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Neurobiological Risk Factors for Suicide Insights from Brain Imaging

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Abstract

Context—This article reviews neuroimaging studies on neural circuitry associated with suicide-related thoughts and behaviors to identify areas of convergence in findings. Gaps in the literature for which additional research is needed are identified.

Evidence acquisition—A PubMed search was conducted and articles published prior to March 2014 were reviewed that compared individuals who made suicide attempts to those with similar diagnoses who had not made attempts or to healthy comparison subjects. Articles on adults with suicidal ideation and adolescents who had made attempts, or with suicidal ideation, were also included. Reviewed imaging modalities included structural magnetic resonance imaging, diffusion tensor imaging, single photon emission computerized tomography, positron emission tomography, and functional magnetic resonance imaging.

Evidence synthesis—Although many studies include small samples, and subject characteristics and imaging methods vary across studies, there were convergent findings involving the structure and function of frontal neural systems and the serotonergic system.

Conclusions—These initial neuroimaging studies of suicide behavior have provided promising results. Future neuroimaging efforts could be strengthened by more strategic use of common data elements, and a focus on suicide risk trajectories. At-risk subgroups defined by biopsychosocial risk factors and multidimensional assessment of suicidal thoughts and behaviors may provide a clearer picture of the neural circuitry associated with risk status—both current and lifetime. Also needed are studies investigating neural changes associated with interventions that are effective in risk reduction.

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Introduction

This paper reviews neuroimaging studies on neural circuitry associated with suicide-related thoughts and behaviors in an effort to recommend next research steps. Multiple neuroimaging methods have been employed to investigate the neural circuitry of suicide-related thoughts and behaviors. These include techniques to study brain structure, including structural magnetic resonance imaging (sMRI) for gray matter (GM) and white matter (WM) morphology and WM hyperintensities (WMH, bright signals on T2-weighted MRIs), and diffusion tensor imaging (DTI) for structural integrity of WM connections. Several functional neuroimaging methods (single photon emission computerized tomography [SPECT], positron emission tomography [PET], and functional magnetic resonance imaging [fMRI]) have been used to study regional brain activity, functional connectivity, and neurotransmitter function.

Evidence Acquisition

A search was performed in PubMed for original research manuscripts written in English prior to March 2014. Combinations of the term *suicide* with terms structural magnetic resonance imaging, functional magnetic resonance imaging, positron emission tomography, single-photon emission computed tomography, diffusion tensor imaging, gray matter, or white matter, were used. Fifty-seven pertinent articles that directly investigated the relationship between aspects of suicide behavior (i.e., attempt history, lethality, and suicide ideation) and neuroimaging findings were chosen and evaluated in a non-quantitative manner.

Evidence Synthesis

In the majority of studies, attempters and non-attempters with a particular diagnosis were compared to each other, and sometimes to a healthy control (HC) group (summarized in Table 1). The most common studied diagnoses were major depressive disorder (MDD) and bipolar disorder (BD), followed by schizophrenia, borderline personality disorder (BPD), traumatic brain injury (TBI), and epilepsy. Studies of adults with attempts are discussed first, followed by adults with ideation. We then summarize findings in older adults and adolescents.

Structural Magnetic Resonance Imaging

Structural magnetic resonance imaging of gray and white matter morphology —Structural imaging has been the method most used in suicide research. Studies using sMRI converge in showing orbitofrontal cortex (OFC) GM decreases in attempters with MDD,[1] BD,[2] schizophrenia,[3] and BPD,[4] and amygdala GM increases in MDD[1] and schizophrenia.[5] The OFC and amygdala are highly interconnected regions, important in regulating emotions and impulses, suggesting that frontotemporal OFC-amygdala structural abnormalities may contribute to emotion and impulse dysregulation associated with attempts. In BPD, OFC decreases were of larger magnitude in attempters with higher medical lethality.[4]

GM findings have been reported in other frontal system components in attempters with schizophrenia,[3,6] BPD,[4] BD,[2] and MDD.[7-9] These include dorsal frontal regions, insula, thalamus, and basal ganglia, implicating more widely distributed frontotemporal anterior connection sites. A study of the cerebellum yielded negative findings.[10]

Studies using sMRI show abnormal frontotemporal WM connections. A study of schizophrenia showed increased inferior frontal WM volume in attempters with self-directed aggression.[11] The sMRI studies also show altered interhemispheric connections. Smaller genual corpus callosum (CC) volume in BD attempters was associated with increased Barratt Impulsivity Scale scores.[12] These studies suggest that WM abnormalities contribute to self-aggression and impulse dyscontrol of suicidal behavior.

White matter hyperintensities—Increased WMH prevalence has been reported in young/mid-adult MDD and BD attempters,[13-15] and in older adults and children. Etiologies contributing to WMH may include cellular loss, ischemia, perivascular space dilatation, ependymal loss, and vascular-related demyelination.[16-18]

Diffusion tensor imaging—The main reported DTI measure is fractional anisotropy (FA), which reflects the directional coherence of diffusion within WM bundles, their architecture, or structural integrity. Decreased frontal FA in BD and MDD attempters has been found.[19-21] In BD, orbitofrontal FA decreases were associated with impulsivity. In MDD attempters, disruptions were found in frontal cortex–basal ganglia WM connections that are important in behavioral control.[20,22] In veterans with TBI and attempt history, FA increases in frontal WM projections were associated with impulsivity.[23] These DTI data further support the contributions of anterior WM abnormalities to impulsive suicide behavior.

Functional Neuroimaging

Single photon emission computerized tomography and positron emission tomography—A SPECT study showed blunted prefrontal cortex (PFC) regional cerebral blood flow (rCBF) responses during word generation in attempters,[24] consistent with the frontal findings described above. Lower frontal, insular, and caudate rCBF predicted attempts in a study with prospective assessment of suicide decedents.[25]

A regional cerebral metabolic rate of glucose (rCMRglu) PET study reported OFC hypometabolism in BPD attempters.[26] Additionally, in rCMRglu PET studies, fenfluramine challenges have probed the serotonin (5-HT) system. Results indicated hypometabolism in right dorsolateral PFC in attempters and in association with ideation.[27] Ventral PFC hypometabolism differentiated between high-lethality and low-lethality attempters.[28] These studies suggest linkages between PFC response, 5-HT, suicide ideation, and attempt medical lethality, thus extending results of postmortem, cerebrospinal fluid, peripheral, and neuroendocrine challenge studies implicating 5-HT in suicide attempts and their lethality.

SPECT and PET neurotransmitter studies in attempters have focused on 5-HT and frontal systems. Findings include alterations in OFC 5-HT synthesis,[29] 5-HT transporter (5-HTT) binding,[30-32] associations among 5-HTT binding and SLC6A4 genetic variations,[33] and

basal ganglia volume[9] and lower frontal 5HT-2a receptor binding.[34,35] Associations have been reported between impulsivity and 5-HTT binding in whole brain, OFC, and other frontotemporal system components.[36,37] Additionally, an association between lower frontal 5HT-2a receptor binding and hopelessness has been reported.[35] Genetic, postmortem, neuroendocrine, and peripheral studies also implicate noradrenergic and dopaminergic systems, and neurotrophic mechanisms, suggesting the need for their study.

Functional magnetic resonance imaging—The few reported fMRI studies of attempters are in MDD. One study of men showed elevated OFC responses to angry faces, suggesting that male MDD attempters have increased sensitivity to disapproval or threat.[38] Male attempters also showed decreased left OFC activation associated with risky gambling task choices.[39] When fMRI was performed during a motor task by attempters,[40] altered activation and functional connectivity within and between regions in a corticostriatal network were shown. In one of the few studies examining internal states and thoughts of suicide, fMRI showed frontal decreases during autobiographic recall of mental pain associated with previous attempts, and frontotemporal increases during recall of suicide actions.[41]

Suicidal Ideation

Study of suicidal ideation is important for understanding the development of risk for attempts. Of the few structural studies of suicide ideation, non-attempters with ideation did not show the WM abnormalities noted in attempters, although one DTI study of ideation in veterans with TBI did show FA reductions in the cingulum, a structure important in emotional memory.[13,42] The absence of frontal WM findings in non-attempters with ideation suggests that these findings are more closely associated with suicidal acts and possibly the more impulsive aspects of some attempts. It is possible that WM disruptions are a consequence of suicide attempt methods that could affect the brain, for example as a consequence of hypoxia, although some studies have noted similar findings in attempters who did not use such methods.[13]

Brain dysfunction has shown some consistencies among ideators and attempters. Performance of a motor activation task by BDII ideators showed frontostriatal findings similar to those in attempters.[43] In another fMRI study of combat-exposed war veterans performing a stop task,[44] ideation was associated with higher frontal error-related activation.

Older Adult Attempters

Biopsychosocial features of aging may confer neurobiological risk for suicide. WMH and other WM pathology may be more prevalent in older adult attempters.[45,46] Early findings of increased WMH in older adults suggested pathologic processes (e.g., vascular disease) more prevalent in older adults.[16-18] However, recent studies reporting similarly increased WMH in younger adults and adolescents suggest that alternative mechanisms may underlie WMH. Although underlying mechanisms may differ, findings in adults aged over 60 years show consistencies with findings in younger adults. For example, older adult MDD attempters also show decreased basal ganglia GM and relationships to reward processing and behavioral control.[47,48] CC WM decreases have been reported in older adult attempters with

mood and anxiety disorders, although in older attempters these were in the posterior third,[49] implicating more involvement of emotion and memory processes. Older adult attempters also show decreases in ventromedial PFC responses to rewards, associated with impulsivity.[50] In light of few comparison studies of older to younger adults, more research is needed on similarities and distinctions between the pathophysiology and neural circuitry underlying suicide behavior across lifespan stages.

Suicide Attempts and Ideation in Children and Adolescents

Neuroimaging research with adolescents is important, as adolescence is a critical period in suicide behavior development. Structural imaging studies of children and adolescents—with epilepsy,[51] as psychiatric inpatients,[52,53] or outpatients with BPD and MDD[54]—show some consistencies with studies in adults, suggesting these abnormalities may relate to development of suicide-related thoughts and behaviors. Findings include smaller OFC WM in young ideators,[51] more prevalent WMHs in MDD young attempters,[52,53] and smaller anterior cingulate GM and WM volumes in adolescents with more suicide attempts.[54]

An fMRI study in MDD adolescents showed increased responses to angry faces in frontal circuitry,[55] similar to that found in adults.[38] However, MDD adolescent attempters did not show differential neural responses during response inhibition on a go–no-go task or decision making in the context of risk.[56,57] These findings suggest increased sensitivity in frontal systems involved in negative emotion processing may characterize adolescent attempters.

Recommendations for Future Research

Despite highly varied methods and small samples, the structural and functional neuroimaging findings converge in implicating frontal neural systems and serotonergic functioning as central in suicide behavior, consistent with studies using non-imaging approaches. As neuroimaging studies are expensive, scanning time limited, and at-risk patients difficult to retain in studies, future neuroimaging efforts could benefit from more strategic approaches.

Common Data Elements

As illustrated above and in Table 1, there is substantial variation in age, gender, psychopathology, imaging methods and regions studied, activation paradigms and behavioral constructs probed. Studies vary in defining “attempters.” Although neuropsychological constructs related to emotion and impulse regulation have been most studied, definitions of these constructs and methods to assess them have varied. Efforts to use common definitions of suicide behavior and neuropsychological processes, and methods to assess them, could lead to better synthesis across studies. Similarly, calibration of imaging hardware and analytic techniques will be needed. In efforts to link brain imaging to age, gender, genetic, postmortem, neurotransmitter, neurotrophic, hormonal, and environmental findings, and to elucidate commonalities and distinctions between suicide behavior in different psychiatric disorders, the use of common data elements could make cross-study comparisons more likely and of greater value. Future studies may benefit from

including new analytic approaches, such as computer learning algorithms comparing imaging data on cases and controls, in larger samples.

However, this field is in its early stages and there is risk to premature focus. Although initial work has focused on frontal systems and related behavioral constructs such as impulsivity and 5-HT, and these have shown importance in attempters, the field is also in need of novel approaches to study other aspects of suicide. For example, few studies have focused on ideation. There is a critical need for investigators who develop ideation-related constructs and innovative methods to probe them.

Suicide Risk and Trajectories

Two major gaps in the study of individuals at risk for suicide over time were identified. First, longitudinal studies are critically needed of individuals at risk, especially beginning in youth, to study biopsychosocial factors and neural trajectories both associated with and not with future attempts. These could reveal predictors and trajectories associated with future attempts, as well as with resilience in individuals who do not make attempts. Second, neuroimaging studies before and after pharmacologic and behavioral interventions could be instrumental in promoting understanding of therapeutic mechanisms in treatment response.

Conclusions

It is an important time for research in the neural circuitry of suicide-related thoughts and behaviors. Important groundwork has been laid by initial neuroimaging studies. Despite the small size and heterogeneity of these studies, some convergent findings provide a promising start. The identification of associations among genetic and molecular mechanisms, brain circuitry, ideation, and behavior could be instrumental in identifying targets for prevention. Future neuroimaging efforts could be leveraged by more strategic use of common data elements and efforts to fill gaps in understanding of suicide risk trajectories. At-risk subgroups defined by risk experiences and psychopathology subtypes may provide a clearer picture of the neural changes associated with suicide risk status—both current and lifetime. Expanding research efforts that examine structural and functional changes related to intervention responses can inform risk and prevention models.

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Table 1

Neuroimaging studies of groups with suicide attempters

Authors and year	Group with history of suicide attempts	Group(s) without attempts	Methods	Findings
Structural Magnetic Resonance Imaging Studies of Gray Matter and White Matter				
Aguilar et al 2008[3]	13 M with SCZ, MA 37 yrs	24 DCs	VBM of GM density	↓ OFC and superior temporal GM density, relative to DCs
Baldacara et al 2011[10]	20 with BD, MA 40 yrs	20 DCs, 22 HCs	VBM of GM and WM brain volume; ROI volume	No significant differences in total brain volume or cerebellar volume
Benedetti et al 2011[2]	19 with BD, MA 45 yrs	38 DCs	VBM of GM volume	↓ GM volume in DLPFC, OFC, ACC, superior temporal, parietal and occipital cortex and ↑ in bilateral superior termporal gyrus, relative to DCs. With lithium ↑ GM volume in same regions (DLPFC, OFC, ACC, superior temporal, parietal and occipital cortex) and ↓ in bilateral superior temporal gyrus
Giakoumatos et al 2013[6]	148 with SCZ, SZA or BD-P, MA 36 yrs	341 DCs, 262 HCs	VBM of GM volume	↓ GM volume in bilateral superior/middle frontal, and inferior/superior temporal regions, left superior parietal and supramarginal regions, and right insula and thalamus, relative to DCs and HCs. High (vs. low) lethality showed ↓ in left lingual area and right cuneus
Matsuo et al 2010[12]	10 F with BD, MA 36 yrs	10 DCs, 27 HCs	ROI area	Anterior CC genu area associated with impulsivity
Monkul et al 2007[1]	7 F with MDD, MA 31 yrs	10 DCs, 17 HCs	ROI volume	↓ OFC GM, relative to HCs. ↓ amyg volumes, relative to DCs
Riisch et al 2008[11]	10 with SCZ, MA 30 yrs	45 DCs, 55 HCs	VBM of GM and WM	↑ bilateral inferior frontal WM volume, relative to DCs. In SCZ ↑ inferior frontal related to self-aggression
Soloff et al 2012[4]	44 with BPD (25 high lethality), MA 30 yrs	24 DCs, 52 HCs	ROI volume	↓ insula GM, relative to DCs. ↓ in high lethality attempters in OFC, middle/superior temporal gyrus, insula, fusifrom gyrus, lingual gyrus and parahippocampal gyrus
Spoletini et al 2011[5]	14 with SCZ, MA 43 yrs	36 DCs, 50 HCs	ROI volume	↑ amyg, relative to DCs and HCs. In the SCZ group, ↑ amyg volume associated with self-aggression
Vang et al 2010[9]	7 (4 with MDD, 2 AD), MA 38 yrs	6 HCs	1231-β-CIT methods to separate 5-HTT and DAT uptake in ROIs	↓ GP and caudate, relative to HCs and correlated with 5-HTT binding. In attempters, GP volumes inversely correlated with non-impulsive temperament
Wagner et al 2011[7]	15 with MDD (10 with suicide behavior, 5 with first degree relatives with suicidal behavior),	15 DCs, 30 HCs	VBM of GM density	↓ inferior frontal cortex, ACC, caudate, amyg/HP formation, relative to HCs. ↓ ACC and caudate, relative to DCs

Authors and year	Group with history of suicide attempts	Group(s) without attempts	Methods	Findings
	MA 41 yrs			
Wagner et al 2012[8]	Same sample as in Wagner et al 2011 above	15 DCs, 30 HCs	Cortical thickness	↓ ventrolateral PFC, DLPFC and ACC, relative to DCs and HCs
Older Adults				
Cyprien et al 2011[49]	21 (85.7% MDD, 36.8% AXD, 10.5% BD), MA 72 yrs	180 DCs, 234 HCs	ROI area	↓ posterior third of CC, relative to DCs and HCs
Dombrovski et al 2012[47]	13 with MDD, MA 66 yrs	20 DCs, 19 HC	ROI voxel counts	↓ putamen GM, relative to DCs and HCs. ↓ in associative and ventral striatum, relative to DCs. Suicide attempters with ↓ putamen GM had higher delayed discounting
Hwang et al 2010[48]	27 M with MDD, MA overall MDD sample 79 yrs	43 DCs, 26 HCs	VBM of GM and WM	↓ GM and WM volume in the frontal, parietal, and temporal regions, insula, lentiform nucleus, midbrain, and cerebellum, relative to DCs
Magnetic Resonance Imaging Studies of Hyperintensities on T2-weighted Images				
Ehrlich et al 2005[14]	62 MDD, MA overall sample 27 yrs	40 DCs	Assessment of WMH	↑ PVH
Pompili et al 2008[13]	44 with BD I or II or MDD, MA 46 yrs	55 DCs	Assessment of WMH	↑ PVH
Older Adults				
Ahearn et al 2001[45]	20 MDD, MA 66 yrs	20 DCs	Assessment of WMH	↑ subcortical GM hyperintensities, and trend towards more PVH
Children and Adolescents				
Ehrlich et al 2003[52]	43 inpatients with varying diagnoses MA overall sample 15 yrs	110 DCs	Assessment of WMH	↑ deep WMH in right parietal lobe associated with suicide attempts
Ehrlich et al 2004[53]	43 inpatients with varying diagnoses (25 MDD) MA overall sample 15 yrs, MA MDD subgroup 15 yrs	110 DCs (23 MDD)	Assessment of WMH	Within the MDD subgroup ↑ in WMH, particularly PVH
Diffusion Tensor Imaging Studies				

Authors and year	Group with history of suicide attempts	Group(s) without attempts	Methods	Findings
Jia et al 2010[20]	16 with MDD, MA 34 yrs	36 DCs, 52 HCs	Voxel-based analyses of FA	↓ FA in the ALIC, relative to DCs and HCs, ↓ FA in the frontal lobe, relative to HCs, and ↓ FA in the lentiform nucleus, relative to DCs
Jia et al 2013[22]	23 with MDD, MA 36 yrs	40 DCs, 46 HCs	Tractography, ROI of FA	↓ mean percentage of fibers through the ALIC to the left OFC and thalamus, relative to DCs. ↓ FA in medial frontal cortex, OFC, thalamus, and total ALIC fibers, relative to HCs
Lopez-Larson et al 2013[23]	19 with TBI, MA 38	40 DCs, 15 HCs	ROI of FA	↑ FA in bilateral thalamic radiations, relative to DCs and HCs
Mahon et al 2012[19]	14 with BD, MA 33 yrs	15 DCs, 15 HCs	Tract-based spatial statistical and voxel-based analyses	↓ FA in OFC WM, relative to DCs. In BD with attempts, OFC WM FA inversely correlated with motor impulsivity
Olvet et al 2014[21]	13 with MDD, MA 33 yrs	39 DCs, 46 HCs	ROI and tract-based spatial statistical of FA and ADC	↓ FA in dorsomedial PFC, relative to DCs and HCs. No difference in ADC
Single Photon Emission Tomography Studies				
Audenaert et al 2001[34]	9 (4 with MDD, 4 AD, 1 brief psychotic disorder, 4 comorbid PDs), MA 32 yrs	12 HCs	123I-5-I-R91150 for 5-HT2a receptors in PFC	↓ PFC binding potential of 5-HT2a receptors
Audenaert et al 2002[24]	20 MDD, MA 32 yrs	20 HCs	99mTc-Ethyl Cystine Dimer rCBF SPECT during letter and category fluency tasks	↓ PFC response during letter and category fluency paradigms, relative to HCs
Bah et al 2008[33]	9 unmedicated M (6 with MDD, 1 AD, and/or 5 PDs), MA 41 yrs	9 HCs	1231-β-CIT for 5-HTT availability, assessment of *SLC6A4* polymorphisms	In attempters, ↓ 5-HTT availability associated with the "s" allele of 5-HTTLPR and 12 repeat allele of STin2
van Heeringen et al 2003[35]	9 (3 with MDD, 4 AD, 1 brief psychotic and/or 4 PDs), MA 32 yrs	13 HCs	123I-5-I-R91150 for 5-HT2a receptors in PFC	↓ PFC binding potential of 5-HT2a receptors. ↓ 5-HT2a binding associated with ↑ hopelessness and harm avoidance
Lindström et al 2004[36]	12 (3 with MDD, 3 MDD + SA, 3 AD, 1 DE-NOS, 1 SP, 3 undiagnosed), MA 39 yrs	12 HCs	1231-β-CIT methods to separate 5-HTT and DAT uptake	No significant differences in 5-HTT or DAT. In attempters, ↑ impulsivity associated with ↓ whole brain 5-HTT binding.

Authors and year	Group with history of suicide attempts	Group(s) without attempts	Methods	Findings
Ryding et al 2006[37]	12 (5 with MDD, 3 AD, 1 AXD and/or 6 PDs), MA 39 yrs	12 HCs	1231-β-CIT methods to separate 5-HTT and DAT uptake	In attempters, ↑ impulsivity associated with ↓ 5-HTT binding in OFC, temporal regions, midbrain, thalamus, basal ganglia, and cerebellum, and ↑ mental energy with ↓ DAT binding in basal ganglia
Willeumier et al 2011[25]	21 scanned previously who completed suicide with mood disorders, MA 36 yrs	36 DCs, 27 HCs	99mTc HMPAO SPECT to assess rCBF	↓ rCBF in superior PFC, operculum, postcentral gyrus, precuneus, caudate and insula.↓ rCBF in the subgenual ACC in 18 of the 21 subjects
Positron Emission Tomography Studies				
Cannon et al 2006[30]	8 BD with current depressive episode, MA 30 yrs (overall BD sample)	10 DCs, 37 HCs	5-HTT binding potential measured with 11C-DASB	↓ 5-HTT binding in the midbrain and ↑ in the ACC, relative to DCs and HCs
Leyton et al 2006[29]	10 high lethality suicide attempters (2 with mood disorder, 8 cluster B PD, 6 SA), MA 38 yrs	16 HCs	Alpha-11C-methyl-L-tryptophan trapping as index of 5-HT synthesis	↓ 5-HT synthesis in OFC and ventromedial PFC
Miller et al 2013[31]	15 with MDD, MA 39 yrs	36 DCs, 32 HCs	11C-DASB to quantify in vivo regional brain 5-HTT binding	↓ 5-HTT binding in midbrain, relative to DCs and HCs
Nye et al 2013[32]	11 with MDD, MA 39 yrs	10 HC	11C-ZIENT PET to measure 5-HTT	↓ 5-HTT in the midbrain/pons and putamen
Oquendo et al 2003[28]	16 with MDD with high lethality attempts/9 MDD with low lethality attempts, MA 43 yrs/30 yrs		18F-FDG PET, fenfluramine vs. placebo challenge	↓ rCMRglu in ventral, medial, and lateral PFC, compared to low-lethality attempters, more pronounced after fenfluramine.↓ ventromedial PFC activity associated with ↓ impulsivity and ↑ suicidal planning. ↓ rCMRglu associated with ↓ verbal fluency
Soloff et al 2003[26]	13 ↑ with BPD (12 with attempts), MA 25 yrs	9 HCs	18F-FDG PET during rest	Bilateral ↓ rCMRglu in the medial OFC
Sublette et al 2013[27]	13 with MDD or BD, MA 36 yrs	16 DCs	18F-FDG PET, fenfluramine vs. placebo	↓ rCMRglu in right DLPFC, more pronounced after fenfluramine, ↑ ventromedial PFC activity, not detected after fenluramine. Suicide ideation correlated negatively with rCMRglu in an overlapping DLPFC region
Functional Magnetic Resonance Imaging Studies				
Jollant et al 2008[38]	13 M with MDD, MA 40 yrs	14 DCs, 16 HCs	Response to intense or mild, angry or happy face stimuli, compared to responses to	↑ response in lateral and ↓ in superior frontal cortex to angry vs. neutral, ↑ anterior cingulate gyrus to mild happy vs. neutral, ↑ cerebellum to mild angry vs. neutral, relative to DCs

Authors and year	Group with history of suicide attempts	Group(s) without attempts	Methods	Findings
			neutral face stimuli	
Jollant et al 2010[39]	13 M with MDD, MA age 38 yrs	12 DCs, 15 HCs	Iowa Gambling Task, ROIs	↓ lateral OFC and occipital cortex activation during risky relative to safe choices, relative to DCs. Poorer gambling task performance, relative to DCs
Marchand et al 2012[40]	6 M with MDD with self-harm, 5 with attempts, MA 28 yrs (overall MDD sample)	16 DCs	Motor activation task	↓ putamen activation and altered functional connectivity in a network involving bilateral motor/sensory cortices and striatum, left temporal and inferior parietal lobule regions and right posterior cortical midline structures
Reisch et al 2010[41]	8 F with attempts, MA 39 yrs	None	Activation during recall of mental pain and suicide action during recent suicide attempts	Recall of mental pain was associated with ↓ activation in DLPFC, rostral PFC and premotor regions. Recall of suicidal action was associated with ↑ activation in the medial PFC, ACC and HP
Older Adults				
Dombrovski et al 2013[50]	15 with MDD, MA 66 yrs	18 DCs, 20 HCs	Reward learning using reinforcement learning model, assessment of expected rewards	↓ pregenual cingulate response to high expected reward and associated with ↑ impulsivity
Children and Adolescents				
Pan et al 2011[56]	15 with MDD, MA 16 yrs	15 DCs, 14 HCs	Go-no-go response inhibition and motor control task	↓ ACC activation to go-no-go vs motor control, relative to DCs
Pan et al 2013[55]	14 with MDD, (sample noted to overlap with 2011 study), MA 16 yrs	15 DCs, 15 HCs	Response to intense or mild, angry or happy face stimuli, compared to responses to neutral face stimuli	↑ ACC-DLPFC circuitry, primary sensory and temporal cortices to mildly angry faces, relative to DCs. Higher primary sensory cortex to mild angry, relative to HCs. ↓ in the fusiform gyrus to neutral faces during angry face runs, relative to DCs. ↓ in primary sensory cortex to intensely happy faces and in the anterior cingulate and medial PFC to neutral faces in the happy face runs. ↓ anterior cingulate-insula functional connectivity to mild angry faces, relative to DCs or HCs
Pan et al 2013[57]	15 with MDD, MA 16 yrs	14 DCs, 13 HCs	Iowa Gambling Task	↓ activation in thalamus during high-risk decisions relative to DCs and ↑ activation in caudate relative to HCs

11C-DASB, (11 C)3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl) benzonitrile; 11C-ZIENT, (11C)2β-carbomethoxy-3β-[4′-((Z)-2-iodoethenyl)phenyl]nortropane; 123I-β-CIT, (123I)β-carboxymethyoxy-3-β-(4-iodophenyl) tropane; 123I-5-I-R91150, 4-amino-N-[l-[3-(4-fluorophenoxy); 5-HT, Serotonin; 5-HT2a, Serotonin 2a; 5-HTT, Serotonin transporter; 5-HTTLPR, Serotonin-transporter-linked polymorphic region; 99mTc, Technetium-99m; ACC, Anterior cingulate cortex; AD, Adjustment disorder; ADC, Apparent diffusion coefficient; ALIC, Anterior limb of internal capsule; Amyg, Amygdala; AXD, Anxiety disorder; BD, Bipolar disorder; BD-P, Bipolar disorder w/ psychosis; BPD, Borderline personality disorder; CC, Corpus callosum; DAT, Dopamine transporter; DC, Diagnostic controls, i.e., subjects with the same diagnosis(es) as the group with attempts; DE-NOS, Depressive episode not otherwise specified; DLPFC, Dorsolateral prefrontal cortex; F, Females; FA, Fractional anisotropy; FDG, Fluorodeoxyglucose; GM, Gray matter; GP, Globus pallidus; HC, Healthy control subjects; HMPAO, Hexamethylpropylene amine oxime; HP, Hippocampus; M, Males; MA,

Mean age; MDD, Major depressive disorder; OFC, Orbitofrontal cortex; PD, Personality disorder; PET, Positron emission tomography; PVH, Periventricular hyperintensities; PFC, Prefrontal cortex; rCBF, Regional cerebral blood flow; rCMRglu, Regional cerebral glucose metabolic rates; ROIs, Regions of interest; SA, Substance abuse; SCZ, Schizophrenia; SLC6A4, serotonin transporter gene; SP, Social phobia; SPECT, Single photon emission tomography; STin2, Serotonin transporter intron 2; SZA, Schizoaffective disorder; TBI, Traumatic brain injury; VBM, voxel-based morphometry; WM, White matter; WMH, White matter hyperintensities