Imaging suicidal thoughts and behaviors: a comprehensive review of two decades of neuroimaging studies

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ABSTRACT

Identifying brain alterations that contribute to suicidal thoughts and behaviors (STBs) are important to developing more targeted and effective strategies to prevent suicide. In the last decade, and especially in the last 5 years, there has been exponential growth in the number of neuroimaging studies reporting structural and functional brain circuitry correlates of STBs. Within this narrative review, we conducted a comprehensive review of neuroimaging studies of STBs published to date and summarize the progress achieved on elucidating neurobiological substrates of STBs, with a focus on converging findings across studies. We review neuroimaging evidence across differing mental disorders for structural, functional and molecular alterations in association with STBs, that converges particularly in regions of brain systems that subserve emotion and impulse regulation including the ventral prefrontal cortex (VPFC) and dorsal PFC (DPFC), insula and their mesial temporal, striatal and posterior connection sites, as well as in the connections between these brain areas. The reviewed literature suggests that impairments in medial and lateral VPFC regions and their connections may be important in the excessive negative and blunted positive internal states that can stimulate suicidal ideation, and that impairments in a DPFC and inferior frontal gyrus (IFG) system may be important in suicide attempt behaviors. A combination of VPFC and DPFC system disturbances may lead to very high risk circumstances in which suicidal ideation is converted to lethal actions via decreased top-down inhibition of behavior and/or maladaptive, inflexible decision-making and planning. The dorsal anterior cingulate cortex and insula may play important roles in switching between these VPFC and DPFC systems, which may contribute to the transition from suicide thoughts to behaviors. Future neuroimaging research of larger sample sizes, including global efforts, longitudinal designs, careful consideration of developmental stages, and sex and gender, will facilitate more effectively targeted preventions and interventions to reduce loss of life to suicide.

Keywords

Attempted Suicide; Suicidal Ideation; Suicide; Neuroimaging; Functional Neuroimaging, Magnetic Resonance Imaging

1. INTRODUCTION

Around one million people die by suicide annually[1]. Globally, suicide is the tenth leading cause of death for all ages and the second leading cause of death among young people aged 15-29 years[1]. In 2013, it was estimated that 9.3 million adults 18 years and older in the United States had suicidal thoughts and 1.3 million attempted suicide[2]. Additionally, a 2011 report estimated that 13% of adolescents planned a suicide attempt in the previous year and 8% attempted suicide[3]. Unfortunately, suicide death rates have continued to rise. For example, since 1999, rates in the U.S. have increased 30%[4]. Predictive value of currently identified non-biological risk factors for suicide is limited[5], and a reliable biological risk marker has yet to be identified. In order to prevent suicide more effectively, there is an urgent need to better understand the mechanisms that confer increased risk for suicidal thoughts and behaviors (STBs), and to identify biological markers of risk to generate more targeted successful prevention strategies and monitor responses to them. In the last decade, and especially in the last 5 years, there has been exponential growth in the number of neuroimaging studies reporting structural and functional brain circuitry correlates of STBs (Figure 1). In the last 10 years, a number of excellent reviews on aspects of this research have emerged[6–10]. Here we review research across structural, functional and neurochemical neuroimaging modalities, providing a narrative review of 130 neuroimaging studies with a focus on the most researched brain circuitries and findings that converge across studies.

2. METHODS

A search was performed in PubMed for original research articles published before March 12, 2018. The following terms were used: “MRI”, “SPECT”, “PET”, "magnetic resonance imaging", "positron emission tomography", "single photon emission computed tomography", “DTI”, "diffusion tensor imaging", “diffusion weighted imaging”, “neuroimaging”, “fMRI”, “functional magnetic resonance imaging”, “spectroscopy” (separated by OR) in combination with the terms “suicide”, “suicidal”, “suicidality” (separated by OR). We selected articles that: (i) were published in a peer-reviewed journal in English and (ii) included groups with suicidal ideation (SI) and/or history of suicide attempt(s) (SA). Of note, non-suicidal self-injury (NSSI) was not included in this review, and studies that did not differentiate NSSI from suicidal behaviors were excluded, because these can be differentiated on the basis of intention, frequency, and lethality and may have partly distinct underlying mechanisms[11].

3. RESULTS

We identified 131 unique articles meeting review criteria (Tables 1-3). The populations studied reflect reports that the majority of people with STBs have a diagnosable mental illness. Major depressive disorder (MDD) or bipolar disorder (BD) account for over half of suicide deaths[12]. After mood disorders and borderline personality disorder (BPD), the prevalence of suicide deaths is highest among people with substance use disorders and schizophrenia (SZ), followed by post-traumatic stress disorder (PTSD) and anxiety

disorders[12].The mental disorders researched varied by study, with each study typically including a single disorder, and the majority of studies conducted in individuals with mood disorders. Most studies compared people with a mental disorder and a history of suicide attempts (suicide attempters, SAs) to people with a mental disorder and/or healthy controls (HCs) without a history of attempt. Fewer studies focused on SI. Most studies employed a cross-sectional design and a single structural or functional imaging modality. The majority were conducted with adults; only a small proportion with adolescents (Figure 1). A subset of studies provided preliminary findings of associations between neuroimaging measures and key risk factors for suicide, e.g. medical lethality of prior attempts, emotion dysregulation, anhedonia, impulsiveness, and reduced cognitive control (for reviews see[13–15]).

Despite modest sample sizes of studies, and the heterogeneity of their clinical samples and neuroimaging acquisition and analysis methods, converging evidence is emerging to support roles for specific brain regions/circuitries in STBs. These are particularly in cortico-striatolimbic systems that subserve emotion and impulse regulation and include prefrontal, cingulate and insula cortices, amygdala, hippocampus, thalamus and striatum regions (Tables 1-3). Within the prefrontal cortex (PFC), studies vary widely in the selection of regions studied, with regions of interest (ROIs) often including overlapping regions that encompass ventral and dorsal, medial as well as lateral, PFC. Thus, while we identify the importance for future study of specific PFC subregions, given their differing connectivity, cellular and molecular features and functions, we discuss the PFC grouped broadly into the ventral prefrontal cortex (VPFC; divided into medial and lateral portions), which has the highest concentration of reported findings, the dorsal prefrontal cortex (DPFC; divided into lateral and medial portions), and the anterior cingulate cortex (ACC). We also discuss findings in the insula, and mesial temporal (hippocampus, amygdala), subcortical (basal ganglia, thalamus) and posterior regions (posterior cingulate cortex, lateral temporal lobes and cerebellum). See Figure 2 for definitions of the brain regions. Since the VPFC, DPFC, ACC, insula, mesial temporal, basal ganglia, thalamus and posterior regions have been studied most frequently in relation to STBs and because most converging evidence exist for the involvement of these regions, we specifically focus our review on findings within these brain areas, as well as in the connections between them. However, additional studies and positive and negative findings not discussed below can be found in Tables 1-3.

We focus our discussion below on findings that are primarily derived from comparisons of individuals with a mental disorder and STBs versus individuals with a mental disorder without STBs (diagnostic controls, DCs), rather than comparisons with HCs, unless otherwise specified. Findings based on a comparison between DCs and individuals with the same mental disorder plus STBs are more commonly reported in the literature and are more likely to reflect specific effects of STBs in that disorder, whereas comparisons with HCs may include more general effects of having a mental disorder. Below we first detail structural,

functional and neurochemical findings within regions and end each section on a region with a summary. We then follow with a section devoted to studies of connectivity among regions within major implicated brain systems.

Ventral Prefrontal Cortex (VPFC)

The *lateral* VPFC (VLPFC) refers to the inferior lateral areas of the frontal cortex encompassing lateral orbitofrontal cortex (OFC, brodmann area (BA)47, lateral BA11), inferior frontal gyrus (IFG, BAs 44, 45), and lateral aspects of the rostral PFC (RLPFC, lateral BA10) (Figure 2). The lateral VPFC plays a key role in cognitive control, including response inhibition, and is activated when behavioral responses are modulated in response to the emotional or motivational context[16,17]. The *medial* VPFC (VMPFC) refers to the medial OFC (medial BA11) and medial aspects of the rostral PFC (RMPFC, medial BA10) (Figure 2). The medial VPFC has a well-established role in self-reflection[18], appraisal of internally-generated emotions (both positive and negative)[16,19], appraisal of past and imagined future events and reward processing[20,21]. Structural, functional and neurochemical alterations in these regions have been associated with maladaptive strategies for regulation of negative affect (e.g., rumination), negative self□referential thinking[22,23], and diminished positive affect (e.g., anhedonia)[24]. Evidence is mounting that emotion dysregulation has a central role in the generation of STBs. This includes elevations in negative, and blunting in positive, subjective emotions, self-referential thoughts, and responses to valenced stimuli[25]. These alterations are thought to contribute to key clinical risk symptoms for STBs including depression, anxiety, rumination, guilt, reduced self-esteem, helplessness, anhedonia and hopelessness[22–24,26–31].

VLPFC

Structural MRI studies have consistently shown lower gray matter volumes of the VLPFC in adult SAs, including SAs with MDD[32–34], BD[35,36] and schizoaffective disorder (SZA)[37]. Findings of lateral OFC volume decreases, extending to medial OFC, in adolescent and young adult SAs with BD[36], suggest these may be early differences. Lower VLPFC thickness, but not volume, is one of the rare findings related to SI in adults with MDD[38], suggesting the VLPFC may be involved not only in suicide behavior but also in the ideation that may generate it.

Gray matter volume decreases in VLPFC were also associated with high lethality of prior suicide attempts in MDD[24] and BPD[36,37]. This converges with longstanding findings from both postmortem studies demonstrating VPFC (ROIs including both VLPFC and VMPFC) differences in people who died by suicide[39], and positron emission tomography (PET) studies of high lethality or high intent SAs, showing VPFC (VLPFC and VMPFC) alterations in serotonin (5-HT) synthesis, transporters and 5-HT1a receptors[40,41] (Table 2). Lower 5-HT1a binding in the OFC was associated with interim SI during a 2-year follow-up in adults with MDD and past attempts[42]. Although conflicting findings exist[43–46], these data provide some

consistent findings of a location and a potential mechanism, i.e. lateral extending to medial VPFC serotonergic dysfunction, as a potential biomarker of risk for high lethality STBs. There have been few molecular imaging studies of other neurotransmitter systems and neurochemicals implicated in STBs.

Functional MRI (fMRI) studies performed while subjects conducted specific behavioral tasks provide evidence that STBs are associated with VLPFC functional abnormalities in response to emotional and other hedonically-valenced stimuli. Increased activation of the IFG and lateral and medial OFC while viewing angry (but not happy, sad or neutral) faces was reported in adult SAs with MDD[47,48]. Higher IFG activation in response to angry faces was also associated with poorer attempt planning and higher impulsivity in adult SAs with MDD[49]. Furthermore, young adult SAs with BPD displayed higher lateral OFC activation while instructed to experience and regulate negative autobiographical memories[50]. Increased activation in a region of interest that included both the medial and lateral OFC was also seen in response to winning a reward[47] in adult SAs with MDD.

The IFG also plays a critical in cognitive control and response inhibition[51]. During performance of a continuous performance task, higher IFG, RLPFC and lateral OFC responses were associated with both attempts and SI in adults with mood disorders with psychotic features, in the absence of task performance differences[52]. Higher lateral OFC was also reported during error trials in a response inhibition task in veterans with SI[53]. In contrast, a second study in adult SAs with SZ using the same continuous performance task showed reduced activation in a cluster encompassing the RLPFC and IFG, extending to the VMPFC and ventral ACC, that was associated with SI but did not further distinguish between ideators with and without a history of attempt[54].

VMPFC

In addition to the structural and PET study findings reported for the VLPFC above that extended to the VMPFC or that were based on an ROI including both VLPFC and VPFC, lower medial VPFC cortical thickness was also associated with greater motor impulsivity in adolescent SAs with MDD[55]. As cortical thickness and surface area contributions to volume are thought to be genetically independent[56] and result from different neurobiological processes[57], it is important to examine these separately in studies of STBs. However, the majority of studies have either not examined thickness and surface area separately from volume or only thickness but without examination of surface area in SAs with MDD[32,58]. Cortical thickness is thought to be influenced by the number and the size of cells within a column, packing density, as well as by the number of connections and the extent of their myelination, while cortical surface area is driven by the number ontogenetic columns that run perpendicular to the surface of brain[59].

Functionally, in addition to higher activation in the lateral and medial OFC in response to angry faces and to winning a reward in adult SAs with MDD[47] as reported above, a recent study using machine learning to investigate adolescent SAs (with and without SI) showed that the medial VMPFC was among the most discriminating regions, within a multivariate pattern of fMRI brain activation in response to actively thinking about life- and death-related concepts, for distinguishing between adolescent suicidal ideators with and without a history of attempt, although in a very small sample size[60].

Summary

Structural neuroimaging studies have consistently shown that alterations in the VLPFC and VMPFC are implicated in SA across a range of mental disorders and age ranges. Reduced VLPFC volumes were also associated with lethality of attempts, potentially mediated by serotonergic dysfunction, although findings of serotonergic dysregulation remain inconsistent. The involvement of structural and functional VLPFC and VMPFC alterations in SI remains understudied. Viewing and regulating negative emotions and motivationally-valenced stimuli has been linked to increased activation of the lateral and medial OFC in adult (including young adults) SAs with MDD and BPD, and associated with poorer attempt planning and higher impulsivity. Finally, higher VLPFC activity, including in the IFG, RLPFC and lateral OFC, during cognitive control and response inhibition in relation to SA and SI in adults with mood disorders has been reported across a number of studies. These increased activations may, in the absence of task performance differences, reflect a need for greater engagement of these regions for reaching similar performance in these individuals with STBs. In contrast, adult SAs with SZ showed reduced activation in these regions during cognitive control, which may suggest that there are some differences in the neural signatures of STBs between mood and psychotic disorders, which will be an important direction for future study.

Dorsal Prefrontal Cortex (DPFC)

The DPFC can be broadly divided into dorsolateral (DLPFC) and dorsomedial PFC (DMPFC). The DMPFC and the DLPFC together support top-down control of emotions and behaviors,[17] cognitive flexibility and complex decision-making[61]. Deficits in these processes are thought to have an important role in STBs, particularly in the transition from SI to behavior, as the threshold to acting is lowered by decreased top-down behavioral inhibition, and diminished flexibility in generating alternate and more adaptive behavioral choices[15,62]. Neuroimaging evidence suggests that the DMPFC (medial portions of BA 8 and 9) is robustly recruited during tasks that require mental state inference[63,64]. The DMPFC is further involved in tracking decision conflict and reinforcement history[65], as well as in emotion regulation[66]. The DLPFC (BA46, lateral BA9) is involved in the conscious active control of planned behavior and cognition, as well as working memory[67]. Access of the DLPFC to memory processing in hippocampal regions is shared by the rostrolateral PFC (lateral frontal pole BA10), which has been implicated in meta-cognitive awareness[68,69].

DLPFC

Although the amount of evidence to date has been less than in VPFC, accumulating findings also support a role for the DLPFC in STBs. Structural MRI studies support lower volume in DLPFC in adult SAs across MDD[32,33,70] and BD[33,35]. Studies showed lower DLPFC thickness in adult SAs with MDD[58] and SZ[71], but have not examined cortical surface area. In addition, lower DLPFC volume was associated with attempt lethality in mood and psychotic disorders[32,37]. Higher baseline 5-HT1a receptor binding potential in the DLPFC was also associated with higher lethality of future attempts and SI during a 2-year follow-up[42].

Fuctionally, decreased lateral (and medial) DPFC when ten adults with self-reported depression listened to their own narrative of their attempt was reported in a study in which imaging was conducted close to the time of the attempts (one to four weeks prior[72]). A study of adolescents with a history of SI showing lower right DLPFC activation during passive viewing of negative emotional scenes, suggests that DLPFC decreases during processing of negative emotional stimuli might be present early in the course of SI[73]. Higher right DLPFC engagement was observed during regulation of responses to negative emotional scenes in the same adolescents, suggesting the direction of DLPFC differences depends on the specific task requirements (passive viewing versus regulating)[73]. Another study in adolescent SAs with MDD suggests that the direction may also relate to the specific emotion, as passive viewing of angry faces, but not happy faces, elicited higher DLPFC responses[74], perhaps due to the high sensitivity to criticism and social rejection previously reported in individuals with STBs[75,76].

The DLPFC's critical role in decision-making in the context of evaluating the motivational value of choices[77] may be especially relevant to STBs. Blunted DLPFC activation was observed when evaluating risky versus safe options in adult SAs with MDD[47] and when evaluating lower immediate rewards versus larger delayed rewards in older adults with MDD and well-planned suicide attempts[78]. This is in line with a behavioral study of older adult SAs with MDD showing lower levels of delay discounting (or impulsive decision-making) and better planning in suicide attempts[79]. Increased DLPFC activation has also been observed in adults with STBs across a range of "cold" cognitive control tasks, especially those requiring inhibition of automatic response tendencies. These included paradigms such as continuous performance, stop signal, go-no go and stroop tasks studied in adult SAs with MDD or BD with psychotic features[52], SZ[80], and ideators with SZ[81] or PTSD and MDD in veterans[53]. Elevated activation in DLPFC was observed in suicidal ideators with past attempts compared to ideators without attempts while performing a continuous performance task[52]. Single photon emission tomography (SPECT) and PET studies showing lower resting regional cerebral blood flow (rCBF) and glucose metabolic rates (rCMRglu) in the DLPFC in adult SAs with

mood disorders[82,83]. Moreover, lower DLPFC rCMRglu was associated with higher lethality of attempt[84] and with SI with a plan versus ideation without a specific plan[85] in adults with MDD.

DMPFC

Structural MRI studies also support lower volume in DMPFC in adult SAs with MDD[32,70] and BD[33,35]. Although less studied than DLPFC in functional neuroimaging, lower DMPFC was reported in the study in which adults with depression listened to their own narrative of their recent attempt, which was especially pronounced during mental pain aspects of the narrative[72]. Furthermore, decreased activation was also found in DMPFC during viewing of angry faces in adult SAs with MDD[48].

Summary

Structural alterations in both the DLPFC and DMPFC have been consistently observed in adults across mental disorders and structural alterations in the DLPFC have been associated with attempt lethality. This latter finding, together with findings of serotonergic dysfunction in the DLPFC being associated with higher lethality of future attempts during a 2-year follow-up, implicates DLPFC structure and serotonergic system functioning in STB risk. With regard to DLPFC and DMPFC functioning, there is convergence in showing differences related to STBs during processing of negative emotional stimuli, although the direction of effects (activation increases versus decreases) in the DLPFC differed across studies, with contributions to the differences unclear as the studies differed across multiple variables. Elevated activation while performing cognitive control tasks (in the absence of performance differences) together with lower resting regional cerebral blood flow and glucose metabolic rates in the DLPFC could suggest that increased DPFC may be recruited for reaching similar task performance perhaps due to lower baseline levels of activation in the DPFC regions. Findings from one study suggests that functional DLPFC alterations during cognitive control can discriminate between suicidal ideators with past attempts and ideators without attempts. Moreover, blunted DLPFC activation when evaluating the value of different decision options may also represent a risk marker for SA, and especially for well-planned attempts. Well-planned versus impulsive suicide attempts have been suggested to be different phenotypes[86]. From papers reviewed, there was a greater concentration of findings in the VPFC in impulsive SAs and in DPFC in planful SAs. Therefore, we speculate that the relative ventral versus dorsal localization of the PFC abnormalities may contribute to the differing phenotypes.

Anterior cingulate cortex (ACC)

The ventral ACC consists of BA25 and ventral BA32 sub- and pre-genual to the corpus callosum and plays a critical role in valuation and control of autonomic viscero-sensory signals, the modulation of physiological responses to stress and the appraisal of internal feelings[16]. The dorsal ACC (dorsal BA24 and 32) plays an important role in the appraisal of

actions (and adaptively adjust behaviour as a consequence) and reward-based decision-making[16].

Structural MRI studies support lower volume in both ventral and dorsal ACC in adult SAs with MDD[34,58] and BD[35], and that was related to a higher number of attempts in adolescents with BPD and MDD[87] and to higher lethality of attempts in adults with BPD[88] and psychotic BD[37]. Lower dorsal ACC (dACC) rCMRglu was associated with higher lethality of attempt[84]. In addition, lower 5-HT1a binding in the ACC was associated with interim SI during a 2-year follow-up in adults with MDD and past attempts[42]. A few studies that investigated neurotransmitter systems other than 5-HT implicated the ACC in relation to SI. For example, a positive association was shown between SI and ACC monoamine oxidase-A (MAO-A) density in adults with BPD[89]. A relation between SI and increased ACC neuroinflammation (as assessed by translocator protein (TSPO) availability) was reported in adults with MDD[90]. Furthermore, dACC GABA concentrations were lower in adult female SA+SI compared to clinical controls without SA or SI, however, this effect was no longer significant after correcting for age[91].

Viewing of angry faces elicited higher dACC responses in adolescent SAs with MDD[74], perhaps due to the high sensitivity to criticism and social rejection previously reported in individuals with STBs[75,76]. In contrast, decreased activation was found in ACC (ROI capturing both ventral and dorsal ACC) during viewing of sad faces in adult SA with MDD[47]. With regard to positive stimuli, blunted ventral ACC responses were found during the anticipation of reward in adult[92], including elderly[93], SAs with MDD. Elevated responses in the ventral ACC have also been reported in relation to positive stimuli. For example, higher activation in ventral ACC was seen in response to happy facial expressions[48] and in response to actual winning[47] (in contrast to blunted response during reward anticipation) in adult SAs with MDD.

Summary

The ACC has mostly been studied in relation to emotional processing. Although various studies have observed dorsal and ventral ACC activation alterations in adolescents and adults with MDD and SA, the direction of alterations seem to be complex and dependent on task condition and stimulus type (positive versus negative). One could perhaps interpret the findings of increased dorsal and ventral activation in response to angry faces and to positive stimuli, together with blunted ventral ACC activation during reward anticipation, as negative biases, as they may reflect reduced reward anticipation (anticipation phase) versus increased activation in response to negative stimuli and in relation to positive prediction errors in response to positive stimuli (outcome phase). The finding of a positive relation between SI and ACC neuroinflammation, together with findings of increased inflammatory markers in the ACC in postmortem studies of people who died by suicide[48] and in blood and cerebrospinal

fluid in people with ideation and a history of violent or high intent attempts[49,50], suggests that neuroinflammation in the ACC may constitute a promising target for future studies of STBs.

Insula

The insular cortex is a key hub in emotional processing with connectivity to PFC, particularly VPFC, as well as mesial temporal structures[94]. The insula plays an important role in interoceptive awareness for positive and negative internal states[95], including emotional and other types of pain, and understanding and sharing of other people's emotional states[96,97]. Only in more recent studies has insula structure and function and related-behavior been investigated for its role in STBs. For example, on a behavioral level, interoceptive deficits have been reported among SAs compared to individuals who only thought about or planned suicide among general psychiatric outpatient adults[98] and predicted SI severity at 6-month follow-up in community adolescents[99].

Smaller insula volume has been reported in adult SAs with BPD[100], in a combined group with SZ/SZA/psychotic BD[37] and elderly with MDD[70]. Lower insula thickness was observed in adults in relation to suicide attempts in SZ[71] and SI in MDD[38]. Smaller insula volume was associated with higher attempt lethality and lower impulsivity in BPD[88,100]. In contrast, larger insula volumes were reported in relation to attempt lethality in adults with BD[101]. It is possible that the type of insula differences relate to specific characteristics of the high lethality attempters, since larger insula volumes were also found in association with higher lifetime history of aggression in BPD[88]. Some findings in the PFC noted above in MDD extended to the insula, including of associations between baseline 5-HT1a binding potential with SI and lethality of future attempts within a 2-year follow-up period[42] and of increased neuroinflammation (TPSO availability)[90].

SPECT research showed higher insula rCBF in adult SAs with MDD[102] at rest and higher insula fMRI activation was found in adults with MDD or BD with psychotic features during a cognitive control task with insula activity related to higher intensity of SI[52]. Higher insula fMRI activation was also associated with lower subjective value of gain and loss in adult SAs with MDD[92]. Lower activation in the posterior insula during social exclusion was found in adult SA's with MDD or BD, which was suggested to indicate a higher tolerance to pain via repeated exposure to painful and provocative experiences in subjects vulnerable for suicide[103].

Summary

Smaller insula volume has been associated with SAs and lower impulsivity in adults across various mental disorders, whilst, both smaller and larger insula volumes have been associated with higher attempt lethality. fMRI studies found higher insular activation related to during reward processing and cognitive control in adult SA with MDD, while lower insula

activation was associated with a higher tolerance to social pain in adult SA's with MDD or BD. Thus, there is preliminary evidence for an involvement of insular structural and functional alterations in SI and SAs. However, since very few studies have focussed on the insula and both decreases and increases in these alterations have been reported, more research is needed to elucidate the role of the insula in STBs. Interestingly, immune challenges activate interoceptive brain pathways (including the insula), triggering alterations in mood and cognition, motivation, and neurovegetative processes[104]. Together with preliminary evidence of increased neuroinflammation in the insula related to SI, this suggests that the insula may be an important region for future studies of neuroinflammation and STBs.

Amygdala and Hippocampus

Due to their roles in processing of emotion, emotional memory and the stress response[105–108], the mesial temporal amygdala, hippocampus and entorhinal cortex (BA28, within the adjacent parahippocampal gyrus) are also thought to be involved in STBs. However, findings have been inconsistent. Larger amygdala volumes were reported in adult SAs with MDD[109] and SZ[110], but more studies have not detected significant amygdala findings[33,38,100,101,111–113]. Smaller hippocampus volumes were reported in adult SAs with MDD[114] and adolescent and young adult SAs with BD[36], and one study reported a smaller parahippocampal gyrus[115]. However, more studies have not detected associations of hippocampus or parahippocampus volume with STBs[33–35,38,101,109–112]. While difficulties detecting differences in these small mesial temporal structures may relate to imaging methods, it may be that mesial temporal alterations are only apparent in specific subgroups of people with STBs. For example, high lethality attempts were associated with smaller volumes of the hippocampus and parahippocampal gyrus in adult SAs with BPD[88,100]. In addition, amygdala and hippocampus volumes were negatively associated with impulsivity in patients with low lethality attempts[88], and amygdala volume positively associated with self-aggression in SAs with SZ[110].

PET studies have shown preliminary evidence for a role of serotonergic alterations in the amygdala and hippocampus in STBs. Increased hippocampus 5-HT2a receptor binding and 5-HT release was observed in adult SAs with BPD[116] and in adults with MDD and high lethality attempts[40] respectively, compared to HCs. Recently, baseline 5-HT1a receptor binding in the amygdala, hippocampus and parahippocampal gyrus was associated with higher SI during a 2-year follow-up in adults with MDD[42].

Few fMRI studies have focused on mesial temporal ROIs. An activation study focusing on the amygdala found no association between SI and amygdala functioning during emotion processing in 10 ideators[117]. Increases were observed during autobiographical recall of mental pain experienced during an ideator's own attempt in right parahippocampal gyrus versus suicide action in left hippocampus[72]. In contrast, parahippocampal gyrus activation was blunted in adult SAs with MDD choosing between a smaller immediate reward versus a

larger but delayed reward, especially when the two rewards were more than 1 year apart[78]. Given the role of the parahippocampal gyrus in prospection[118], its blunted response to prospects with longer versus shorter delays may represent a neural substrate of impaired prospection in SAs[119–121], potentially undermining the deterrents and alternative solutions during a suicidal crisis.

Summary

Although structural alterations in the amygdala and the hippocampus have been consistently implicated in mental disorders[122–124], the majority of studies reviewed do not report structural alterations in these regions in relation to STBs. These mixed findings could perhaps be explained if additional involvement of the amygdala and hippocampus in STBs beyond their role in mental disorders is subtle with small effects only apparent in studies with very large sample sizes. This is consistent with a post-hoc power analysis based on observed effect sizes in the largest study on subcortical volumes in STBs to date[111]. Alternatively, mesial temporal structural alterations may only become apparent in specific subgroups of people with STBs. Preliminary evidence suggests serotonergic alterations in the amygdala and hippocampus linked to SA as well as SI across mental disorders, and altered functioning in these regions in relation to increased autobiographical recall of mental pain, blunted immediate reward processing and impaired prospection in patients with SA, although molecular and functional studies focussing on these regions are still scarce.

Striatum and Thalamus

The ventral striatum includes the nucleus accumbens and ventral parts of the putamen and caudate[125] and is a core region of the reward network[126]. Dorsal striatum, including dorsal caudate and putamen, functions include initiating action, inhibitory control, and stimulus-response learning[127]. The striatum projects to the frontal lobe via the thalamus[125], which is also involved in sensory processing[128].

Lower caudate and putamen volumes have been reported in adult SAs with MDD in comparison to MDD non-attempters[34,129] and HCs[130], and putamen volumes were negatively associated with impulsivity[129]. Lower putamen binding of the serotonin transporter (5-HTT) was also reported in adult SAs with MDD compared to HCs[131], and was negatively associated with impulsivity[132]. However, striatal 5-HT binding was positively associated with SI in adult SAs with MDD[133]. With regard to the thalamus, higher volumes were reported in veterans with traumatic brain injury and suicide attempts[134] and higher 5-HT synthesis reported in adult SAs with a mix of psychiatric diagnoses[40]. However, other studies, including the largest study to date of individuals with STBS (N=451), have not detected associations of striatum and thalamus volume with STBs[33,38,111].

Few fMRI studies have examined striatum and thalamus regions. Positive correlations were observed between intensity of past SI and dorsal striatum responses during cognitive control in adults with MDD or BD with psychotic features[52]. Lower putamen activation in adults with BD during a motor task was associated with higher SI[135]. Higher thalamus activation was observed when viewing knives (versus landscapes)[136] and higher thalamus activation during response inhibition (go-no-go task) was associated with higher levels of mental pain and suicide intent[137] in adults with SAs and MDD.

Summary

Mixed findings were reported for the involvement of structural alterations in the striatum and thalamus in relation to STBs, with the largest sample to date showing no associations in people with MDD. Increased dorsal striatum responses were found during cognitive control in the absence of performance differences in individuals with SI, suggesting greater engagement of this region to reach similar levels of cognitive control. Higher thalamus activations were reported during emotion processing and inhibition and associated with SI in adult SA with MDD. Structural and 5-HTT alterations in the dorsal striatum specifically linked to impulsivity in adult MDD with SA converge with findings of functional alterations in the dorsal striatum in relation to diminished cognitive and affective control associated with SI. Of note, alterations in the ventral striatum have been proposed to underlie reduced reward anticipation and anhedonia in individuals with STBs[138]. No studies reported ventral striatal *activity*, however, ventral striatal *connectivity* findings during reward processing and under rest are discussed in the "Structural and Functional Connectivity" section below.

Posterior Structures

The temporal association cortices are involved in perceptual processing of faces and other complex object features[139,140], auditory information and language[141]. Consistent with this, structural MRI findings in lateral temporal cortex were observed in adult SAs with SZ/SZA/psychotic BD and other disorders, such as mood disorders, in which psychotic misperceptions can be observed. Lower middle and superior temporal gyrus volume was found in adult SAs with primary psychotic disorders[37,142] and BPD[100], and lower thickness of middle and superior temporal gyri were observed in adult SAs with SZ[71]. Lower middle and superior temporal volumes were also associated with high lethality attempts in adults SAs with BPD[88,100]. Serotonin system studies have yielded various results including lower 5-HTT temporal binding associated with higher impulsivity in adult SAs with different mental disorders[132], and higher baseline 5-HT1a temporal lobe receptor binding in adults SAs with MDD[42] associated with higher levels of SI at 2-year follow-up. Functional MRI studies also suggest a role of the lateral temporal lobe in emotion processing in STBs. Specifically, adolescent SAs with MDD showed enhanced right middle temporal gyrus activation during passive viewing of angry, happy and neutral facial expressions[74] and during recall and re-imagination of suicidal episodes in adult SAs with MDD[72]. SI was associated with increased

superior temporal activation during error processing in veterans with traumatic brain injury[53]. In contrast, lower perfusion in these temporal regions during rest (measured by rCBF) was reported in adults with MDD and SA[82,143].

A few studies implicate other posterior brain regions including posterior cingulate cortex (PCC) and cerebellum in STBs (Tables 1-3). The PCC is implicated in psychological processes that may be linked to STBs, including controlling the vividness of negative mental imagery[144] and enhancing self-referential processing[145]. Lower PCC gray matter volume was found in adult SAs with MDD[146]. Decreased PCC activation was observed during cognitive control in adult SAs with psychotic mood disorders[52] and during self-referential processing in adolescent ideators with MDD[147], although adult SAs with depressive disorders, compared to HCs, showed increased PCC response when viewing knives[136].

The cerebellum is increasingly recognized for its involvement in emotional processes[148,149]. Lower volumes of the cerebellum were reported in adult and adolescent SAs with MDD or BD[36,70,146,150]. Functionally, while adult SAs with MDD showed increased cerebellum activation during recall and re-imagination of their own suicidal episode[72] and while viewing angry faces, they showed decreased activation while viewing happy faces[48]. Decreased activation was also observed while passively viewing negative emotional pictures in adolescents with a history of SI[73]. Finally, ketamine-induced reductions in SI were associated with increases in rCMRglu including in cerebellum[151].

Summary

Lower middle and superior temporal gyri volumes have been reported in 6 studies across a range of mental disorders, and related to high lethality attempts and higher impulsivity. Serotonergic alterations in these regions have not been extensively investigated and directions of reported effects are mixed. Increased activation in middle and superior temporal gyri have also been reported in adults and adolescents with SA and MDD, especially in relation to emotion processing. Preliminary evidence suggests a role for the PCC and cerebellum in STBs, especially in relation to self-referential, and (autobiographical) emotion processing, but studies investigating these regions remain scarce. Of interest, one study suggests that ketamine-induced changes in SI are associated with ketmaine-induced increased in cerebellum rCMRglu. This medication-related finding is a potential lead in understanding brain mechanisms that may be helpful targets for suicide prevention interventions, but requires replication.

Structural and Functional Connectivity

Disturbances in the structure and function *within* brain regions can result in alterations in brain networks, including the ability of brain regions to coordinate their activity in a system. System dysfunction can also result from abnormalities in the connections between regions.

Increasingly, abnormalities in the structural and functional connections *between* brain regions within larger-scale brain networks have been reported in studies of STBs.

Connections of the medial VPFC with other cortical midline structures (PCC, precuneus) and temporal and parietal regions are implicated in the brain's default mode network and play an important role in self-referential processes, social cognition, autobiographical memory and prospective imaging[118]. Lower resting functional connectivity was reported in the default mode network in adolescents with MDD and SI[152]. These findings are in line with findings of lower resting functional connectivity of rostral ACC with medial OFC, precuneus and temporal pole in adults with MDD and SI[153] and within the precuneus in young adult SAs with MDD[154]. Structurally, lower fractional anisotropy (FA; thought to reflect the structural integrity of white matter and the neuronal connections it contains[155]) in the medial VPFC was reported in adult SAs with BD, which was associated with higher motor impulsivity[156]. Lower FA was also reported in the ventral cingulum (connecting posterior and temporal default mode network regions) in adults with MDD and SI[38]. Lower FA of the corpus callosum genu, that provides connections of interhemispheric anterior default mode network regions, was associated with a higher number of SAs in BD, MDD and BPD[157,158].

The limbic network includes the amygdala, medial and lateral OFC, medial temporal regions, thalamus and basal ganglia and is involved in emotional and autonomic processes[159]. Using task fMRI, lower amygdala-medial VPFC/rostral PFC connectivity was found in adolescent and young adult BD SAs while viewing happy and neutral facial expression, associated with higher lethality of attempts and current SI[36]. During rest, greater amygdala connectivity with lateral OFC, insula and middle temporal gyrus was found in adult SAs with MDD, with greater amygdala-parahippocampus connectivity associated with SI[160]. These functional connectivity alterations are in line with lower FA in the uncinate fasciculus, that provides major amygdala connections, in adolescents SAs with BD[36].

The medial OFC together with ventral striatum and the ventral tegmental area form core hubs of a reward network, with additional limbic regions, DLPFC and dACC forming a wider reward network subserving reward-related memory and evaluation[126]. An fMRI study investigating connectivity during reward processing showed a positive correlation between SI and connectivity of the left ventral striatum with dACC, DMPFC and DLPFC during loss trials in adults with MDD[161]. Using resting state fMRI, Kim et al.[162] found reduced connectivity in circuitry resembling this reward network, including the OFC, striatum and thalamus, in adults with MDD and recent (past month) SI. This is in line with findings of lower structural connectivity between VPFC/OFC and striatal regions in adults with MDD and SI (33% also had prior SA)[163], and between the ACC and OFC (as measured by graph theory) in adult SAs with MDD[164]. Lower FA was also reported in the anterior limb of the internal capsule

(connecting striatal and thalamic regions with the PFC) in adults with MDD and attempts[165,166].

The left and right DLPFC and DMPFC together with parietal regions comprise a network key in cognitive control of thought, emotion and behavior (executive control network[167]). Lower executive control network coherence during rest has been associated with both lifetime SI and past attempts in adolescents with MDD[152], in line with findings of lower DLPFC resting state connectivity in young adult SAs with MDD associated with higher impulsivity[168] and reduced white matter integrity (FA) in the DMPFC in adult SAs with MDD[169].

Alterations in dACC connectivity have been linked to STBs in the context of conflict-monitoring, with different patterns of dACC connectivity associated with SI versus SA in adults with recent-onset SZ[170]. That is, the presence of lifetime SI was *positively* associated with magnitude of functional connectivity of dACC with the precuneus, a core hub of the default mode network. This may suggest a reduced capacity of the dACC to 'switch off' default mode network activity associated with more internally focused attention, when activation of externally focused cognitive processing is required[170]. In contrast, history of suicide attempts was *negatively* associated with dACC connectivity with DPFC (BA9, 8, lateral BA10), lateral VPFC (BA45), PCC, parietal regions (BA7,40) and superior and middle temporal gyri (BA22, 39, 40)[170]. These findings may suggest that SI and SA have divergent bases in dACC connectivity with default mode network versus lateral PFC circuitries, respectively, in the context of monitoring conflict in adult SAs with recent-onset SZ. This is supported by findings of abnormal conflict-related dACC connectivity with VLPFC, OFC, insula and striatum associated with SI intensity, but altered dACC connectivity with DLPFC and frontal motor regions associated with past suicide attempts in adults with MDD or BD with psychotic features[171]. In addition, decreased functional connectivity of the dACC with bilateral insula while viewing angry faces was also reported in adolescent SAs with MDD[74]. Connectivity between the dACC and insula plays an important role in detecting salient internal and external stimuli to guide behavior[172] and has been implicated in the anticipation of aversive experiences, especially in depressed individuals[173]. Reduced connectivity between the dACC and bilateral insula may indicate inefficient strategies to process the salience of, and select contextually appropriate behavioral responses to, negative emotional stimuli.

Summary

Emerging evidence suggests that resting state functional connectivity in the default mode network, and white matter tracts connecting regions within this network, play a role in both SI and SA across mental disorders. Functional and structural connectivity alterations in the affective network have also been associated with SI and SA, as well as lethality of attempts, both during emotion processing and during rest. Connectivity abnormalities in the reward network have mostly been examined in adults with MDD, and both structural and functional

connectivity changes in regions of this network have been associated with SI and SA in this group. Connectivity changes within and between regions implied in the cognitive control network has been less extensively studied in relation to STBs, and the few studies conducted suggest a role of lower resting state functional connectivity within this network in STBs in adolescents and young adults with MDD. In addition, functional connectivity of dACC is implicated in STBs, but with divergent connectivity patterns related to SI versus SA.

4. DISCUSSION

While the literature primarily includes cross-sectional studies with small sample sizes, differing clinical populations and a wide range of imaging methods, there is emerging convergence in the brain regions implicated in STBs. Taken together with the recent increased momentum in studies on STBs (Figure 1), it is very hopeful that significant advances in our understanding of brain mechanisms contributing to STBs are on the horizon. A critical frontier is to identify markers for elevated risk, especially short term risk in the transition from SI to attempt. While the majority of studies to date were on SAs, some studies specifically investigated associations with SI, and brain regions found to be associated with STBs have known roles in processes thought to contribute to STBs. Below we briefly summarize the most convergent findings from the literature reviewed above, and propose directions for future neuroimaging studies on the neurobiology of STB.

A Tentative Brain Model of STBs

Figure 3 summarizes convergent findings emerging from the reviewed literature on brain alterations associated with STBs. Abnormalities in an extended VPFC system, including regions of the default mode, affective and reward networks such as the ventral and rostral ACC, insula, medial and lateral OFC, mesial temporal regions, ventral striatum and posterior structures (lateral temporal, PCC, precuneus, cerebellum), and in the connections among these regions, may be important in the excessive negative and blunted positive internal states that can stimulate SI. This is in line with the well-established role of this extended VPFC system in functions implicated in SI including appraisal of internally-generated emotions, self-referential processing, recall of emotional episodic memories, imagining future positive and negative events, valuation of rewards, and integrating environmental stimuli to modulate subjective emotional states[16,17,67,118,126,148]. A more lateral and dorsal system, including DMPFC, DLPFC and dACC, and together with the IFG, may facilitate suicide behaviors through their role in cognitive control of thought, emotion and behavior as well as cognitive flexibility, complex decision-making (e.g. valuation of different decision options) and planning[16,17]. A combination of VPFC and DPFC/IFG system disturbances may lead to very high risk circumstances in which SI may convert to lethal actions via decreased top-down inhibition of behavior or maladaptive, and inflexible decision-making and planning.

Alterations in the connections between these systems may contribute to the transition from suicidal thoughts to behaviors. For example, the dACC has connections to both the "emotional" ventral limbic system and the "cognitive" dorsal prefrontal system[174]. Consistent with this, findings suggest differential connectivity of the dACC in relation to SI versus a history of attempt, with dACC connectivity with VPFC, insula and striatal regions primarily associated with SI and dACC connectivity with DPFC regions associated with suicide attempts. The insula is also implicated in both SI and attempts and may perhaps be important for the transition from SI to attempt. Although the involvement of the insula in STBs has had little direct research focus, its critical involvement in interoceptive processing, detecting salient internal and external stimuli, experiencing emotion and self-awareness[175–177] suggests an important role of the insula in SI. Additionally, the insula is implicated in disconnection from bodily experiences, which in turn may lower the threshold to engaging in behaviors that harm the body (in line with the acquired capability theory[178]) thus suggesting a role of the insula in suicide behaviors. In line with important roles of dACC and insula circuitry (as part of the 'salience network') in mediating or switching between the extended medial VPFC (default mode, affective, reward) systems and the DPFC/IFG (executive control) system[179–181], the dACC and insula may represent integral hubs that facilitate the transition from SI to attempt. However, this suggestion of the dACC and insula's ability of mediating dynamic interactions between the medial VPFC and DPFC/IFG systems and through these interactions playing a role in the transition from SI to attempt remains highly speculative and will need to be confirmed in future, preferably longitudinal, studies on the neurobiology of STB.

Future directions

The literature reviewed underscores the need for future studies to include larger sample sizes and careful attention to developmental stages. In addition, studies employing longitudinal designs are critically needed to identify risk markers for future suicide attempts in order to develop improved preventive strategies. Recent preliminary evidence, from a rare longitudinal study of adolescents and young adults with mood disorders over about 3 years, showed that those with future attempts had lower VPFC volume and decreased FA in VPFC and DPFC connections[182], suggesting that these may be potential predictors for STBs already present in adolescence. Longitudinal study over short time intervals are largely absent from the literature and are critically-needed to assess proximal suicide risk.

Furthermore, studies focusing on identifying brain alterations that predict or fluctuate with changes in STBs following treatment could provide urgently needed biomarkers for response of STBs to existing interventions and could help develop novel treatments specifically targeting these biomarkers. Preliminary evidence has implicated brain circuitry that may mediate the reduction of suicide risk by treatments such as lithium and ketamine[183–185]. For example, ketamine-induced reductions in SI were associated with increases in baseline rCMRglu in a cluster including the cerebellum and occipital cortex[151]. In addition, in 57 adults

with BD with and without a history of attempt, lowest DLPFC, OFC, ACC, superior temporal cortex, parietal and occipital cortex volumes were observed in SAs off-lithium, followed by SAs and non-attempters on lithium, with the largest volumes in people with non-attempting BD patients on lithium[35]. However, the study of other pharmacological and non-pharmacological treatments that can directly (e.g. deep brain stimulation) or indirectly target the involved circuitry is needed.

Although adolescents have been less studied than adults, some findings have been similar. For instance, alterations in structure of the VMPFC, VLPFC, DLPFC, DMPFC, ACC, lateral temporal regions and parahippocampal gyrus were observed in both adolescents and adults with SA. Furthermore, lower connectivity in regions related to the default mode network during rest have been consistently reported across adolescents, young adults and adults with SI and/or SA. Greater DLPFC activity in response to angry faces was also observed in both adolescents and adults with STBs. The highly limited number of studies in adolescents and a lack of different life stages in single studies prevents drawing conclusions about the overlap in functional brain alterations across different stages of life and brain maturation. Thus, there is some converging evidence across adolescent and adult samples, however, not all adult findings have been observed in adolescents (see Tables 1-3 for a complete overview). This may at least in part be due to the continued maturation of involved brain systems so that not all features may be expressed until adulthood[186,187].

Most studies only included a single disorder, impeding conclusions around shared versus unique neural substrates of STBs across different mental disorders. Different studies employed different in- and exclusion criteria, imaging methods and STB assessments. Nonetheless, gray matter alterations in the VLPFC, DLPFC, ACC, and insula have been consistently reported across the diagnostic categories reviewed (i.e., MDD, BPD, BD, SZ), while lateral temporal alterations were more uniquely observed in psychotic disorders and BPD. Reduced white matter integrity in ventral PFC regions was reported in relation to STBs in both BD and MDD and lower FA in the corpus callosum was associated with a higher number of attempts across BD, MDD and BPD. Functional brain alterations in relation to emotion processing and regulation was investigated only in MDD, BD and BPD, with consistent findings of increased VLPFC activation in response to negative emotional stimuli across MDD and BPD, while the only study of adolescents with BD focused on amygdala-PFC connectivity[36]. Higher DLPFC activation during cognitive control tasks, in the absence of task performance differences, was also consistently reported across MDD, BD, SZ and PTSD. In contrast, higher versus lower IFG activation during cognitive control was observed in mood disorders versus SZ, respectively. Alterations in dACC connectivity with default mode, affective and reward network related regions in relation to SI, and alterations in dACC connectivity with DLPFC in relation to SA during cognitive control, has been observed across MDD, BD and SZ. Other functional domains such as reward processing, decision making,

social exclusion and self-referential processing, as well as resting state fMRI, have only been investigated in a single disorder, i.e. depression. In one of the few studies to assess SAs across MDD and BD (published subsequent to our literature search), VPFC gray matter volume reductions and uncinate fasciculus FA reductions were common to both disorders, suggesting that they may be important in risk for attempts across mood disorders[188]. Preliminary findings of that study also indicated there may be differences in involved regions in SAs between the disorders, with greater uncinate involvement in attempters in BD and dorsal frontal white matter in MDD. These findings suggest both transdiagnostic and unique gray and white matter targets for suicide prevention across mental disorders.

The examination of sex differences in STBs is a major gap in the neuroimaging literature and a critical area for study. There are well-established sex-dependent features known in STBs[189], such as a higher rate of attempts in females and a higher lethality of attempts in males[190–192]. Moreover, increased death rates by suicide between 1999 and 2017 as reported by the CDC showed the rate of increase was substantially higher for females than males (53% and 26% respectively). Female suicide rate increases were particularly high in youth/early adulthood (ages 10-24) and middle age (45-64 years), when females have their highest risk, while the highest risk for males is age 75 and older[193]. Of the studies in this review, 11 (8.4%) had exclusively female and 15 (11.5%) exclusively male samples. Authors of six studies (4.6%) commented on this homogeneity as a limitation, and 14 (10.7%) provided a rationale for single sex studies. These included the need to avoid potential confounds of previously reported sex-based effects e.g., previous reports of sex differences in cortical responses with similar fMRI tasks (n=5) and corpus callosum structure (n=2); high male representation in the group under investigation, such as military veterans (n=3); female-skewed prevalence of BPD (n=1); males and females imaged on different scanners (n=1); small number of male SAs (n=1); and an attempt to replicate previous work (n=1). Ninety studies (68.7%) included sex as a covariate, controlling for potential differences. A small percentage of studies (13.8%) included sex as a variable to assess potential interactions with STBs. Five studies (3.8%) reported sex-related findings, though no relationship with STBs[37,147,194–197] and one study (0.8%) reported more females than males studied were SAs but reported no neuroimaging-related findings[198]. Chase and colleagues[199], in a study that controlled for sex, noted that one participant identified as transmale. Careful consideration is warranted in how sex and gender are evaluated and categorized for analyses, including the importance of allowing subjects to identify by gender and this self-identification of gender is considered in all studies. This is particularly important because transgender and sexual-minority individuals are at increased risk for STBs and death by suicide[200,201]. Collectively, these STB neuroimaging research data highlight the urgent need for future work on sex and gender.

Integration of neuroimaging research across differential mechanistic levels including genetic, molecular, social, and environmental risk factors will be crucial to the elucidation of a holistic

STB pathophysiology and mechanisms associated with vulnerability and resilience and thus tailored intervention development. Sophisticated analytic methods, such as machine learning techniques[60], can be utilized to allow imaging risk markers to be identified at the level of the individual instead of at a group level, a key ingredient for clinically viable biomarkers[202] and precision medicine. In addition, the use of high resolution ultra-high field strength MRI methods and more specific functional neuroimaging tasks may further enhance ability to parse roles of specific brain regions, such as PFC subregions[203]. Molecular imaging has produced important leads, such as in serotonergic and inflammation mechanisms (Table 2), consistent with post-mortem, genetic and peripheral biomarker studies implicating an important role of the serotonergic system and inflammatory mechanisms in STBs[204,205]. Imaging of molecular mechanisms other than serotonin remains scarce, with for example only four magnetic resonance spectroscopy (^{1}H-MRS) studies examining glutamatergic and Gamma-Aminobutyric Acid (GABA)-ergic mechanisms that have been published to date (Table 2). Given post-mortem findings of altered glutamatergic and GABA-ergic gene expression and receptor availability in suicide victims mainly in the prefrontal cortex, ACC and hippocampus[206–208], future ^{1}H-MRS should clarify the role of these neurotransmitters in STBs in vivo. In addition, a generation of new methods to identify other currently implicated and novel molecular mechanisms is needed. For example, a link between oxytocin and SI was recently suggested[209].

Future studies should also further investigate the more elusive subjective aspects of suicide risk, such as SI, as well as implicated psychological constructs such as hopelessness, rumination and anhedonia[210–212], which may be relevant across diagnoses. Similarly, social experiences such as childhood maltreatment and peer bullying form a strong prelude to STB in later life[209,213,214], and impact on the neural structures implicated in STB (e.g. DMPFC structure and function[215,216]). Therefore, adverse experiences should be taken into account in future studies on the neurobiology of STB.

Links identified between neuroimaging measures and behaviors outside of the scanner could facilitate the development of less invasive and more easily and widely disseminated risk detection methods. Furthermore, investigations of larger samples can be facilitated by international collaborations that pool existing data across many different samples, such as the MQ HOPES (https://www.mqmentalhealth.org/research/profiles/overcome-and-predict-the-emergence-of-suicide) and ENIGMA STB (http://enigma.ini.usc.edu/ongoing/enigma-stb/) consortia. These initiatives represent cost-effective ways to substantially increase statistical power, which could provide more robust and reliable findings[217], and ability to study age, gender and sex effects, as well as unique and shared mechanisms associated with STBs across different mental disorders. Furthermore, large combined datasets will provide a unique opportunity to identify and test reproducibility of different pathways to suicide that may differ across many parameters including a range from the impulsive to the highly planned. Such

efforts will need to take into account the variety of assessment methods used for STBs across studies. One way to address with this important challenge is through the examination of the presence versus absence of suicidal behavior (attempts), and/or suicidal ideation (with or without intent and/or a plan) across assessment types (see for example Renteria et al.[111]). Another approach could involve standardization of scores across different instruments by developing a common metric[218]. Standardization of STB assessment across future studies would significantly facilitate the sharing of data, and thereby advancing our understanding of brain-based STB vulnerability.

Conclusions

More than two decades of neuroimaging studies on STBs suggests a transdiagnostic model for STBs in which an extended VPFC system may be important in the excessive negative and blunted positive internal states that can stimulate SI and a DPFC/IFG system that may facilitate suicide attempt behaviors. Interactions between these systems are likely important in the transition from ideation to attempt, perhaps mediated by dACC and insula regions, but require further investigation. With the exponential growth of research on STBs, including the initiation of large global efforts, it is hopeful that suicide prevention will soon be more effectively targeted, reducing the tragic loss of life to suicide.

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Conflicts of interest

The authors declare no competing financial interests. HPB received an honorarium for a talk at Aetna.

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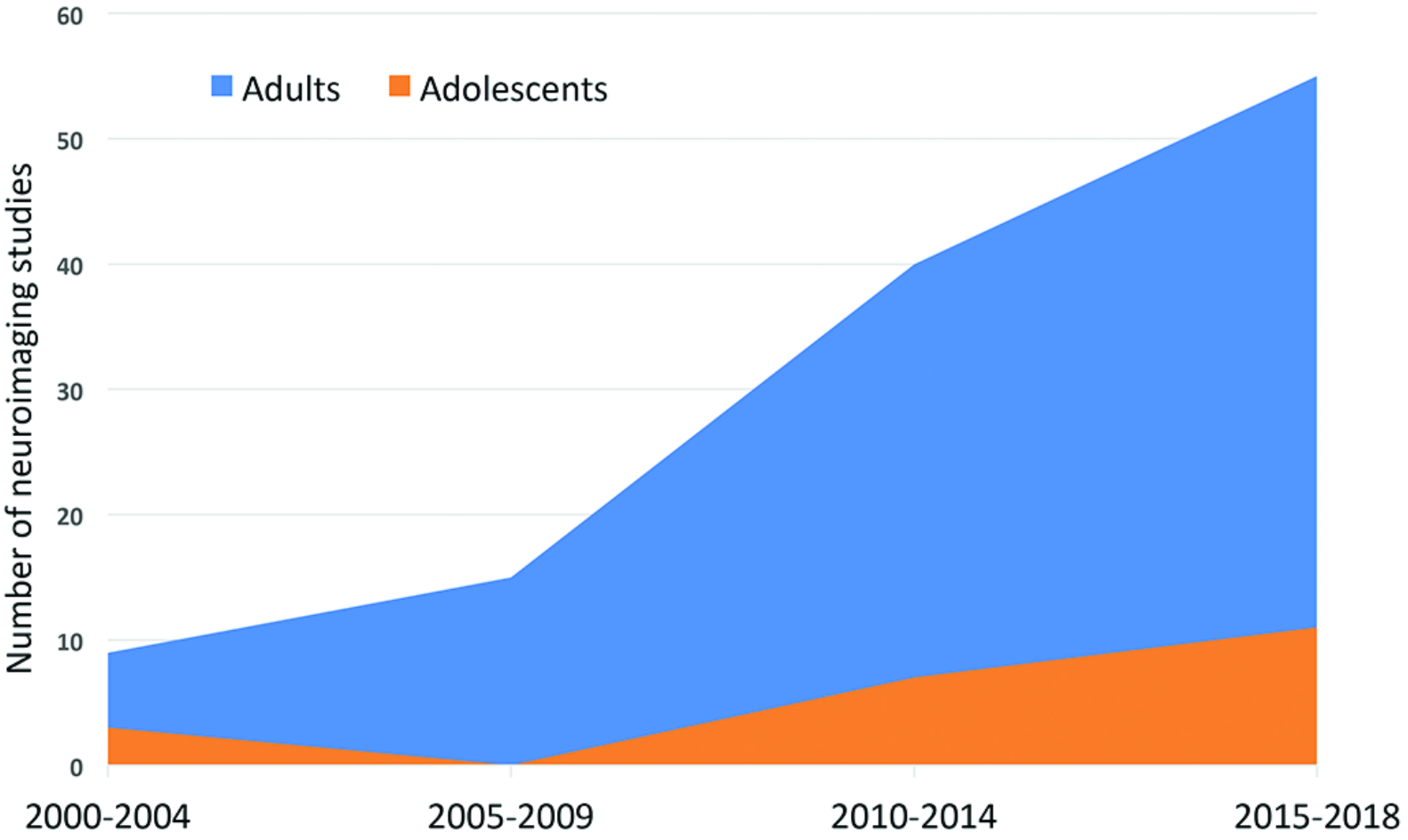
FIGURE LEGENDS

Figure 1: **Number of neuroimaging studies on suicidal thoughts and behaviors published in the last two decades.** The figure was based on the studies included in this review, calculated separately for studies including adolescents and studies only including adults and divided into separate 4-year time bins for publication date.

Figure 2: **Overview of brain regions and structural connections included in this review** (A) Brain regions that have been most reported in neuroimaging studies investigating structural, functional and molecular brain alterations associated with suicidal thoughts and behaviors, with a subset of regions grouped more broadly into ventral prefrontal cortex, dorsal prefrontal cortex, insula, mesial temporal, subcortical, and posterior regions. (B) White matter tracts implicated in suicidal thoughts and behaviors reported in diffusion tensor imaging studies. DMPFC, dorsomedial prefrontal cortex; dACC, dorsal anterior cingulate cortex; RMPFC, rostromedial prefrontal cortex; mOFC, medial orbitofrontal cortex; vACC, ventral anterior cingulate cortex; PCC, posterior cingulate cortex; Thal, thalamus; VS, ventral striatum; Hippo, hippocampus; Amyg, amygdala; DLPFC, dorsolateral prefrontal cortex; RLPFC, rostrolateral prefrontal cortex; IFG, inferior frontal gyrus; lOFC, lateral orbitofrontal cortex; Put, putamen; Caud, caudate.

Figure 3: A tentative brain circuitry model of suicidal thoughts and behaviors. Medial VPFC (ventral ACC, OFC, RPFC), insula, amygdala, hippocampus, lateral temporal regions, posterior midline structures (posterior cingulate cortex and precuneus), dACC, ventral striatum, thalamus and cerebellum contribute to the generation of suicidal ideation through their roles in excessive negative and blunted positive internal states, negative self-referencing, impairments in future thinking and rumination. DPFC (DLPFC and DMPFC), IFG and dACC alterations further exacerbate suicidal thoughts and facilitate suicide behaviors due to their involvement in diminished cognitive control of thought, emotion and behavior and impairments in cognitive flexibility and valuation of different decision options. Alterations in bottom-up and top-down connections between these extended medial VPFC and DPFC/IFG systems may contribute to the transition from suicidal thoughts to behaviors. The dACC and insula may mediate this transition. Dashed lines indicate speculative associations that need further confirmation by future structural and functional connectivity studies. DMPFC, dorsomedial prefrontal cortex; dACC, dorsal anterior cingulate cortex; RPFC, rostral prefrontal cortex; OFC, orbitofrontal cortex; vACC, ventral anterior cingulate cortex; PCC, posterior cingulate cortex; Thal, thalamus; VS, ventral striatum; Hippo, hippocampus; Amyg, amygdala; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; Put, putamen; Caud, caudate.


60
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30
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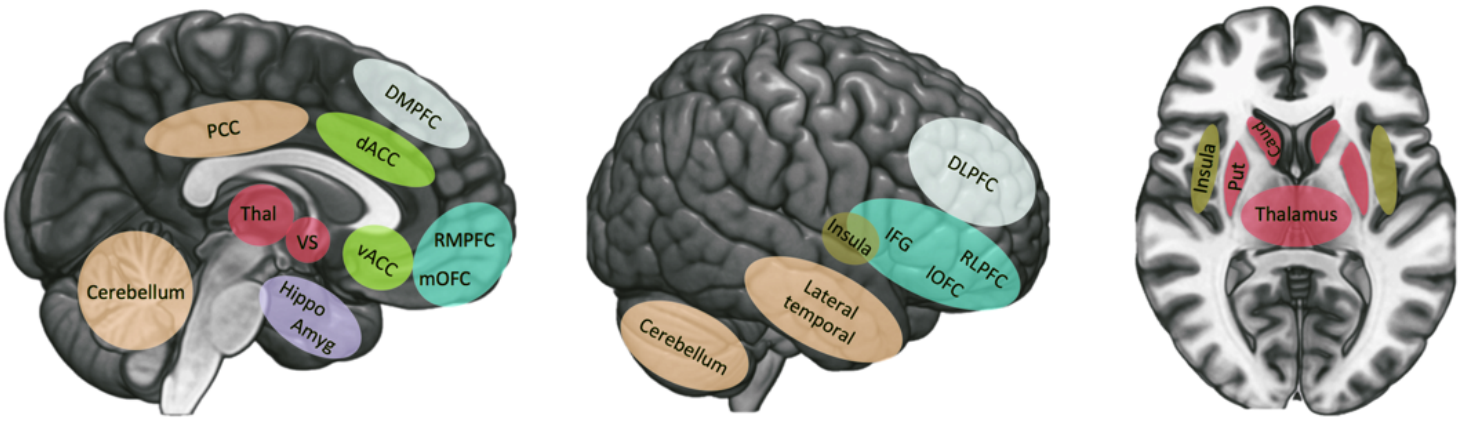
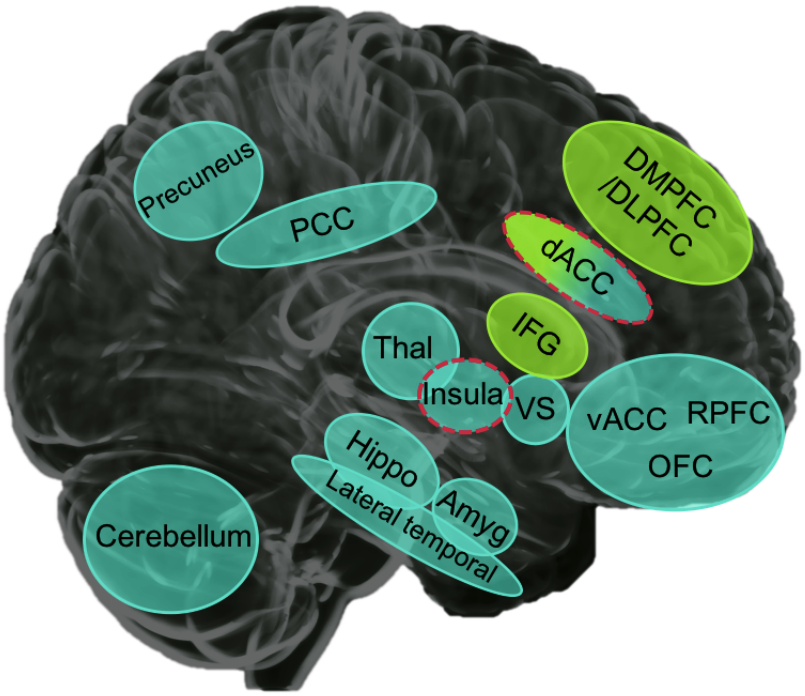
Number of neuroimaging studies
Adults
Adolescents
2000-2004
2005-2009
2010-2014
2015-2018


PCC
DMPFC
dACC
Thal
VS
vACC
RMPFC
mOFC
Cerebellum
Hippo
Amyg
DLPFC
Insula
IFG
RLPFC
lOFC
Lateral temporal
Cerebellum
Insula
Caud
Put
Thalamus
Striatum & Thalamus
Dorsal Prefrontal Cortex (DPFC)
Posterior regions
Mesial temporal
Ventral Prefrontal Cortex (VPFC)
Anterior Cingulate Cortex (ACC)



Diminished cognitive control of emotion and behavior, cognitive inflexibility, impaired valuation of different decision options

Mediating dynamic interactions between the extended VPFC and DPFC/IFG systems

Enhanced negative and blunted positive internal states, negative self-referencing, impairments in future thinking, rumination

Table 1. Findings from Structural Imaging Studies of Suicidal Thoughts and Behaviors

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
STRUCTURAL MAGNETIC RESONANCE IMAGING STUDIES OF GRAY AND WHITE MATTER							
Suicide attempt studies							
Goodman et al 2011[87]	BPD + MDD	13 SA	13 HC	20 (77)	SA: 15.8 (1.1), HC: 16.2 (0.8)	ROI volume: OFC, ACC, DMPFC, DLPFC	Number of SA associated with ↓ ACC (BA24) volume (combined WM and GM), and ↑WM (not GM) in posterior cingulate (BA 23), however, similar association with BPD symptom severity for both findings.
Fradkin et al 2017[55]	MDD	29 SA	29 HC	46 (79)	SA: 17.6 (1.82), HC:16.9 (1.72)	WB cortical thickness and surface area	In HC: motor impulsivity associated with ↑ RMPFC/RLPFC thickness. In SA: motor impulsivity associated with ↓ RMPFC/RLPFC thickness. In SA: non-planning impulsivity associated with ↑ paracentral lobule thickness. No findings medicated vs unmedicated.
Cao et al 2016[168]	DD	35 SA	18 DC, 47 HC	66 (66)	SA: 20.63 (3.65), DC: 21.39 (3.05), HC: 20.53 (1.84)	WB VBM GMV and WMV (SPM)	SA + SI vs DC + SI: No differences between groups
Johnston et al 2017[36]	BD	26 SA	42 DC, 45 HC	43 (63)	SA: 20.5(3.0), DC:20.6 (3.2), HC:20.8(3.3)	WB, VBM GMV (SPM)	SA +SI vs DC: ↓ GMV in right medial/lateral OFC (BA11/47), hippocampus, bilateral cerebellum
Pan et al 2015[115]	MDD	28 SA	31 DC, 41 HC	ND	SA: 16.0 (1.27), DC: 16.06 (1.47), HC: 14.48 (1.84)	WB GMV, WMV and cortical thickness	SA + SI vs DC: ↓ caudal middle frontal gyrus (BA8) volume, temporal pole (BA38) thickness, parahippocampal gyrus (BA34) volume
Peng et al 2014[146]	MDD	20 SA	18 DC, 28 HC	38 (58)	SA: 27.75 (7.21), DC: 31.06 (7.39), HC: 28.61 (5.45)	WB VBM GMV (SPM)	SA vs DC (SI not reported): ↓ left PCC, which correlated negatively with dysfunctional attitudes.
Gosnell et al 2016[33]	MDD, BD, AA, ANX	20 SA	20 DC, 20 HC	28 (47)	SA: 28.9 (9.98), DC: 29.25 (11.1), HC: 28.9 (10.0)	ROI volume: thalamus, insula, basal ganglia, hippocampus, amygdala, corpus callosum, cortical lobes.	SA vs DC: ↓ right precentral gyrus, right IFG, right caudal middle frontal gyrus (DPFC), left precentral lobule and total temporal cortex. No association between SI (regardless of history of SA) and any of the ROIs
Soloff et al 2012[100]	BPD	44 SA	24 DC, 52 HC	76 (63)	SA: 29.6 (8.0), DC: 25.9 (5.7), HC: 25.9 (7.2)	ROI VBM GMV (SPM), ROIs: IFG, OFC, ACC, middle and superior temporal cortex, insula, hippocampus, parahippocampus, fusiform gyrus, lingual gyrus and amygdala	SA vs DC: ↓ insula and larger lingual and middle and superior temporal gyri. In SA: HL associated with ↓ lateral OFC, middle and superior temporal gyri, insula, fusiform gyrus, lingual gyrus and parahippocampal gyrus
Monkul et al 2007[109]	MDD	7 SA	10 DC, 17 HC	34 (100)	SA: 31.4 (13.9), DC: 36.5 (7.5), HC: 31.3 (8.3)	ROI manual shape tracing, ROIs: OFC, ACC, PCC, amygdala and hippocampus. DLPFC, subgenual PFC, thalamus, temporal lobe, caudate and lateral ventricles in exploratory analyses	SA vs DC: ↑ right amygdala

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Besteher et al 2016[71]	SCZ	14 SA	23 DC, 50 HC	46 (53)	SA: 34.4 (12.1), DC: 28.8 (9.7), HC: 29.5 (7.9)	WB cortical thickness and mean curvature	SA vs DC: SA ↓ in right DLPFC and superior and middle temporal gyri, temporopolar cortex, and insula
Giakoumatos et al 2014[37]	SCZ, SZA or BD-P	148 SA (97 HL, 51 LL)	341 DC, 262 HC	387 (52)	SA-HL: 35.6 (11.7), SA-LL: 36.9 (12.2), DC: 35.9 (13.3), HC: 38.1 (12.5)	WB GMV, cortical surface area and thickness	SA vs DC: ↓ GMV in bilateral superior and middle frontal gyri (DLPFC), and inferior and superior temporal gyri, left superior parietal and supramarginal cortex, and right insula and thalamus. High (vs. low) lethality: ↓ GMV in left lingual area and right cuneus across all attempters; left dorsal ACC (BA32), left inferior parietal cortex, left inferior temporal gyrus, and right middle temporal gyrus in BD-P; left lingual gyrus, bilateral pericalcarine, right cuneus and right lateral occipital cortex in SZ; left middle frontal gyrus (DLPFC) in SZA.
Rüsch et al 2008[219]	SCZ	10 SA	45 DC, 55 HC	42 (38)	SA: 30.3 (6.5): DC 37.3 (11.6)	WB VBM GMV and WMV (SPM)	SA vs DC: ↑ WMV in bilateral posterior lateral OFC and IFG. No GMV differences
Matsuo et al 2010[220]	BD	10 SA	10 DC, 27 HC	47 (100)	SA: 36.2 (10.1), DC:44.2 (12.5), HC: 36.9 (13.8)	ROI volume, manual shape tracing of CC genu, anterior body, posterior body, isthmus and splenium	SA vs DC: no significant differences. In SA: impulsivity associated with ↓ anterior corpus callosum genu
Lijffijt et al 2014[113]	BD	51 SA	42 DC, 45 HC	138 (100)	SA: 36.6 (10.7), DC: 41.1 (11.3)	ROI volume, ROIs: superior frontal gyrus, rostral and caudal middle frontal gyrus, frontal pole, IFG, medial and lateral OFC, rostral and caudal ACC	SA vs DC: no differences. Lower PFC GMV only in SA with previous hospitalization
Soloff et al 2014[88]	BPD	51 SA (16 HL, 35 LL)		41 (80)	SA-HL: 36.1 (9.2): SA-LL: 27.4 (5.9).	ROI volume VBM of GMV (SPM), ROIs: OFC, ACC, middle and superior temp gyrus, insula, (para-)hippocampus, lingual gyrus, amygdala	HL vs LL SA: ↓ GMV in bilateral middle and superior temporal gyri, left lingual gyrus, bilateral lateral OFC, right insula, bilateral fusiform gyrus, right parahippocampus, left ventral and dorsal ACC and left hippocampus. In HL SA: aggression associated with ↑ ventral and dorsal ACC, lateral OFC, middle and superior temporal gyri and right insula, and impulsivity associated with ↑ right middle and superior temporal gyri and ↓ insula. In LL SA: impulsivity associated with ↓ right middle and superior temporal gyri, bilateral insula, bilateral lingual gyrus, ventral ACC, fusiform gyrus, lateral OFC, hippocampus and amygdala
Aguilar et al 2008[142]	SCZ	13 SA	24 DC	0 (0)	SA: 37.1 (11.0), DC: 42.7 (10.2)	WB VBM GMV (SPM)	SA vs DC: ↓ medial OFC and superior temporal gyrus
Ding et al 2015[32]	Past MDD/BD	67 SA	82 DC, 82 HC	98 (42)	SA: 39.2 (10.6), DC: 39.4 (9.7),HC: 37.8 (8.1)	WB and ROI VBM GMV (SPM) and cortical thickness and surface area, ROIs: OFC, VLPFC, VMPFC (including ACC), and DLPFC	SA vs DC: ↓ OFC (BA47, lateral part of BA11) in exploratory WB analysis. In SA: lethality last SA associated with ↓ right DPFC BA8/9/46), OFC, left VLPFC (BA44/45). Number SA associated with ↓ right DPFC and left OFC. No associations with SI.

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Gifuni et al 2017[221]	Past MDD/BD	61 SA	75 DC, 73 HC	120 (47)	SA: 38.3 (10.7), DC: 38.4 (9.1), HC: 39.2 (7.0)	ROI volume SBM, ROI: corpus callosum	SA vs DC: no differences. No correlation corpus callosum volume and SI, age at first SA and number of SA
Gifuni et al 2016[112]	Past DD/BD	73 SA	89 DC, 91 HC	120 (47)	SA: 39.2 (10.6), DC: 39.4 (9.5), HC: 38.3 (8.2)	ROI volume, ROIs: amygdala, hippocampus, caudate, globus pallidus, putamen, nucleus accumbens, ventral diencephalon and thalamus	SA vs DC: no differences. In SA: lethality SA associated with ↓ left and right nucleus accumbens
Harenski et al 2017[222]	SCZ, SZA, BD-P, or MDD-P	18 SA	18 DC, 59 HC, 26 HC	0 (0)	SA: 38.9 (11.73), DC: 40.2 (10.23), HC: 32.5 (11.16), CHC: 33.0 (9.49)	WB and ROI VBM GMV (SPM), ROIs: posterior superior temporal cortex, temporal poles and medial PFC	SA vs DC: ↓ left and right temporal pole
Nery-Fernandes et al 2012[194]	BD	19 SA	21 DC, 22 HC	41 (66)	SA: 39.8 (11.4), DC: 42.0 (8.6), HC: 37.7 (13.5)	ROI volume VBM GMV (SPM), ROI: corpus callosum	SA vs DC: no differences
Vang et al 2010[130]	MDD, AD	7 SA	6 HC	ND	SA: 40 (11.83), matched HC, no details	ROI volume, ROIs: subcortical structures	SA vs HC: ↓ globus pallidus and caudate, and correlated with 5-HTT binding. In SA: non-impulsive temperament associated with ↓ globus pallidus GMV
Baldaçara et al 2011[223]	BD	20 SA	20 DC, 22 HC	41 (66)	SA: 39.94 (11.2), DC: 41.9 (8.9), HC: 37.7 (13.6)	ROI volume VBM GMV and WMV (SPM), ROIs: cerebellum	SA vs DC: no differences total brain volume or cerebellar volume
Wagner et al 2011[34]	MDD	10 with SA and/or first-degree relative with SA	15 DC, 30 HC	50 (83)	SA: 41.0 (12.5): DC: 34.1 (10.5), HC: 35.1 (10.4).	WB VBM GMV(SPM)	SA vs DC: ↓ rostral ACC (BA24) and right caudate
Wagner et al 2012[58]	MDD	10 with SA and/or first-degree relative with SA	15 DC, 30 HC	50 (83)	SA: 41.0 (12.5), DC: 34.1 (10.5), HC: 35.1 (10.4)	WB cortical thickness	SA vs DC: ↓ VLPFC (BA47), DLPFC (BA46) and dorsal ACC (BA32). Patients with own versus relative with SA: no differences in dorsal ACC, VLPFC, DLPFC.
Duarte et al 2017[101]	BD	20 SA	19 DC, 20 HC	34 (57)	SA: 41.10 (12.64): DC: 42.26 (11.70), HC: 37.40 (10.20)	WB and ROI volume VBM GMV (SPM), ROIs: OFC, DLPFC (including IFG), ACC, amygdala, hippocampus, thalamus and insula	SA vs DC: ↑ right rostral ACC (BA24). In SA: HL SA was associated with ↑ insula, LL SA was associated with ↓ OFC (BA47)

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Benedetti et al 2014[224]	BD	32 SA	104 DC	93 (68)	SA (5-HTTLPR l/l): 41.4 (10.7), SA (5-HTTLPR *s): 46.4 (12.8), DC (5-HTTLPR l/l): 48.5 (10.4), DC (5-HTTLPR *s): 46.8 (12.6)	WB GMV (SPM)	SA vs DC: no differences.
Lee et al 2016[150]	MDD	19 SA	19 DC, 20 HC	41 (73)	SA: 42.0 (10.8), DC: 41.1 (15.2)	ROI volume GMV (SPM), ROIs not specified	SA vs DC: ↓ right cerebellum and left angular gyrus
Spoletini et al 2011[110]	SCZ	14 SA	36 DC, 50 HC	35 (39)	SA: 42.9 (11.3), DC: 39.8 (11.4): HC: 40.0 (16.6)	ROI volume GMV (FSL), ROIs: lateral ventricles, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens	SA vs DC: ↑ right amygdala
Benedetti et al 2011[35]	BD	19 SA (with/without Lithium)	38 DC (with/without Lithium)	38 (67)	SA-L-: 43.6 (10.4), SA-L+: 45.6 (11.3), DC-L-: 45.9 (10.5), DC-L+: 46.2 (13.3)	WB VBM GMV (SPM)	SA vs DC: ↓ DPFC (BA6/8/9), RLPFC (BA10), OFC (BA11/47), dorsal ACC (BA32), parietal and occipital cortex and ↑ in bilateral superior temporal gyrus. SA with lithium vs without: ↑ DPFC (BA6/8), OFC (BA11/47), ACC (BA24/32), parietal and occipital cortex and ↓ in bilateral superior temporal gyrus
Colle et al 2015[114]	MDD	24 SA	39 DC	39 (62)	SA: 44.2 (11.9), DC: 47.7 (12.6)	ROI volume GMV (SACHA, automatic segmentation), ROI: hippocampus.	SA vs DC: ↓ hippocampus. No difference between SA in last month versus SA >1 month ago
Dombrovski et al 2012[129]	MDD	13 SA	20 DC, 19 HC	30 (58)	SA: 66.0 (6.4), DC: 67.7 (7.0), HC: 70.5 (7.5)	ROI voxel count basal ganglia (caudate, putamen, pallidum)	SA vs DC: ↓ putamen, associative and ventral striatum voxel count. In SA: delay discounting associated with ↓ putamen voxel count
Cyprien et al 2011[225]	MDD, ANX, BD	21 SA or SI	234 DC, 180 HC	222 (51)	SA: 72.2 (4.3), DC: 71.0 (3.8), HC: 71.0 (3.8)	ROI volume manual shape tracing, ROI: corpus callosum	SA vs DC: ↓ posterior third of corpus callosum
Hwang et al 2010[70]	MDD	27 SA	43 DC, 26 HC	0 (0)	SA:79.1 (5.6), DC:79.6 (5.1), HC: 79.5 (4.3)	WB VBM GMV and WMV (SPM)	SA vs DC: ↓ GMV in DPFC (BA6/8/9/46), precentral gyrus, postcentral gyrus, superior parietal lobe, inferior parietal lobe, cuneus, superior temporal gyrus, insula, cerebellum, midbrain, ↓ WMV in DPFC (BA6/8/9/46), precentral and postcentral gyrus, inferior parietal lobe, precuneus, occipital lobe, external capsule, cerebellum
Lopez-Larson et al 2013[134]	TBI	19 SA	40 DC, 15 HC	0 (0)	18-55	ROI volume, ROI: thalamus	SA vs DC: ↑ right thalamus
Jia et al 2010[165]	MDD	16 SA	36 DC, 52 HC	55 (53)	SA: 34.2 (13.7), DC: 34.7 (12.5), HC: 37.1 (16.0)	WB VBM GMV and WMV (SPM)	SA vs DC: no differences

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Kim et al 2015[226]	PD	12 SA	25 DC	23 (64)	16-60	WB VBM GMV and WMV (SPM)	SA vs DC: no differences
Rentería et al 2017[111]	MDD	153 SA or SI+plan, 298 SI-plan	650 DC, 1996 HC	ND	SA+SI: 21.10-53.8 (across 7 samples), DC: 22.9-54.8, HC: 22.9-55.4.	ROI volume, ROIs: nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, ICV	SA+SI with plan vs DC: no differences. SI vs DC: no differences
Suicidal ideation studies							
Thomas et al 2004[227]	PTSD + Childhood maltreatment	47 SI, 17 SA	14 DC, 121 HC	89 (49)	DC: 11.71 (2.6): HC: 11.74 (2.5)	ROI volume manual shape tracing (IMAGE), ROI: pituitary	SI (with SA) vs DC: ↑ pituitary
Taylor et al 2015[38]	MDD	21 SI, including 10 with past SA	53 DC, 91 HC	108 (65)	SI: 33.5 (9.1), DC:37.5 (8.9), HC: 29.9 (9.1)	WB and ROI volume GMV and cortical thickness, ROIs: OFC, cingulate cortex, insula, amygdala, parahippocampus, thalamus, basal ganglia	SI+SA vs DC: ↓ cortical thickness of left insula, left caudal middle frontal gyrus (DLPFC), left superior parietal cortex, left superior temporal gyrus. No GMV differences
Caplan et al 2010[228]	Epilepsy & MDD, ANX, ADHD	11 SI (No past SA)	40 DC	28 (55)	SI: 11.04 (2.06), DC:9.43 (2.07)	ROI volume manual shape tracing, ROIs: middle frontal gyrus, superior frontal gyrus, OFC, temporal lobe	SI vs DC: ↓ right orbital frontal gyrus WMV and ↑ left temporal lobe GMV
MAGNETIC RESONANCE IMAGING STUDIES OF WHITE MATTER HYPERINTENSITIES							
Suicide attempt studies							
Ehrlich et al 2003[229]	MDD, BD, PsD, conduct/ADHD	43 SA	110 DC	39 (26)	Entire sample: 14.6 (3.4). No further details provided.	WMH (Modified version of Coffey scale)	SA vs DC: ↑ DWMHs in parietal lobes. All SA subjects had lesions in right posterior parietal lobe
Ehrlich et al 2004[198]	MDD, BD, PsD, conduct/ADHD	43 SA	110 DC	41 (27)	Entire sample: 14.6 (3.4). No further details provided.	WMH (Modified version of Coffey scale)	↑ WMH associated with past SA, driven by PVH. SI not associated with WMH
Ehrlich et al 2005[230]	MDD	62 SA	40 DC	68 (67)	Entire sample: 26.7 (5.5). No further details provided.	WMH (Modified version of Fazekas scale)	SA vs DC: ↑ PVH, not DWMH. No association with SI
Pompili et al 2007[231]	MDD, BD	29 SA	26 DC	41 (63)	SA: 42.2 (13.5), DC: 44.6 (14.0)	WMH (Modified version of Fazekas scale)	SA vs DC: ↑ WMH. SI was not associated with WMH

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Pompili et al 2008[232]	MDD, BD	44 SA	55 DC	57 (58)	SA: 45.57 (16.10), DC: 47327(14.54)	WMH (Modified version of Fazekas scale)	SA vs DC: ↑ PVH, no difference DWMH
Ahearn et al 2001[233]	MDD	20 SA	20 DC	17 (85)	SA: 66.0 (5.8), DC: 66.4 (5.7)	WMH (Coffey and Boyko scales)	SA vs DC: ↑ subcortical GM hyperintensities, and trend towards more PVH
Sachs-Ericsson et al 2014[234]	MDD	23 SA	223 DC	149 (67)	SA: 66.74 (6.6), DC: 69.8 (7.5)	WMH (Duke Neuropsychiatric Imaging Research Laboratory modified version of MrX software)	SA vs DC: ↑ WM lesions in the left hemisphere. ↑ increase over time in bilateral WMH in SA, which was predicted by the number of depressive episodes.
DIFFUSION TENSOR IMAGING STUDIES							
Suicide attempt studies							
Johnston et al 2017[36]	BD	26 SA	42 DC, 45 HC	43 (63)	14-25	WB FA maps (SPM)	SA vs DC: ↓ FA in left uncinate fasciculus, right uncinate fasciculus and right cerebellum
Lischke et al 2017[158]	BPD	13 SA	8 DC, 20 HC	41 (100)	18-45	Tractography based FA and MD with seeds in genu, splenium and body of corpus callosum	SA vs DC: no differences. Number of attempts associated with ↓ FA and MD in splenium and FA in the genu
Lee et al 2016[235]	SCZ	15 SA	41 DC	41 (73)	18-60	WB FA, MD, AD and RD maps (FSL)	SA vs DC: ↑ FA in left corona radiata (anterior, superior, posterior), superior longitudinal fasciculus, posterior limb and retrolenticular part of internal capsule, external capsule, posterior thalamic radiation, sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), ↓ AD in retrolenticular part of internal capsule, posterior thalamic radiation and sagittal stratum. No differences in MD and RD.
Kim et al 2015[226]	PD	12 SA	25 DC	23 (64)	16-60	FA, MD, AD and RD maps (FSL), Tracts: corona radiata, inferior longitudinal fasciculus, inferiorfronto-occipital fasciculus, superior longitudinal fasciculus, posterior thalamic radiation, internal capsule, splenium of corpus callosum	SA vs DC: ↑ FA in posterior and superior corona radiata, sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), superior longitudinal fasciculus, posterior thalamic radiation, retrolenticular part of internal capsule and splenium of the corpus callosum. No differences in MD, RD and AD. In SA: positive correlation between suicidal ideation and FA of the right retrolenticular part of internal capsule and right and left posterior thalamic radiation. In DC: positive correlation between suicidal ideation and FA of splenium, right retrolenticular part of internal capsule and left posterior thalamic radiation
Mahon et al 2012[156]	BD	14 SA	15 DC, 15 HC	18 (41)	SA: 33.3 (14.1), DC: 36.5 (12.3), HC: 33.7 (12.6)	WB FA maps	SA vs DC: ↓ FA in white matter tract in medial VPFC. In SA: medial VPFC FA negatively correlated with motor impulsivity

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Olvet et al 2014[169]	MDD	13 SA	39 DC, 46 HC	52 (53)	18-65	ROI FA and ADC maps (FSL), ROIs: mOFC, DMPFC, rACC, dACC	SA vs DC: ↓ FA in DMPFC. No difference in AD
Jia et al 2010[165]	MDD	16 SA	36 DC, 52 HC	55 (53)	SA: 34.2 (13.7), DC: 34.7 (12.5), HC: 37.1 (16.0)	WB and ROI analysis of FA, MD and RD maps (DTIstudio), ROIs: bilateral lentiform nucleus, bilateral hippocampus, and bilateral thalamus	SA vs DC: ↓ FA and AD in the left anterior limb of internal capsule and ↓ FA and ↑ RD in right lentiform nucleus
Jia et al 2014[166]	MDD	23 SA	40 DC, 46 HC	59 (54)	SA: 36.3 (14.5, DC: 34.0 (14.5), HC: 33.3 (11.4)	Tractography based FA with seed in left anterior limb of the internal capsule	SA vs DC: ↓ percentage of projecting fibers connecting the anterior limb of the internal capsule to the left OFC and left thalamus
Lopez-Larson et al 2013[134]	TBI	19 SA	40 DC, 15 HC	0 (0)	18-55	ROI FA maps (FSL), ROI: anterior thalamic radiation	SA vs DC: ↑ FA in bilateral anterior thalamic radiation. Positive correlation impulsivity and FA in right anterior thalamic radiation
Cyprien et al 2016[157]	BD, MDD	45 SA	46 DC, 30 HC	121 (100)	18-50	ROI FA, MD, RD, AD maps (FSL), ROIs: genu, body and splenium of corpus callosum	SA vs HC: no differences that survived multiple comparison correction. Number of attempts associated with ↓ FA in genu, body and splenium of corpus callosum. FA in splenium negatively correlated with suicidal intent.
Bijttebier et al 2015[164]	past MDD	13 SA	15 DC, 17 HC	32 (72)	18-65	Tractography combined with network-based statistics	SA vs DC: ↓ structural connectivity in network including medial VPFC, temporal gyrus, precuneus, cuneus, parietal cortex, amygdala, hippocampus, occipital regions. Decreased connectivity between left olfactory cortex and left ACC
Suicidal ideation studies							
Myung et al 2016[163]	MDD	24 SI	25 DC, 31 HC	52 (65)	18-62	Tractography combined with network-based statistics and graph analysis	SA vs DC: ↓ structural connectivity in left hemisphere network including striatal regions, frontal regions (DLPFC, IFG, lateral OFC and RMPFC), lateral occipital and superior parietal regions. Betweenness centrality of left rostral middle frontal gyrus (DLPFC) positively correlated with suicidal ideation. Participation coefficient of left rostral middle frontal gyrus (DLPFC) positively correlated with impulsivity
Taylor et al 2015[38]	MDD	21 SI, including 10 with past SA	53 DC, 91 HC	108 (65)	20-50	ROI FA and MD maps (FSL), ROIs: internal capsule, thalamic radiation, cingulum bundle, corpus callosum, uncinate fasciculus	SA vs DC: ↑ RD and ↓ FA in the corona radiata, the hippocampal region of the cingulum and the anterior thalamic radiation

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**

Symbols & Abbreviations: *Percentages are rounded to the nearest whole number; **Results are reported for SA or SI in comparison with diagnostic controls. If no diagnostic controls were included in the study, results based on SA or SI compared to healthy controls are reported; AA: alcohol abuse; ACC: anterior cingulate cortex; AD: adjustment disorder; ADHD: attention deficit hyperactivity disorder; ANX: anxiety disorder; BA: Broadman's Area; BD: bipolar disorder; BD-P: bipolar disorder with psychotic symptoms; BPD: borderline personality disorder; DC: diagnostic controls; DD: depressive disorder; DLPFC: dorsolateral prefrontal cortex; DMPFC: dorsomedial prefrontal cortex; DWMH: deep white matter hyperintensities; FA: fractional anisotropy; GM: grey matter; GMV: grey matter volume; HC: healthy controls; HL: high lethality; IFG: inferior frontal gyrus; LL: low lethality; MD: mood disorder; MDD: major depressive disorder; MDD-P: major depressive disorder with psychotic features; ND: not detailed; OFC: orbitofrontal cortex; PCC: posterior cingulate cortex; PD: personality disorder; PFC: prefrontal cortex; PsD: psychosis; PVH: periventricular hyperintensities; RLPFC: rostrolateral prefrontal cortex; RMPFC: rostromedial prefrontal cortex; ROI: region of interest; SA: suicide attempt; SBM: surface based morphometry; SCZ: schizophrenia; SI: suicidal ideation; SUD: substance use disorder; SZA: schizoaffective disorder; SPM: Statistical Parametric Mapping toolbox; TBI: traumatic brain injury; VBM: voxel based morphometry; VLPFC: ventrolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex; WB: whole brain; WM: white matter; WMH: white matter hyperintensities; WMV: white matter volume; 5-HTTLPR l/l: serotonin transporter long/long genotype; 5-HTTLPR*s: serotonin transporter s allele carriers genotype.

Table 2. Findings from Molecular Imaging Studies of Suicidal Thoughts and Behaviors

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
SINGLE PHOTON EMISSION TOMOGRAPHY STUDIES							
Suicide attempt studies							
Audenaert et al 2001[236]	MDD, AD, PsD	9 SA	12 HC	8 (38)	19-48	123I-5-I-R91150 for 5-HT2a receptors in PFC	SA vs HC: ↓ binding potential of 5-HT2a receptors in PFC
Audenaert et al 2002[143]	MDD	20 SA	20 HC	24 (60)	19-50	99mTc-Ethyl Cystine Dimer rCBF SPECT during letter and category fluency	SA vs HC: ↓ perfusion in IFG, ACC, temporal gyrus, hypothalamus during verbal fluency task
van Heeringen et al 2003[237]	MDD, AD, PsD	9 SA	13 HC	ND	19-47	123I-5-I-R91150 for 5-HT2a receptors in PFC	SA vs HC: ↓ binding potential of 5-HT2a receptors in PFC
Amen et al 2009[102]	MDD	12 SA	12 DC, 12 HC	3 (8)	19-64	99mTc HMPAO SPECT to assess rCBF	SA vs DC: ↓ rCBF in subgenual ACC, ↑ rCBF in right insula, dorsal ACC
Willeumier et al 2011[82]	MD	21 SA	36 DC, 27 HC	5 (24)	15-66	99mTc HMPAO SPECT to assess rCBF	SA vs DC: ↓ rCBF in frontal, temporal and parietal regions
Fountoulakis et al 2004[238]	MDD	13 SA, 10 SI	33 DC	ND	21-60	99mTc HMPAO SPECT to assess rCBF	SA vs DC: no differences. SI vs no-SI: no differences
Henningsson et al 2009[239]	MDD, PD	9 SA	9 HC	ND	23-67	123I-β-CIT for 5-HTT binding potential, assessment of Val66Met polymorphisms	Within SA: carriers of the Val/Val genotype of Val66Met had ↑ 5HTT binding potential in the parietal cortex and in the occipital lobes
Bah et al 2008[240]	MDD, AD, PD	9 SA	9 HC	0 (0)	23-67	123I-β-CIT for 5-HTT binding potential, assessment of SLC6A4 polymorphisms	SA vs HC: no differences. In SA: presence of S-allele of 5-HTTLPR genotype associated with lower 5-HTT binding potential in frontal, parietal and occipital cortex
Lindström et al 2004[241]	MDD, AD, PD	12 SA	12 HC	4 (17)	23-67	123I-β-CIT methods to separate 5-HTT and DAT uptake	SA vs HC: no differences in 5-HTT or DAT binding. In SA: impulsivity associated with ↓ whole brain 5-HTT binding
Ryding et al 2006[132]	MDD, AD, ANX, PD	12 SA	12 HC	4 (17)	23-67	123I-β-CIT methods to separate 5-HTT and DAT uptake	SA vs HC: no differences in 5-HTT or DAT binding. In SA: impulsivity associated with ↓ 5-HTT binding potential in inferior/orbital frontal cortex, temporal regions, midbrain, thalamus, basal ganglia
Vang et al. 2010[130]	MDD, AD	7 SA	6 HC	3 (23)	SA: 40 (11.83), matched HC, no details	123I-β-CIT methods to separate 5-HTT and DAT uptake	SA vs HC: not reported. In SA: significant negative correlation between 5HTT binding and globus pallidus volume
Suicidal ideation studies							
Fountoulakis et al 2004[238]	MDD	13 SA, 10 SI	33 DC	ND	21-60	99mTc HMPAO SPECT to assess rCBF	SI vs DC: no differences. SI vs no-SI: no differences

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
POSITRON EMISSION TOMOGRAPHY STUDIES							
Suicide attempt studies							
Soloff et al 2003[196]	BPD	13 SA	9 HC	22 (100)	18-49	[18F]FDG PET during rest	SA vs HC: ↓ rCMRglu in bilateral medial OFC
Yeh et al 2015[133]	MDD	5 SA	5 DC, 10 HC	0 (0)	20-25	4-[18F]-ADAM for SERT availability	SA vs DC: ↑ SERT binding potential in the midbrain, thalamus, striatum and PFC. Suicidal ideation associated with ↑ SERT binding potential in the same 4 regions
Soloff et al 2014[197]	BPD	21 SA	12 DC, 27 HC	32 (53)	BPD: 27.5 (7.2), HC: 28.8 (8.2)	[18F]altanserin for 5-HT2a receptor binding potential	SA vs DC: ↑ binding potential of 5-HT2a receptors in the occipital cortex in females only
Soloff et al 2007[116]	BPD	12 SA	2 DC, 11 HC	25 (100)	19-46	[18F]altanserin for 5-HT2a receptor binding potential	SA vs HC: ↑ binding potential of 5-HT2a receptors in the hippocampus, medial temporal cortex and occipital cortex. No associations with number of attempts
Cannon et al 2006[46]	BD	8 SA	10 DC, 37 HC	36 (65)	BD: 30 (9), HC: 32 (9)	[11C]DASB for 5-HTT binding potential	SA vs DC: ↓ 5-HTT binding in the midbrain and ↑ in the rostral ACC
Oquendo et al 2003[84]	MDD	25 SA (9 LL, 16 HL)		15 (60)	LL: 30.4 (8.7), HL: 42.9 (10.4)	[18F]FDG PET, fenfluramine vs. placebo challenge	HL vs LL SA: ↓ rCMRglu in ACC (BA24/32), IFG (BA44) and DPFC (BA6/8/9), more pronounced after fenfluramine challenge. Lower VMPFC rCMRglu associated with lower impulsivity, higher suicidal intent and higher lethality
Sullivan et al 2015[41]	MDD	29 SA	62 DC	59 (65)	18-65	[11C]WAY-100635 for 5-HT1a receptor binding potential	SA vs DC: no differences in 5-HT1a receptor binding. High vs Low lethality SA: ↑ 5-HT1a receptor binding potential in the raphe nuclei. Positive association 5-HT1a receptor binding potential in the raphe nuclei and suicidal intent. Positive association 5-HT1a receptor binding potential in the raphe nuclei and PFC and suicidal ideation
Miller et al 2016[44]	BD, MDD	11 SA	6 DC, 31 HC	29 (60)	21 - 61	[11C]DASB for 5-HTT binding potential	SA vs DC: no differences in 5-HTT binding
Yeh et al 2015[242]	MDD	8 SA	9 DC, 17 HC	18 (53)	20-65	4-[18F]-ADAM for SERT availability	SA vs DC: no differences in SERT binding in individual regions, but ↑ PFC/midbrain SERT binding ratio. Suicide intent positively associated with PFC/midbrain SERT binding ratio
Leyton et al 2006[40]	MD, PD, SUD (all HL)	10 SA	16 HC	7 (28)	SA: 37.7 (6.4), HC: 35.5 (12.0)	Alpha-11C-methyl-L-tryptophan trapping as index of 5-HT synthesis	SA vs HC: ↓ 5-HT synthesis in lateral and medial OFC extending into VMPFC, ↑ 5-HT synthesis in thalamus, paracentral lobule, occipital cortex and hippocampus. Negative correlation suicide intent and serotonin synthesis in lateral OFC and VMPFC
Parsey et al 2006[43]	MDD	9 SA	16 DC, 43 HC	49 (69)	MDD: 38.0 (13.4), HC: 38.8 (15.9)	[11C]McN 5652 for 5-HTT binding potential	SA vs DC: no differences in SERT binding

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Miller et al 2013[243]	MDD	15 SA	36 DC, 32 HC	41 (49)	SA: 38.5 (11.5), DC: 41.0 (10.5), HC: 32.6 (11.3)	[11C]DASB for 5-HTT binding potential	SA vs DC: ↓ 5-HTT binding potential in midbrain
Nye et al 2013[131]	MDD	11 SA	10 HC	8 (38)	SA: 38.5 (13.6), HC: 21.3 (2.4)	[11C]ZIENT for SERT binding potential	SA vs HC: ↓ 5-HTT in the midbrain/pons and putamen
Mann et al 2018[45]	MDD	8 SA	8 DC, 8 HC	ND	21-53	[11C]WAY-100635 for 5-HT1a receptor binding potential, [18F]altanserin for 5-HT2a receptor binding potential	SA vs DC: no difference in 5-HT1a and 5-HT2a receptor binding
Oquendo et al 2016[42]	MDD	51 past SA, 15 future SA	49 DC	61 (61)	18-65	[11C]WAY-100635 for 5-HT1a receptor binding potential, [11C]DASB for 5-HTT binding potential	Future attempt versus no future attempt: no differences in 5-HTT binding. Higher lethality of future attempts associated with ↑ 5-HT1a receptor binding potential in insula, DPFC, ACC and raphe nuclei. SI at follow up associated with ↑ 5-HT1a receptor binding in raphe nuclei, amygdala, hippocampus, parahippocampul gyrus, temporal lobe, ACC, DPFC, medial PFC, OFC, insula, occipital lobe, parietal lobe
Sublette et al 2013[83]	MDD, BD	13 SA	16 DC	19 (66)	SA: 36.0 (11.5), DC: 42.2 (13.0)	[18F]FDG PET, fenfluramine vs. placebo challenge	SA vs DC: ↓ rCMRglu in right DLPFC, more pronounced after fenfluramine challenge, and ↑ rCMRglu in VMPFC, not more pronounced after fenfluramine. SI negatively correlated with rCMRglu in DLPFC
Suicidal ideation studies							
Holmes et al 2018[90]	MDD	9 SI	5 DC, 13 HC	13 (48)	MDD: 31 (12), HC: 33 (11)	[11C](R)-PK11195 for TSPO availability index of neuroinflammation)	SI vs no-SI: ↑ TSPO availability in ACC and insula
Kolla et al 2016[89]	BPD		28 DC, 14 HC	56 (100)	18-51	[11C]Harmine for MAO-A VT (index of MAO-A density)	Positive association MAO-A VT in PFC and ACC with SI, but also with depressive symptom scores
Van Heeringen et al 2017[85]	MDD	17 SI + plan, 11 SI	12 DC, 20 HC	38 (63)	SI+plans: 46.1 (10.9), SI: 42.6 (11.6), DC: 51.2 (6.5), HC: 43.8 (13.1)	[18F]FDG PET during rest	SI+plans vs SI: ↓ rCMRglu in RLPFC and inferior parietal lobe
Ballard et al 2015[151]	MDD	12 SI	8 DC	6 (30)	MDD: 48 (12)	[18F]FDG PET during rest, ketamine challenge	Baseline SI associated with ↑ rCMRglu in infralimbic cortex. Ketamine induced reductions in SI associated with reductions in rCMRglu in infralimbic cortex and increases in rCMRglu in cluster including lingual gyrus, occipital cortex and cerebellum

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
MAGNETIC RESONANCE SPECTROSCOPY STUDIES							
Suicide attempt studies							
Jollant et al 2017[244]	past MDD	15 SA	10 DC, 33 HC	35 (60)	15 -55	Proton MRS;. Metabolites: glutamate, glutamine, N-acetylaspartate, myo-inositol, aspartate, glutathione, GABA, N-acetylaspartylglutamate, total choline. ROI: right dorsal PFC	SA vs DC: no significant differences. Choline levels positively correlated with current suicidal ideation
Prescot et al 2018[91]	history or current MDD, PTSD and/or SUD	57 with SA or SI	24 DC	16 (20)	SA+SI: 37.2 (9.1), DC: 36.2 (9.7)	Proton Magnetic Resonance Spectroscopy. Metabolites: GABA, N-acetylaspartylglutamate, glutamine, glutamate, creatine. ROI: dorsal ACC	SA vs DC: no significant differences. In females only, ↓ GABA in SA+SI compared to DC but no longer significant after correcting for age differences
Rocha et al 2015[245]	past BD	19 SA	21 DC, 22 HC	41 (66)	SA: 39.8 (11.4), DC: 42.0 (8.6), HCL 37.7 (13.5)	Proton MRS; Metabolites: N-acetylaspartate, choline, creatine, myo-inositol. ROI: medial OFC	SA vs DC: no significant differences
Suicidal ideation studies							
Gabbay et al 2017[195]	MDD		44 DC, 36 HC	46 (50)	12-21	Proton MRS; Metabolites: GABA and GLX. ROI: rostral ACC	No correlation between GABA and GLX levels in rostral ACC and SI

Symbols & Abbreviations: *Percentages are rounded to the nearest whole number; **Results are reported for SA or SI in comparison with diagnostic controls. If no diagnostic controls were included in the study, results based on SA or SI compared to healthy controls are reported; ACC: anterior cingulate cortex; AD: adjustment disorder; ANX: anxiety disorder; BD: bipolar disorder; BPD: borderline personality disorder; DAT: dopamine transporter; DC: diagnostic controls; DLPFC: dorsolateral prefrontal cortex; DPFC: dorsolateral prefrontal cortex; FDG: fludeoxyglucose; GABA: gamma-aminobutyric acid; GLX: glutamate + glutamine; HC: healthy controls; HL: high lethality; IFG: inferior frontal gyrus; LL: low lethality; MAO-A: monoamine oxidase A; MDD: major depressive disorder; MRS: magnetic resonance spectroscopy; ND: not detailed; OFC: orbitofrontal cortex; PET: positron emission tomography; PD: panic disorder; PFC: prefrontal cortex; PsD: psychotic disorder; rCBF: regional cerebral blood flow; rCMRglu: regional cerebral metabolic rate for glucose; RLPFC: rostrolateral prefrontal cortex; SA: suicide attempt; SERT: serotonin transporter; SI: suicidal ideation; SP: social phobia; SPECT: single photon emission computed tomography; SUD: substance use disorder; TSPO: translocator protein, VMPFC: ventromedial prefrontal cortex; 5-HT: serotonin, 5-HTT: serotonin transporter

Table 3. Findings from Functional Imaging Studies of Suicidal Thoughts and Behaviors

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES							
Suicide attempt studies							
Resting State fMRI							
Cao et al 2016[168]	DD	35 SA	18 DC, 47 HC	66 (66)	SA: 20.63 (3.65), DC: 21.39 (3.05), HC: 20.53 (1.84)	WB fractional zALFF	SA vs DC: ↑ zALFF in right superior temporal gyrus, left middle temporal gyrus, left middle occipital gyrus, left angular gyrus, ↓ zALFF in left RLPFC. In SA: negative correlation impulsivity and zALFF in left RLPFC
Cao et al 2015[246]	No DX	19 SA	20 HC	22 (56)	SA: 19.8 (1.6), HC: 20.3 (1.7)	WB ReHo	SA vs HC: ↓ ReHo in left fusiform gyrus, lateral OFC (BA47), hippocampus, right angular gyrus, bilateral parahippocampal gyrus, DLPFC (BA46) and cerebellum, ↑ ReHo in right inferior parietal lobe, left precuneus, right medial OFC (BA11)
Zhang et al 2016[154]	DD	35 SA	18 DC, 47 HC	66 (66)	SA: 20.63 (3.65), DC: 21.26 (3.02), HC: 20.48 (1.86)	ICA of DMN	SA vs DC: ↓ FC in the right precuneus, ↑ FC in the left lingual gyrus and left cerebellum
Kang et al 2017[160]	MDD	19 SA	19 DC	20 (53)	SA: 42.0 (10.8), DC: 41.1 (15.2)	Amygdala seed-based FC	SA vs DC: ↑ FC left amygdala with right insula and left OFC (BA11), ↑ FC right amygdala with left middle temporal gyrus. In SA: positive correlation between SI and right amygdala FC with right parahippocampal gyrus
Cognitive control							
Pan et al 2011[247]	MDD	15 SA	15 DC, 14 HC	25 (57)	12-17	Go-no-go response inhibition, WB	SA vs DC: ↓ dorsal ACC and insula activation during response inhibition, driven by greater activity in DC compared to both SA and HC (i.e., no evidence for abnormal response inhibition circuitry in SA)
Richard-Devantoy et al 2016[137]	MDD	25 SA	22 DC, 27 HC	47 (61)	18-55	Go-no-go response inhibition, WB	SA vs DC: no significant differences. Suicidal intent was positively associated with thalamus activity during response inhibition
Minzenberg et al 2014[54]	SCZ	8 SA+SI, 10 SI only	17 DC	10 (26)	18-50	Continuous performance, ROI frontal cortex	SA+SI vs SI: ↓ goal-related left dorsal premotor cortex (BA6) activity. SI vs no-SI: ↓ goal-related ventral ACC, VMPFC, VLPFC, DLPFC (BA9), RMPFC (BA10), RLPFC (BA10) extending to DMPFC (BA8), dorsal ACC (BA24/32). Intensity of ideation negatively correlated with goal-related activity in DMPFC (BA6/8), dorsal ACC (BA32), DLPFC (BA9), RMPFC (BA10), RLPFC (BA10), IFG (BA44/45)

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Minzenberg et al 2015[52]	MD-P	8 SA+SI, 8 SI only	14 DC	13 (43)	18-50	Continuous performance, WB	SA+SI vs SI: ↓ activity in PCC, cuneus and precuneus and ↑ activity right OFC (BA47), right RLPFC (BA10), premotor cortex (BA6), DLPFC (BA9/46), insula during goal-representation. Positive correlation between intensity of SI and goal-related IFG (BA45), lateral and medial OFC (BA11/47), insula and dorsal striatum activity
Minzenberg et al 2015[170]	SCZ	8 SA+SI, 7 SI only	17 DC	6 (19)	18-50	Continuous performance, dorsal ACC seed-based FC	SA+SI vs SI: ↓ dorsal ACC FC with RMPFC and RLPFC (BA10), DMPFC (BA8), DLPFC (BA9), dorsal ACC (BA32), IFG (BA45), superior temporal gyrus, middle temporal gyrus, precuneus, and PCC during conflict monitoring. SI vs no-SI: ↑ dorsal ACC-precuneus FC during conflict monitoring. Intensity of ideation was positively correlated with dorsal ACC FC with paracentral lobe, precuneus, left caudate, right putamen, right lateral globus pallidus and left thalamus.
Minzenberg et al 2016[171]	MD-P	8 SA+SI, 8 SI only	14 DC	13 (43)	18-50	Continuous performance, dorsal ACC seed-based FC	SA+SI vs SI: ↑ dorsal ACC FC with left DLPFC (BA9), frontal motor areas (BA4/6), inferior temporal gyrus, middle temporal gyrus, dorsal ACC (BA24/32) during conflict monitoring. SI vs no-SI: ↑ dorsal ACC FC with left DLPFC (BA9), DMPFC (BA8), premotor cortex (BA6), superior parietal cortex, inferior parietal cortex, superior temporal gyrus, middle temporal gyrus. Intensity of ideation positively correlated with dorsal ACC FC with bilateral premotor cortex (BA6), inferior and superior parietal cortex, middle and inferior temporal gyri, middle occipital gyrus and occipital regions, negatively correlated with IFG OFC (BA11/47), insula, putamen, globus pallidum, premotor area (BA6), somatosensory cortex (BA5/7) during conflict monitoring.
Minzenberg et al 2015[80]	SCZ	8 SA (all past SI)	9 DC (all past SI)	—	18-50	Stroop, ROI frontal cortex	SA vs DC: ↑ left DPFC (BA6/8) during cognitive control.
Vanyukov et al 2016[78]	MDD	13 SA	13 DC, 22 HC	30 (63)	46-90	Delay discounting, WB	SA vs DC: ↓ left DLPFC (BA9) activation with increasing value of smaller immediate reward, with a larger decrease in people with better planned SA. Longer versus shorter delay of delayed reward associated with ↓ left parahippocampal gyrus and middle occipital gyrus activation during trials
Decision making and reward processing							
Pan et al 2013[248]	MDD	15 SA	14 DC, 13 HC	23 (55)	12-17	Iowa gambling, WB	SA vs DC: ↓ right thalamus activation during risky choices. No association between activity in thalamus and lethality of attempt and severity of SI

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Olié et al 2015[47]	MDD	15 SA	23 DC, 35 HC	0 (0)	18-60	Iowa gambling, ROI OFC, VLPFC, MPFC, ACC, DPFC	SA vs DC: ↓ activation in left DPFC (BA8/9/46) during risky choices, ↑ activation in bilateral DPFC, right OFC (BA11/47), right dorsal and ventral ACC (BA24/32) during winning
Baek et al 2017[92]	past MDD	10 SA	12 DC, 22 HC	24 (55)	18-44	Risk and loss aversion, ROI striatum, OFC, VMPFC, ventral ACC, midbrain	SA vs DC: ↓ subgenual ACC (BA25) activity in response to potential gain. In SA: insula activity correlated negatively with the subjective value of probabilistic gain and loss
Jollant et al 2010[249]	MDD	13 SA	12 DC, 15 HC	0 (0)	22-59	Iowa gambling, ROI OFC, ACC, occipital cortex, precuneus/angular gyrus, thalamus, cerebellum, caudate, cuneus, superior frontal gyrus, parietal cortex	SA vs DC: ↓ lateral OFC (BA47) and occipital cortex activation during risky choices. No differences in activation during gain vs loss trials. No associations with SI
Dombrovski et al 2013[93]	MDD	15 SA	18 DC, 20 HC	31 (59)	60+	Probabilistic reversal learning, WB	SA vs DC: ↓ activity in ventral ACC (BA24/25/32) during expected reward. Poor planning of attempt associated with ↓ activity of paralimbic network (ventral ACC/VMPFC, PCC, precuneus) during expected reward
Memory							
Reisch et al 2010[72]	SR-depression	8 SA		8 (100)	SA: 38.5 (13.1)	Recall of a mental pain, suicide action and neutral conditions using autobiographical scripts of a recent episode of SA, WB	Recall of own suicidal episodes (mental pain and suicide action) vs neutral condition: ↓ activation in left DLPFC (BA46), right RLPFC (BA10), left DMPFC (BA6), ↑ right parahippocampal gyrus, right cuneus, left middle temporal gyrus and cerebellum. Recall of suicide action vs mental pain: ↑ activation in the left DMPFC (BA6), right dorsal ACC (BA32) and left hippocampus
Silvers et al 2016[50]	BPD	46 SA	14 DC	60 (100)	SA: 30.0 (9.8), DC: 26.7 (5.0)	Reappraisal of negative autobiographical memories, ROI lateral OFC	SA vs DC: ↑ lateral OFC activation during both reappraisal and immersion, and ↓ precuneus and cuneus activation during reappraisal of memories. In SA: regulation success associated with greater cuneus and precuneus activity
Emotion processing							
Pan et al 2013[74]	MDD	14 SA	15 DC, 15 HC	25 (57)	12-17	Viewing of angry, happy and neutral faces, WB activity and right dorsal ACC seed-based FC	SA vs DC: ↑ activity in right dorsal ACC, bilateral primary sensory cortex, left DLPFC (BA9), right middle temporal gyrus, ↓ activity in insula and ↓ FC between dorsal ACC and bilateral insula in response to angry faces. In DC: suicidal ideation was negatively correlated with left DLPFC activation during angry faces
Johnston et al 2017[36]	BD	26 SA	42 DC, 45 HC	43 (63)	14-25	Viewing of happy, neutral and fearful faces, amygdala seed-based FC	SA vs DC: ↓ FC amygdala with left OFC (BA11/47), RPFC (BA10), ventral ACC (BA32) in response to happy and neutral faces. SA lethality associated with ↓ FC amygdala with left ventral PFC in response to happy, neutral and fearful faces. In SA: SI was negatively correlated with FC between amygdala and RPFC (BA10)

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Olié et al 2015[47]	MDD	15 SA	23 DC, 35 HC	0 (0)	18-60	Viewing of angry, happy, sad and neutral faces, ROI OFC, VLPFC, MPFC, ACC, DPFC	SA vs DC: ↑ activation in left OFC and VLPFC in response to angry faces, and ↓ activation in right ACC in response to sad faces
Kim et al 2017[136]	DD	14 SA	22 HC	26 (72)	20-47	Viewing of angry, happy, sad and neutral faces, and pictures of suicidal means, WB	SA vs HC: ↑ activation in the left DLPFC, IFG, thalamus and PCC when viewing knives versus natural landscapes. No differences in activity while viewing emotional faces
Jollant et al 2008[48]	MDD	13 SA	14 DC, 16 HC	0 (0)	SA: 40.3 (11.3), DC: 43.9 (10.6), HC: 32.4 (9.8)	Viewing of angry, happy and neutral faces, WB	SA vs DC: ↑ activation in in right lateral OFC (BA47) and ↓ activation in right DMPFC (BA6) in response to intense angry faces, ↑ activation in right rostral ACC (BA32) and ↓ activation in right cerebellum to mild happy faces, ↑ activation in right cerebellum in response to mild angry faces
Vanyukov et al 2015[49]	MDD	18 SA	13 DC, 18 HC	26 (53)	60+	Angry and fearful faces versus shape matching, WB	SA vs DC: no differences. In SA, higher activation of IFG (BA44/45) while matching angry faces was associated with poorer planning of attempt
Self-referential processing							
Quevedo et al 2016[147]	DD	43 HS	39 LS, 37 HC	72 (61)	HS: 14.9 (1.6), LS: 14.9 (1.8), HC: 14.5 (1.5)	Emotional Self-Other Morph-Query (ESOM-Q), WB	HS vs LS: ↓ activity in RMPFC (BA10) and in a cluster including parahippocampus, hippocampus, and amygdala during happy self faces versus happy other faces. When controling for depression severity: HS vs LS: ↓ PCC/precuneus and rostral ACC/BA10 during self faces.
Social exclusion							
Olié et al 2017[103]	past MD	36 SA	41 DC, 28 HC	105 (100)	19-54	Social exclusion (Cyberball), WB	SA vs DC: ↓ activation in left supramarginal gyrus and posterior insula during social exclusion
Suicidal ideation studies							
Resting State fMRI							
Cullen et al 2014[250]	MDD		41 DC, 29 HC	54 (77)	MDD: 15.7 (2), HC: 16.0 (2)	Amygdala seed-based FC	No significant correlation between amygdala FC and suicidal ideation
Ordaz et al 2018[152]	MDD	40 SI (33% past SA)		30 (75)	14-17	ICA of DMN, ECN, and SN	↓ Network coherence of left ECN, anterior DMN and SN associated with ↑ lifetime SI, only association with left ECN remained after controlling for depressive and anxiety symptom severity. Left ECN also associated with past SA at a trend-level
Chase et al 2017[199]	MDD	34 SI (18 past SA)	40 HC	50 (68)	18-35	PCC seed-based FC	SI vs HC: ↑ dorsal PCC FC with left middle temporal gyrus. SA vs no-SA: ↑ dorsal PCC FC with left IFG
Du et al 2017[153]	MDD	28 SI	20 DC, 30 HC	55 (71)	SI: 32.5 (9.9), DC: 37.1 (10.6), 35.7 (10.2)	Rostral ACC seed-based FC	SI vs DC: ↓ FC right rostral ACC to medial OFC and right middle temporal gyrus, finding for right middle temporal gyrus remained when corrected for depressive symptom severity

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Kim et al 2017[162]	MDD	23 SI (7 past SA)	23 DC, 36 HC	68 (83)	SA: 47, SI: 57, DC: 52.7, HC: 56.5	Graph theory and network-based analysis	SI vs DC: ↓ FC in a network including left lateral OFC, left and right caudate, right putamen, left middle temporal gyrus, left and right thalamus and left postcentral gyrus. Node strength, clustering coefficient, regional efficiency of lateral OFC, left and right thalamus negatively correlated with SI
Cognitive control							
Matthews et al 2012[53]	MDD, PTSD, TBI	13 SI	13 DC	0 (0)	SI: 29.5 (4.7), DC: 27.1 (3.6)	Stop signal response inhibition, WB	SI vs DC: ↑ left dorsal ACC (BA24), RLPFC (BA10), DLPFC (BA9/46), supramarginal gyrus, OFC (BA11), DMPFC (BA6) and superior temporal gyrus during error processing
Lee et al 2015[81]	SCZ		28 DC, 17 HC	8 (18)	SH: 43.6 (11.3), DC: 38.9 (7.3), HC: 37.9 (12.9)	Go-no-go response inhibition, WB	Positive correlation right DLPFC (BA9) activity during response inhibition and current SI in self-harm but no association in no-self-harm group
Zhang et al 2013[251]	SCZ	14 SI	19 DC, 15 HC	24 (50)	18-45	N-back, dynamic causal modelling with PCC and MPFC seeds	High vs Low risk: ↓ no difference in activation of and connectivity between VMPFC and PCC. VMPFC activity was positively related with suicide risk
Decision making and reward processing							
Quevedo et al 2017[161]	MDD		38 DC, 30 HC	44 (65)	DC: 30.7 (7.7), HC: 32.0 (6.1)	Card guessing, ventral striatum seed-based FC	Positive correlation between SI and left ventral striatum FC with DMPFC, DLPFC and dorsal ACC during loss trials.
Motor control							
Marchand et al 2012[138]	MDD	5 SA	17 DC	0 (0)	22-45	Motor activation, putamen seed-based FC	Positive correlation between SI and left putamen FC with left DMPFC and right putamen, and right putamen FC with left putamen. Left putamen FC with DMPFC also associated with depressive symptom severity
Marchand et al 2013[252]	MDD, BD	22 SI	18 DC	ND	21-45	Motor activation, PCC seed-based FC	Positive correlation between SI and PCC FC with left DLPFC, DMPFC and IFGs in MDD but not BD. PCC FC with IFG and DLPFC also associated with depressive symptom severity
Marchand et al 2011[135]	BD-II	10 SI	6 DC, 19 HC	0 (0)	BD-II: 32.9 (7.5), HC: 33.7 (12.5)	Motor activation, ROI putamen	Negative correlations between a history of SI and activation in left putamen
Emotion processing							
Marchand et al 2011[117]	BD	10 past SI (3 past SA)	6 DC, 19 HC	0 (0)	21-60	Viewing of happy, fearful and neutral faces, ROI amygdala and subgenual ACC	No correlation between brain activity during the task and history of SI

Authors, year	Mental disorder	SA group/ SI group	Groups w/o SA and/or SI	Female n (%)*	Age	Methods	Findings**
Just et al 2018[60]	No DX	17 SI (9 past SA)	17 HC	26 (77)	SI: 22.9 (3.6), HC: 22.1 (2.8)	Neurosemantic analyses of concepts related to suicide, positive and negative affect, machine learning on voxels with stable semantic tuning curves	SI could be discriminated from HC with 91% accuracy. Most discriminating regions were the left VMPFC, left DMPFC extending to dorsal ACC, right middle temporal gyrus, left inferior parietal cortex, and left IFG. SI+SA group could be discriminated from SI without SA with 94% accuracy, with most discriminating regions including the left VMPFC, left DMPFC extending to dorsal ACC, right middle temporal gyrus.
Emotion regulation							
Miller et al 2018[73]	No DX	14 SI (4 past SA)	32 without SI	29 (63)	13-20	Emotion regulation, WB	SI vs no-SI: ↓ activity in thalamus, IFG/DLPFC (BA44/9), temporoparietal junction and cerebellum and ↑ activity in temporal pole during passive viewing of negative pictures, ↑ activity in DLPFC (BA9) during regulation of negative emotional pictures
NEAR-INFRARED SPECTROSCOPY STUDIES							
Suicide attempt studies							
Tsujii et al 2017[253]	MDD	30 SA	38 DC, 40 HC	69 (64)	SA: 37.6 (10.0), DC: 38.8 (9.7), HC: 38.2 (10.2)	Verbal fluency	SA vs DC: ↓ verbal fluency task induced changes in mean oxy-HB in left precentral gyrus
Suicidal ideation studies							
Pu et al 2015[254]	MDD	31 SI	36 DC, 67 HC	76 (57)	SI: 57.3 (15.7), DC: 58.7 (16.5), HC: 58.1 (17.8)	Verbal fluency	SI vs DC: ↓ verbal Fluency task induced changes in oxy-Hb in right DLPFC, lateral OFC and right RLPFC

Symbols & Abbreviations: *Percentages are rounded to the nearest whole number; **Results are reported for SA or SI in comparison with diagnostic controls. If no diagnostic controls were included in the study, results based on SA or SI compared to healthy controls are reported; ACC: anterior cingulate cortex; BA: Broadman's Area; BD: bipolar disorder; BD-II: bipolar II disorder; BPD: borderline personality disorder; DC: diagnostic controls; DD: depressive disorder; DLPFC: dorsolateral prefrontal cortex; DMN: default mode network; DMPFC: dorsomedial prefrontal cortex; ECN: executive control network; FC: functional connectivity; HC: healthy controls; HS: high suicidality; ICA: independent component analysis; IFG: inferior frontal gyrus; LS: low suicidality; MDD: major depressive disorder, MD-P: psychotic mood disorder, MPFC: medial prefrontal cortex; ND: not detailed; OFC: orbitofrontal cortex; oxy-HB: oxygen-hemoglobin; PCC: posterior cingulate cortex; PFC: prefrontal cortex; PTSD: posttraumatic stress disorder; ReHo: regional homogeneity; RLPFC: rostrolateral prefrontal cortex; RMPFC: rostromedial prefrontal cortex; SA: suicide attempt; SCZ: schizophrenia; SI: suicidal ideation; SN: salience network; SR-depression: self-reported depression; ROI: region of interest; TBI: traumatic brain injury; VLPFC: ventrolateral prefrontal cortex, VMPFC: ventromedial prefrontal cortex; WB: whole brain; zALFF: z score amplitude of low frequency fluctuations