whole brain, ROI (posterior, medial, and anterior Insula, somatosensory cortex) Electrical Stimulation Task	NSSI > HC ↓ intensity-modulated activity in AI[c,k]
Brown *et al.*, 2017 (90)	MDD+BPD+NSSI$_{Adult}$ = 14 MDD+NSSI$_{Adolescent}$ = 13 HC$_{Adolescent}$ = 15 HC$_{Adult}$ = 17	MDD+BPD+NSSI = 23.6 ± 4.1[e] MDD+NSSI = 15.5 ± 2.0[e] HC$_{Adolescent}$ = 14.5 ± 1.7[e] HC$_{Adult}$ = 23.2 ± 4.4[e]	Whole brain Cyberball Task *Contrast*: exclusion vs. inclusion	MDD+BPD+NSSI > HC$_{Adult}$ and MDD+NSSI > HC$_{Adolescent}$ ↑ ventral ACC; MDD+NSSI > MDD+BPD+NSSI, HC$_{Adolescent}$ ↑ putamen[c,d]
Demers *et al.*, 2019 (97)[i]	NSSI = 25[j]	13–21	Whole brain Masked Emotional Face Task *Contrast*: masked fearful vs. masked happy	↑ Emotional awareness ↑ right SMA and right IFG activity[c,k]
Groschwitz *et al.*, 2016 (88)	MDD+NSSI = 14 MDD = 14 HC = 15	15.2 ± 1.8[e]	Whole brain, ROI (VLPFC, mPFC) Cyberball Task *Contrast*: exclusion vs. inclusion	MDD+NSSI > MDD ↑ mPFC, VLPFC, parahippocampus[c,d]
Osuch *et al.*, 2014 (98)	NSSI = 13[j] PC = 15[j]	16–24	Task connectivity, whole brain Cold Stimulus Task *Contrast*: experimenter or self, instruction or administration of cool or cold stimuli vs. fixation	NSSI > PC ↑ parahippocampal gyrus, IFG, amygdala, right midbrain/pons, right middle frontal gyrus across all conditions[c,d]
Perini *et al.*, 2019 (89)	NSSI = 27[j] HC = 27	15–18	Whole brain, multivoxel pattern analysis Social Processing Task	Whole brain gray matter, multivariate analysis resulted in 68% accuracy for classification[c,k]
Plener *et al.*, 2012 (95)	NSSI = 9[j] HC = 9	14–18	Whole brain Emotional and Self-injuring Image Task	NSSI > HC ↑ OFC, inferior parietal cortex, inferior/middle frontal cortex to NSSI stimuli[c,k]
Poon *et al.*, 2019 (93)	NSSI-HR = 19[j] NSSI-LR = 52[j]	12–14	ROI (caudate, putamen, NAcc, vmPFC) Card Guessing Task *Contrast*: win vs. neutral	NSSI-HR > NSSI-LR ↑ bilateral putamen after reward receipt[f,h]
Quevedo *et al.*, 2016 (87)[a]	DEP+NSSI = 50 DEP = 36 HC = 37	14.8 ± 1.6[e]	Whole brain Interpersonal Self-processing Task *Contrast*: perspective vs. baseline	DEP+NSSI > DEP and HC ↑ dorsal PFC, precuneus, PCC, superior parietal lobule, left/right limbic structures, fusiform, MTG across all conditions; DEP+NSSI > DEP, HC ↑ amygdala, hippocampus, parahippocampus, fusiform during mother's perspective[c,d]
Sauder *et al.*, 2016 (92)	Self-injury = 19[j] HC = 19	13–19	ROI (striatum, OFC, amygdala) Monetary Incentive Delay Task *Contrast*: reward cue vs. neutral cue	Self-injury > HC ↓ putamen, OFC, amygdala to reward cues[c,k]

Table 2. Continued

Publication	Sample	Age, Years	Method	Select Findings
Schreiner *et al.*, 2017 (96)[l,m]	NSSI = 24[j] HC = 17	13–21	Task connectivity, PPI (amygdala seed) Emotional Face Matching Task	NSSI > HC ↑ right amygdala connectivity clusters: 1) right lingual gyrus, occipital pole, occipital/temporal fusiform, 2) right lateral occipital cortex, superior parietal lobule during entire task[c,k]

In the age column, values are range or mean ± SD.

ACC, anterior cingulate cortex; AI, anterior insula; ANX, anxiety disorders; BP, bipolar disorder; BPD, borderline personality disorder; dACC, dorsal anterior cingulate cortex; DEP, depressive disorder including major depressive disorder, dysthymia, or depressive disorder not otherwise specified; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; HC, healthy control; HR, high risk; HS, high suicidality; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; LS, low suicidality; MDD, major depressive disorder; MFG, middle frontal gyrus; MOG, middle occipital gyrus; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; NAcc, nucleus accumbens; NSSI, nonsuicidal self-injury; NSSI-HR, high risk for nonsuicidal self-injury based on thoughts; NSSI-LR, low risk for nonsuicidal self-injury based on absence of thoughts; OFC, orbitofrontal cortex; PC, psychiatric control subjects with no nonsuicidal self-injury history; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PPI, psychophysiological interaction; ROI, region of interest; SA, suicide attempt history; self-injury, self-inflicted injury including suicide attempt; SI, suicidal ideation; SFG, superior frontal gyrus; SMA, supramarginal gyrus; TPJ, temporoparietal junction; VLPFC, ventrolateral prefrontal cortex; VPFC, ventral prefrontal cortex.

[a]Indicates strong methodological approach (i.e., clinical-control comparison, interview assessment of STBs/NSSI, data analysis, large sample); [b]Overlapping sample; [c]Age effects not reported; [d]Sex effects not reported; [e]Age range not reported; [f]Sex effects null; [g]Also includes structural magnetic resonance imaging (Table 1); [h]Age effects null; [i]Overlapping sample; [j]Comorbid disorders (see Table S2 for inclusion and exclusion criteria); [k]Female-only sample; [l]Overlapping sample; [m]Also includes resting-state magnetic resonance imaging (Table 3).

psychophysiological interaction, quantifying condition-related differences in time series correlation between activity in a seed region of interest and other brain regions (70,71). Sample characteristics, methodological approaches (e.g., whole brain, region of interest), and select findings (including age and sex effects) are provided in Table 2.

Suicidal Thoughts and Behaviors

Self-processing. Distorted self-referential thinking is a hallmark of adolescent MDD (72), and these biases potentiate suicidal thinking (73). Two recent studies focused on processing images of one's own versus others' faces—a subdomain of self-referential processing. Quevedo *et al.* (74) compared adolescents reporting low and high suicidality—composite scores of ideation and attempts. High-suicidality youth exhibited greater activation in the bilateral cuneus and middle occipital gyrus compared with low-suicidality and healthy participants across all conditions. Additionally, both suicidality groups showed greater activation in the right DLPFC (74). Within the same sample, high ideators and attempters also showed greater task connectivity between the amygdala and the DLPFC, dorsal ACC, dorsomedial PFC, and precuneus compared with low ideators (75). Amygdala-seed psychophysiological interaction connectivity was elevated in the high ideators and attempters relative to the low-ideation group in the DLPFC, dorsomedial PFC, and precuneus, and by contrast, connectivity with inferior parietal lobule was elevated in the high-ideation group compared with low-ideation group and attempters. Greater connectivity with the rostral ACC during self versus other face trials also was found for the left amygdala in attempters (compared with all groups) but for the right amygdala in high ideators (relative to low ideators and control subjects) (75).

Impulsivity and Social Reward Processes. Impulsive decision making and experiencing social rejection are known correlates of suicidal behaviors (21,76). Although nonattempters showed greater left hippocampal activation during low-risk (but not high-risk) decisions relative to healthy adolescents and suicide attempters during an Iowa Gambling Task (77), it did not survive post hoc correction for multiple comparisons. Healthy and attempter youth did not differ. The investigators also administered a response inhibition task, and nonattempters exhibited greater activation within the right ACC relative to attempters but not relative to healthy control subjects (78).

One study used the Chatroom Interact Task (79) to probe neural response following social acceptance and rejection. Experience of peer victimization moderated the relationship between right anterior insula activation (rejection vs. acceptance) and suicidal ideation (80). A study using the Cyberball task (81) found that compared with low ideators and control subjects, high ideators (including attempters) showed reduced activation in the insula and putamen across conditions, but subsequent analyses indicated a pattern of increased activation in the ACC, superior frontal gyrus, and middle frontal gyrus among attempters versus ideators (82).

Emotion Processing. Pan *et al.* (83) tested response to face stimuli morphed to different levels of emotional intensity. The most consistent findings emerged during the 50% angry face condition; relative to nonattempters, attempters showed greater activation in attentional control circuitry (right ACC, left DLPFC), the primary sensory cortex, and the right middle temporal gyrus (83). Group differences in psychophysiological interaction showed reduced connectivity between a right ACC seed and the bilateral insula when viewing 50% angry faces versus baseline for depressed attempters relative to depressed nonattempters and healthy control subjects. Recent work from the same research group, however, failed to replicate these effects (84).

Table 3. Resting-State Functional Connectivity Patterns Related to Suicidal Thoughts and Behaviors and Nonsuicidal Self-injury

Publication	Sample	Age, Years	Method	Select Findings
Suicidal Thoughts and Behaviors				
Cao *et al.*, 2015 (106)	SA = 19 HC = 20	SA: 19.84 ± 1.61[a] HC: 20.30 ± 1.72[a]	Voxelwise ReHo	SA > HC ↑ MFG, parietal, precuneus ↓ cerebellum, fusiform, hippocampus, paraphippocampal, angular, IFG, MFG[b,c]
Cao *et al.*, 2016 (107)[d]	MDD+SA = 35 MDD = 18 HC = 47	15–25	Voxelwise ALFF	MDD+SA > MDD, HC ↑ MTG, STG, MOG[b,c]
Cao *et al.*, 2020 (103)[d,e]	MDD+SA = 35 MDD = 18 HC = 47	15–25	ICA networks	MDD+SA > MDD ↓ aDMN-SN ↑ FPN-SN, FPN-aDMN; MDD+SA > HC ↓ aDMN-pDMN, aDMN-FPN ↑ FPN-SN[b,c]
Cullen *et al.*, 2014 (100)[f]	MDD = 41 HC = 29	12–19	Seed-based	MDD-related AMYG seed did not relate to suicide severity[b,c]
Ordaz *et al.*, 2018 (104)[g]	MDD = 40	14–17	ICA networks	↑ Lifetime ideation severity ↓ coherence in ECN, aDMN, SN[h,i]
Schreiner *et al.*, 2019 (101)[f]	MDD = 58	12–19	Seed-based	↑ Suicide severity ↑ precuneus-cerebellum, IFG; ↓ PCC-cerebellum, cingulate[h,i]
Schwartz *et al.*, 2019 (105)[e,g]	MDD = 33	14–17	ICA networks	6-mo follow-up: ↓ ideation severity ↑ SN coherence[h,i]
Zhang *et al.*, 2016 (102)[d]	MDD+SA = 35 MDD = 18 HC = 47	15–25	ICA networks	MDD+SA > MDD ↑ DMN-cerebellum, lingual ↓ DMN-precuneus[h,i]
Nonsuicidal Self-injury				
Cullen *et al.*, 2020 (108)[j]	NSSI = 18[k]	13–21	Seed-based	↓NSSI with NAC treatment = ↓ AMYG-SMA, ↑ AMYG-inferior frontal, ↓ NAcc-superior medial frontal[h,l]
Santamarina-Perez *et al.*, 2019 (109)[e]	NSSI = 24[k] HC = 16	12–17	Seed-based	NSSI > HC ↓ AMYG-ACC, insula; ↓mPFC-precentral/postcentral gyri, insula; ↓NSSI with treatment = ↓ AMYG-ACC, ↑ AMYG-parahippocampal, ↓ mPFC-AMYG/striatum[h,i]
Schreiner *et al.*, 2017 (96)[i,m]	NSSI = 25[k] HC = 20	13–21	Seed-based	NSSI > HC ↓ AMYG-ACC/SMA, ↑ AMYG-angular/temporal gyri[h,l]

In the age column, values are range or mean ± SD.

ACC, anterior cingulate cortex; aDMN, anterior default mode network; ALFF, amplitude of low-frequency fluctuation; AMYG, amygdala; DMN, default mode network; ECN, executive control network; FPN, frontoparietal network; HC, healthy control; ICA, independent component analysis; IFG, inferior frontal gyrus; MDD, major depressive disorder; MFG, middle frontal gyrus; MOG, middle occipital gyrus; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; NAC, *N*-acetylcysteine; NAcc, nucleus accumbens; NSSI, nonsuicidal self-injury; PCC, posterior cingulate cortex; pDMN, posterior default mode network; ReHo, regional homogeneity; SN, salience network; SA, suicide attempt history; SFG, superior frontal gyrus; SMA, supramarginal gyrus; STG, superior temporal gyrus.

[a]Age range not reported; [b]Age effects null; [c]Sex effects null; [d]Same sample; [e]Indicates strong methodological approach (i.e., clinical-control comparison, interview assessments of STBs/NSSI, data analysis, and/or longitudinal design); [f]Overlapping sample; [g]Overlapping sample; [h]Age effects not reported; [i]Sex effects not reported; [j]Overlapping sample; [k]Comorbid disorders (see Table S3 for inclusion and exclusion criteria); [l]Female-only sample; [m]Also includes functional magnetic resonance imaging (Table 2).

During a gender-judgement emotional face task, BD attempters exhibited reduced bilateral amygdala connectivity to the left VPFC (across happy and neutral conditions) and to the right rostral PFC for neutral faces versus baseline. Within the attempter group, suicidal ideation negatively correlated with amygdala–right rostral PFC connectivity, and attempt lethality negatively correlated with amygdala–left VPFC connectivity (53). Among adolescent ideators, there was evidence of greater right DLPFC activation during effortful regulation when viewing negative images compared with nonideators. There was, however, reduced activation among ideators during passive viewing of negative stimuli within the right thalamus, left cerebellum/lateral occipital region, right DLPFC, and right temporal parietal junction (85)

One study utilized machine learning to establish a biological, neurocognitive basis for altered representations of suicide (e.g., death) and emotion (e.g., gloom) words. During the presentation of each word, participants were asked to actively think about the construct. Findings showed distinct neural signatures in the left inferior parietal region and left IFG that were predictive of suicide ideator group membership (86). A similar classification approach also discriminated suicide ideators and attempters. A critical next step is to determine whether these neural signatures can identify ideators prior to the attempt.

Nonsuicidal Self-injury

Self-processing. Quevedo *et al.*'s (87) task required participants to use their own (direct) or others' (indirect: mother, best friend, classmate) perspective when considering self-characteristics. Relative to a combined sample of depressed and healthy adolescents, depressed self-injurers

exhibited greater activation across all perspectives in the dorsal PFC, precuneus, PCC, superior parietal lobule, left/right temporal limbic structures (amygdala, parahippocampus, hippocampus), fusiform, and middle temporal gyrus. The mother perspective condition (compared with baseline) yielded similar findings among self-injurers in the amygdala, hippocampus, parahippocampus, and fusiform.

Social (Reward) Processing. Several NSSI studies probed neural response to social exclusion during the Cyberball Task. Relative to depressed adolescents, depressed self-injurers showed increased activation in the medial PFC, ventrolateral PFC, and parahippocampus during exclusion versus inclusion trials, suggesting that self-injurers may view social exclusion more negatively (88) [cf., (89)]. In a subsequent study among the self-injuring youth, there was enhanced activation in the left putamen within the same contrast relative to adults with BPD and healthy youth (90).

Research also explored alterations in incentive processing given known associations in adolescent MDD (91). Compared with healthy adolescents, there was blunted reward anticipation in the putamen, OFC, and amygdala in self-injuring youth (92). Among youth at high risk for NSSI (based on thoughts) but without any history of self-injurious behaviors, there was greater bilateral putamen activation following reward receipt compared with youth at low risk for NSSI, suggesting hypersensitivity to reward (93). Although alterations in anticipatory and consummatory reward processing may underlie risk for NSSI, divergent associations between mental disorders and reward responsiveness [e.g., MDD (91) vs. attention-deficit/hyperactivity disorder (94)] may influence this effect.

Emotion Processing. Researchers used a variety of emotion processing tasks to investigate neural alterations in NSSI. Plener *et al.* (95) showed self-injurers and healthy youth International Affective Picture System and self-injury images (e.g., razors). Compared with healthy youth, self-injurers exhibited greater activation in the OFC, inferior parietal cortex, and inferior/middle frontal cortex to NSSI stimuli (95). During an emotion face-matching task, there was no evidence of emotion-specific effects. However, NSSI and healthy youth showed divergent amygdala task connectivity, but it is not clear whether this reflects NSSI or MDD (or other comorbid disorders) (96). Finally, Demers *et al.* (97) found associations in self-injurers' emotional awareness and response to viewing masked fearful faces (relative to happy faces) in the supramarginal gyrus and right IFG.

Pain Processing. When comparing psychiatric control subjects with self-injurers, a painful cold compress was either self-administered (analogue to self-injury) or experimenter-administered. Compared with psychiatric control subjects, self-injurers showed greater activation in the parahippocampal gyrus, IFG, and amygdala across conditions (98). Bonenberger *et al.* (99) also probed pain via unpleasant electrical stimulation. Healthy control subjects exhibited anterior insula activation varying with increasing electrical stimuli intensity, but among self-injurers, this association was blunted (99).

RESTING-STATE MRI

The resting-state MRI literature on adolescent STBs and NSSI is smaller relative to structural and task-based functional MRI, and interpretations are challenging, given mixed methods and results (Table 3). Investigators primarily applied seed-based approaches, which focus on time series correlations between a region of interest and the rest of the brain voxelwise. Several studies applied data-driven approaches (e.g., independent component analysis) to explore commonly assessed networks (e.g., default mode network [DMN]). Two studies use voxel-based approaches to characterize local connectivity or timeseries variability.

Suicidal Thoughts and Behaviors

Seed-Based. Cullen *et al.* (100) identified depression-related differences in amygdala seed-based resting-state functional connectivity (RSFC), but this was not related to suicide severity. However, using an expanded sample of depressed youth, within-group analyses showed that suicidal ideation severity associated with greater connectivity between a right precuneus seed and the cerebellum and right IFG, as well as lower connectivity between a left PCC seed and the cerebellum and cingulate (101).

Network-Based. Compared with psychiatric control subjects, attempters showed increased connectivity between an independent component analysis–derived DMN component and the cerebellum and lingual gyrus, and decreased connectivity with precuneus. Across independent component analysis networks, however, there was reduced positive RSFC between the anterior portion of the DMN and the salience network (SN), less negative anterior DMN–right frontoparietal network connectivity, and increased right frontoparietal network–SN and DMN–cerebellum connectivity in patients with versus without an attempt history (102,103). Among depressed adolescents, lower average connectivity/coherence in the left frontoparietal executive control network, anterior DMN, and SN associated with greater lifetime ideation severity (104). Within this same sample, increasing SN coherence predicted lower ideation severity over time (105).

Voxelwise. Young adults with a lifetime attempt history but no current mental disorders showed greater regional homogeneity (measuring local synchrony) in the middle frontal gyrus, parietal lobe, and precuneus, and reduced regional homogeneity in the cerebellum, fusiform, hippocampus, parahippocampal gyrus, angular gyrus, IFG, and middle frontal gyrus compared with healthy control subjects (106). Zhang *et al.* (102) and Cao *et al.* (103) reanalyzed data to examine fractional amplitude of low-frequency fluctuation, which characterizes voxelwise intensity of spontaneous blood oxygen level–dependent signal fluctuations across a low-frequency band. Depressed patients with an attempt history showed increased amplitude of low-frequency fluctuation in the medial temporal, superior temporal, and middle occipital gyri compared with patients and healthy control subjects (107).

Nonsuicidal Self-injury

Relative to healthy females, adolescents with an NSSI history exhibited reduced left amygdala-seed RSFC with a cluster

spanning the ACC and supramarginal gyrus, as well as increased RSFC with the angular gyrus and a temporal gyrus cluster (96). These youth underwent an 8-week open-label *N*-acetylcysteine trial. Reductions in NSSI frequency after treatment were associated with decreases in left amygdala–right supramarginal gyrus and right nucleus accumbens–left superior medial frontal cortex RSFC, and with increases in right amygdala–right inferior frontal cortex RSFC (108). Finally, relative to healthy adolescents, youth with an NSSI history showed reduced amygdala-seed connectivity with the ACC and a cluster spanning the right planum temporale and right insula, as well as reduced medial PFC connectivity with the precentral/postcentral gyri and left insula. Reductions in NSSI frequency posttreatment were associated with greater negative amygdala–ACC, greater amygdala–brainstem/parahippocampal gyrus, reduced positive medial PFC–amygdala/striatum, and more negative medial PFC–intracalcarine cortex RSFC. Medial PFC–amygdala connectivity also correlated with change in suicidal ideation but not with change in suicidal behavior following treatment (109). Although limited, findings suggest that amygdala-seed connectivity is altered in adolescents with an NSSI history, particularly with the ACC (96,109).

DISCUSSION

Neural alterations in youth with lifetime STBs and NSSI history show modest convergence. First, reduced VPFC and OFC volume is associated with STBs (53–55), and there is reduced volume in the ACC for youth reporting STBs (59) and NSSI (64,69). Second, blunted striatal activation characterized STBs (82) and NSSI (92), and there was reduced frontolimbic connectivity in suicide ideators and attempters (75). Last, RSFC showed reduced positive connectivity between the DMN and SN in attempters (102,103), and for NSSI behaviors, growing evidence implicates frontolimbic alterations (96). As a whole, self-injurious behaviors were related to top-down and bottom-up neural alterations.

The overlap in neural correlates of suicidal and nonsuicidal behaviors is not surprising given the high co-occurrence (1). However, the inability to elucidate specific neural circuitry may reflect 1) sample overlap (i.e., NSSI youth in STB studies; STB youth in NSSI studies) and 2) inconsistent reporting of both STB and NSSI histories (see Tables S1–S3 for overlap and reporting issues). Nonetheless, this review highlights tentative differences—focusing on research applying strong methodological approaches (see bolded publications in Tables 1–3)—that may prove fruitful to explore. Consistent with Schmaal *et al.* (32), youth STB research is characterized by alterations within prefrontal (53–55) and limbic (62,75,102,103) systems whereby a compromised regulatory system may potentiate suicidal thinking, and perturbations in top-down and bottom-up connections may lead to suicidal behaviors. A key difference is that disruptions across regulatory, approach, and avoidance systems may be even more pronounced in youth given ongoing PFC neuromaturation through young adulthood (30,31). By contrast, NSSI research reveals ACC structural alterations (64,69) as well as disruptions in amygdala and ACC connectivity (96), which contributes to hyperarousal and reduced impulse control—central features of NSSI (110,111). Whether this neural pathway is unique to NSSI remains unclear, as STB research also shows ACC (59) and limbic (75) alterations, and NSSI research has not clarified which ACC (69) and amygdala (96) subregions are more closely linked to NSSI.

Neurodevelopmental Model of STBs and NSSI

This review highlights promising neural diatheses related to STBs and NSSI. These diatheses are shaped by distal factors occurring during a critical period of neuromaturation (30,31). Specific genes (e.g., *5-HTTLPR*) (112,113) influencing neuromaturation have known associations with self-injurious behaviors (114,115). Trauma and maltreatment occurring during developmentally sensitive periods impact cortical and subcortical development (116), directly affecting top-down (e.g., ACC) and bottom-up (e.g., striatum) processes implicated in STBs and NSSI (117). This may be compounded by environmental [e.g., poverty (118)], parental [e.g., mental disorders (119)], and youth [e.g., stress (120), psychiatric symptoms (121)] factors—each affecting neuromaturation and, potentially, increasing STB and NSSI vulnerability.

In the context of proximal antecedents, these neural alterations may confer increased STB and NSSI risk (Figure 2). For example, the timing of puberty is important, as early onset for girls versus late onset for boys may increase risk for internalizing disorders (122). Earlier onset of mental disorders shapes brain development [e.g., (123)] and relates to self-injurious behaviors (1). Additionally, adolescent interpersonal stress [e.g., loss (21,25), peer victimization (22,24)] may initially act on cortical regions by compromising cognitive flexibility and future-oriented thinking (124), which over time may potentiate suicidal and nonsuicidal thinking (125,126). Repeated and chronic stress may tax limbic systems that modulate arousal and approach behaviors, disrupt bottom-up and top-down connections, and potentially facilitate the transition from ideation to behavior (32,127).

Although sex differences in STBs and NSSI are well documented (4,5,7), there is insufficient evidence showing discrete neural circuitry underlying these effects. One possibility is that neural diatheses do not differ, but rather, stress exposure may differentially trigger underlying diatheses. For example, females with MDD report a higher frequency of interpersonal stress (128), whereas males with MDD experience more achievement-related stressors (129). The neurobiology of MDD may be similar (91), but the antecedent trigger may differ. Research incorporating stress-based interviews (21) and ambulatory approaches [e.g., experience sampling (130), passive sensor data (131)] may clarify how the type, intensity, and timing of stress exposure impact self-injurious behaviors.

Recommendations for Future Research

Future research addressing key methodological limitations may be better positioned to elucidate unique neural pathways for suicidal and nonsuicidal behaviors. Herein, we provide 5 core recommendations. First, reporting lifetime mental disorders and associated comorbidity will clarify whether effects can be attributed to the targeted behaviors or the underlying disorders. Interview-based assessments of mental disorders, STBs, and NSSI are preferable. Self-reports are prone to misattributions and retrospective biases (132), and interviews ensure shared definitions of what constitutes a suicide attempt

or an NSSI episode. Given the high co-occurrence of STBs and NSSI (1), consistently reporting suicidal and nonsuicidal behaviors is essential.

Second, comparing STB or NSSI samples with healthy individuals makes it challenging to attribute neural alterations to self-injurious behaviors versus mental disorders. Comparing suicide attempters with ideators or comparing adolescents reporting NSSI behaviors with psychiatric control subjects may clarify whether there are neural mechanisms implicated in thinking about versus engaging in self-injurious behaviors (133).

Third, small samples are ill-equipped to explore age, sex, and gender effects (2,3) (see Table S1–S3 for sample sex characteristics). Larger, diverse samples are key, given the inherent heterogeneity (e.g., frequency, method, underlying disorders, medication use), and are consistent with initiatives to replicate brain-based effects in representative youth samples (134).

Fourth, longitudinal research is scant. A substantial number of participants characterized by suicidal and nonsuicidal thoughts will engage in self-injurious behaviors over time. Longitudinal research—particularly studies incorporating fine-grained ambulatory stress assessments (38)—will have an opportunity to identify distal neural markers that may facilitate the transition from thinking to acting in the context of proximal stressors. This methodological approach can clarify why certain individuals who ideate about suicide or initiate nonsuicidal behaviors transition to suicidal behaviors (131).

Fifth, additional neuroimaging modalities—including diffusion tensor imaging (56,135) and electrophysiology (136,137)—may provide complementary information. There also may be innovative ways to integrate neuroimaging modalities [e.g., (138,139)] and apply novel data analytic strategies (86).

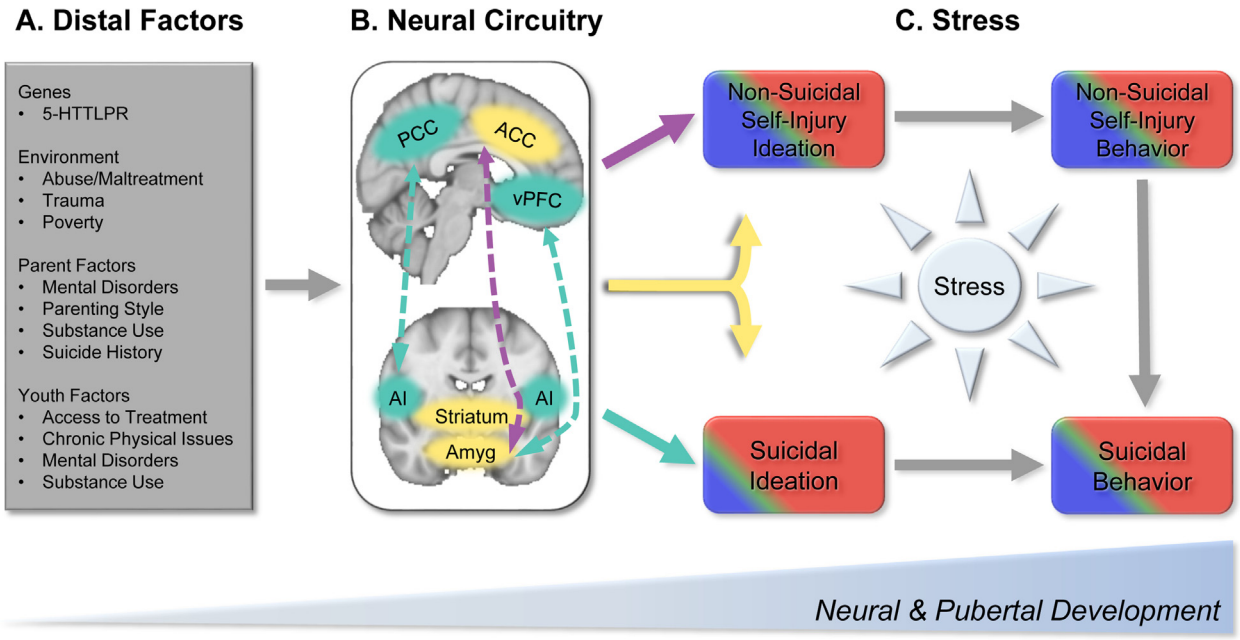

Figure 2. The neurodevelopmental model of suicidal thoughts and behaviors (STBs) and nonsuicidal self-injury (NSSI) highlights distal and proximal processes that may potentiate risk for self-injurious behaviors during a critical period of development. **(A)** There are a wide range of distal risk factors that shape neuromaturation, including genetic, environmental, parental, and youth factors. These distal factors occur in the context of ongoing pubertal and neuromaturation from childhood to young adulthood. **(B)** This review highlights a number of brain regions and connectivity patterns that show alterations potentially unique to STBs (teal) and NSSI (purple), or common across both (yellow). In STBs, these include connections between the default mode network (hub in the posterior cingulate cortex [PCC]) and salience network (hub in the anterior insula [AI]), as well as between the ventrolateral prefrontal cortex and amygdala. NSSI shows alterations in connections between the anterior cingulate cortex (ACC) and amygdala. Both STBs and NSSI implicate structural and functional alterations in the striatum, amygdala, and ACC. **(C)** Coupled with acute stressors—particularly interpersonal stress—these distal neural markers may increase risk for engaging in suicidal and nonsuicidal behaviors. Acute stress may directly impact brain development, and concurrently may disrupt top-down cortical processes related to self-referential processing rumination, and future-oriented thinking, which may lead to suicidal and nonsuicidal thinking. Stressors that become chronic in nature may tax limbic systems, which modulate arousal and approach behaviors. Disruptions to bottom-up and top-down connections may, for some, facilitate the transition from thinking to acting. More broadly, stress also elicits a range of negative emotions (e.g., sadness, anger), and in the absence of effective emotion regulation strategies, this may then lead to STBs and/or NSSI. Presently, there is not sufficient evidence attributing sex differences in STBs and NSSI to discrete neural circuitry. Epidemiological research, however, shows that NSSI thoughts and behaviors are more common in female (red) vs. male (blue) adolescents, though estimates vary [e.g., (6,7)]. Similarly, suicidal thinking (15% vs. 9%) and behaviors (6% vs. 2%) are more common in females vs. males [e.g., (4)]. Although not often examined in large epidemiological cohorts, NSSI and STBs is proportionally higher among transgender and gender-nonconforming youth (green) (140,141). Accounting for stress exposure using interview and ambulatory approaches may shed key insights into shared and unique neural markers that lead to suicidal vs. nonsuicidal behaviors. Amyg, amygdala; vPFC, ventral prefrontal cortex.

Summary

Initial research probing neural correlates of STBs and NSSI has identified promising brain-based markers. From a neurodevelopmental perspective, an important next step is to elucidate pathways differentially leading to suicidal versus nonsuicidal behaviors by incorporating multimodal neuroimaging approaches in the context of fine-grained stress assessments while accounting for wide-ranging distal risk factors that influence neuromaturation. Longitudinal research following youth through this developmental period may reveal neural circuitry that potentiates risk for self-injurious behaviors and provide novel targets for treatment.

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