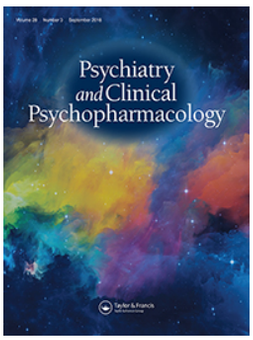

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Yasin Hasan Balcioglu & Samet Kose

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Neural substrates of suicide and suicidal behaviour: from a neuroimaging perspective

Yasin Hasan Balcioglu [a] and Samet Kose [b,c,d]

[a]Neurology, and Neurosurgery, Forensic Psychiatry Unit, Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Istanbul, Turkey; [b]Department of Psychology, Hasan Kalyoncu University, Gaziantep, Turkey; [c]Department of Psychiatry, University of Texas Medical School of Houston, Houston, TX, USA; [d]eCenter for Neurobehavioral Research on Addictions, Houston, TX, USA

ABSTRACT

In this article, we have reviewed neuroimaging studies on the neural circuitry associated with suicidal behaviour in order to identify the neural substrates of suicidal behaviour. The Medline and ScienceDirect databases were comprehensively and systematically searched and articles published from 1990 through 2017 were reviewed. Reviewed brain-imaging modalities included structural magnetic resonance imaging, diffusion tensor imaging, positron-emission tomography, single-photon emission computed tomography, resting-state functional Imaging, and functional magnetic resonance imaging. Although subject characteristics and imaging methods vary across studies, convergent findings involving the structure and function of frontostriatal network and fronto-limbic structures, and the serotonergic system were identified. These neuroimaging studies of suicide behaviour have provided crucial information on the neural circuitry associated with suicide risk. Future studies examining neural changes associated with before and after pharmacologic and behavioural interventions would be instrumental in suicide risk reduction.

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Magnetic resonance imaging; neuroimaging; positron-emission tomography; single-photon emission computed tomography; suicide

Introduction

Globally, near one million people were estimated to commit suicide per year [1]. The number of non-fatal suicide attempts is 10–20 time more frequent, and the strongest risk factor for suicide is a history of self-harm or suicide attempts [2]. Research into suicide is one of the most attractive fields for the clinicians in medicine. The early reports of the studies of suicide were traced in the early nineteenth century. At that time, detailed statistical data about suicide published in the United States [3]. Until mid-twentieth century, research on suicide was generally restricted to demographic statistics and clinical variables that related with suicide and suicide methods of the victims. In the 1950s, research into suicide took more complex approach. Researchers began to focus on clinical variables associated with suicide such as psychopathology and personality, instead of dealing with raw population statistics [3]. In the mid-1960s, neurobiological aspects of suicide emerged into the research field. One of the first studies of this kind was performed by Bunney and Fawcett. They observed elevated levels of 17-hydroxycorticosteroid, a breakdown product of cortisol, prior to suicide in the urine samples of suicide attempters [4]. This was a milestone in the research on suicide; however, because the researchers would not be able to predict which patients would attempt suicide, it required collection of plenty of urine samples in psychiatric population. Later studies examined post-mortem brain tissues and analysed neurotransmitter and hormone metabolism in suicide cases. Besides post-mortem techniques, modern methods, such as genetics and neuroimaging, have been utilized to uncover suicide neurobiology in the late twentieth century.

To date, several neurobiological models have been asserted to elucidate the aetiology of suicide. The widely acknowledged explanation comes from the stress-diathesis explanatory model which argues for an interaction between life stressors and a biological susceptibility to suicidal behaviour. According to this model, vulnerable individuals give abnormal or exaggerated responses to otherwise neutral stimuli [5]. Suicide prevention poses major challenges and there is no robustly accurate assessment tool for suicide risk yet. The understanding of biological correlates of the diathesis warrants a better opportunity for the prediction and prevention of suicidal behaviour; however, available diagnostic tools are scarce and no reliable biomarkers have been employed to help clinicians to predict suicide or to target with treatment [6]. The insufficient knowledge regarding linkage of symptoms accompanying suicide and neuronal function led difficulties for generating meaningful and clinically relevant

CONTACT Samet Kose sametkose@gmail.com

propositions about the suicide. Fortunately, findings from post-mortem studies of the suicidal brain and in-vivo neuroimaging studies pointed out a neurobiological basis for the diathesis, which extends to the several changes from cells to the neuronal circuitries and greater structures. Advanced neuroimaging techniques enabled researchers to examine the association between the brain regions and the neurochemistry in emotional, cognitive, and behavioural components of the suicide.

Cellular changes in the suicidal brain

Previous research relies on in-vitro (post-mortem) studies regarding suicide aetiology. Sampling of cortical and subcortical tissues of people who have died by suicide demonstrated several changes in neurons, astrocytes and oligodendrocytes [6]. As serotonergic system is the most recognized for being involved in the aetiopathogenesis of suicide, molecular and pathological studies have focused on this system. Asberg et al. described a reduced 5-HIAA (5-hydroxy indole acetic acid; the principle metabolite of serotonin) in cerebrospinal fluid in suicide attempters [7]. Congruous with this revolutionary finding, Arango and Mann concluded that suicidal patients had less 5-HT (5-hydroxytryptophan) in their brainstems. In the post-mortem brainstem studies of the suicide victims, more serotonin neurons, more tryptophan hydroxylase 2 (TPH2; the rate-limiting enzyme in the synthesis of serotonin) gene expression and protein per neuron seemed to be associated with suicide [8]. Given evidence indicating an overall decrease in 5-HT neurotransmission in both cortical and subcortical regions of suicide attempters, increased TPH2, TPH proteins, and mRNA levels could be attributed to a compensatory mechanism to alleviate central 5-HT transmission, and/or a response to increased stress [3]. On the other hand, several changes in noradrenergic system in suicide have been demonstrated. Deficient noradrenaline neurons in locus coeruleus in the brains of suicide victims have been found [9].

Neurotrophins such as brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF) are well-known for their functions in neuronal survival and plasticity. Decreased expressions of these molecules and respective receptors have been implicated in the aetiology of suicide and mood disorders [3]. Decreased regional neuronal dendritic branching was noted among suicide victims [10]. Non-neuronal cells or glias are known for their roles as neural stem cell, in neurogenesis and neuronal survival. Using post-mortem brain tissues, less glial cells, particularly astrocytes and oligodendrocytes, have been shown to be associated in major depressive disorder (MDD) and suicide [3]. Microarray studies have demonstrated astrocyte dysfunction, without decrease in cell number, may be related to MDD and suicide [11]. Oligodendrocytes are primarily responsible for myelination and oligodendrocyte dysfunction have been suggested to play a role in MDD and suicide in a study of a molecular signature of depression in amygdala with myelination deficit [12].

PROSPERO checklist of the searching strategy and selection criteria

- ✓ The Medline and ScienceDirect databases are comprehensively and systematically searched
- ✓ Literature published from 1990 through 2017 are in consideration
- ✓ Different combinations of the keywords "*suicide*", "*suicide attempt,*" "*suicidal behavior,*" "suicidality," "*structural neuroimaging,*" "*functional neuroimaging,*" "*molecular neuroimaging,*" "magnetic resonance," "*diffusion tensor imaging,*" "functional magnetic resonance imaging," "positron emission tomography," "*single-photon emission computed tomography*" are polled
- ✓ Inclusion is based on following;
  - published in English
  - studied in human subjects
  - compared both suicidal and control subjects
- ✓ Unpublished studies, case reports, thesis, and conference papers are excluded
- ✓ Several highly cited and regarded comprehensive review articles are cited due to space considerations
- ✓ Available open-access and institutional-access articles are recruited
- ✓ The articles are filtered through an inspection of the abstracts, in order to select most suitable articles related to the topic
- ✓ The reference lists of the relevant articles are also checked manually for additional publications matching the scope of our review
- ✓ The authors avoid incorporating duplicated samples of the key papers; however, studies with similar populations and methods are included when they are of a high-impact nature.

Neuroimaging research into the suicidal brain

Neuroimaging has provided one of the best modern tools for examining the pathophysiology of psychiatric disorders in the living brain. Neuroimaging can provide many different quantitative measures (including morphometry, metabolism, and functional activity). Neuroimaging research using groups of subjects can determine whether psychiatric disorders are associated with changes in the size or shape of specific brain regions, the functional activity within these regions, or their concentration of particular neurotransmitters, receptors, or key metabolites. Recent studies provided an appreciation for the unique ability of neuroimaging modalities to shed light on current understanding of multifaceted and riddling nature of suicidal behaviour. These modalities allowed researchers to examine the relationships between cognitive, emotional, and behavioural components of suicide and altered neuroanatomy and neural function. Neuroimaging studies of the suicidal brain can be divided into three categories as; structural imaging, functional imaging, and molecular imaging.

Structural neuroimaging

Structural neuroimaging techniques are used to generate an image of neuroanatomical differences between

patient and healthy controls. Brain-imaging techniques have supported the post-mortem findings, pointing out a biological substrate for neuropsychological disturbances related to suicide, such as decision-making, problem solving, and impairments in fluency. Structural abnormalities are considered as trait factors for suicidal behaviour [5]. Most of the structural studies of the brain have been conducted through magnetic resonance imaging (MRI). A variety of neuroanatomical abnormalities, such as volume alterations, have been linked to suicide in numerous psychiatric disorders. Decreased grey matter (GM) and white matter (WM) volumes in the prefrontal cortex (PFC), the orbitofrontal cortex (OFC), the left angular gyrus, the right cerebellum, the nucleus raphe, the nucleus lentiformis, insula, hippocampus, the rectal gyrus, the superior temporal gyrus, caudate, and the corpus callosum (CC) have been reported in suicidal patients [1,5,13–16]. These structural alterations generally appears to be particularly involved in the processing of the punishing aspect of salient event and may therefore mediate in planning behaviour on the basis of negative stimuli [5].

The OFC is implicated as a key brain region for emotion and impulse regulation; GM volume reduction in this structure is demonstrated in both adult and adolescent suicidal patients with mood disorders, schizophrenia and borderline personality disorder (BPD). It was considered as a supportive evidence to the suggestion that emotion and impulse dysregulation may be associated with suicidal behaviour [17,18]. The GM volume in the right superior temporal gyrus, another important region for social emotion processing, has been found decreased in the adolescent suicide attempter group with MDD [19].

The CC serves as a bundle of neurons that allow the both hemispheres to communicate each other, and its structural abnormalities have also been demonstrated in a variety of psychiatric disorders. MDD, which may indicate the role of negative environmental stimuli through the neurodevelopment leading to reduced CC size as in suicide attempters [20]. In summary, most volumetric MRI studies revealed smaller GM volumes primarily in the frontal and temporal cortical regions, the CC, and insula in suicide attempters with different psychiatric diagnoses [1].

Several lines of evidence acquired from MRI studies have implicated an involvement of the frontostriatal network in the aetiology of suicide. This network comprises emotion regulation pathway between subcortical GM areas (i.e. basal ganglia) and the PFC. GM and WM hyperintensities belong to the parts of frontostriatal network are up to eight times more likely to be seen in the patients with suicide attempts compared to patients without suicide attempts [1]. It was reported that deep WM, periventricular WM, and subcortical GM hyperintensities are in close relationship with suicidal behaviour [21–23]. However, it is unclear that whether hyperintensities could be a residual lesion of the brain due to suicide attempt (i.e. cerebral anoxia due to suicide by hanging) or predictors of suicidal behaviour. Hyperintensities and other abnormalities might implicate disruptions within the frontostriatal pathway and may generate a predisposition to depressive episodes and suicidal behaviour.

Smaller GM volumes of right caudate nucleus, bilateral globus pallidus, rostral part of the anterior cingulate cortex (ACC), and left limbic cingulate gyrus have been reported in the suicide attempter cohort [24–27]. As the parts of frontostriatal network, ACC and striatum seem to be important in suicidal behaviour especially in depressive states. The ACC acts as a bridge between limbic system and frontal cortex. It integrates cognitive activity with affective experience [10]. Deficits in frontal-ACC-striatum circuitry may contribute to impaired decision-making and dysfunctional patterns of emotional regulation [28]. It is also speculated that morphological changes in the frontolimbic structures, such as in the frontostriatal network, could be related to severity and lethality of suicide attempt [27]. Taken together, these structural changes within frontostriatal pathway may result in an impaired control of behaviour and emotion that leads to suicidal behaviour. The ACC is linked with control of impulsive behaviour and caudate nucleus is also implicated in dopaminergic reward processes [29,30]. Putamen is also involved in reward processes, impulsivity, and motor skills. MDD suicide attempters were found to have reduced putamen GM volume compared to MDD non-attempters and healthy controls [31]. Impairments in both brain regions might precipitate suicidal behaviour. Deficits in the putamen may result in short-sighted, immediate-reward decisions and hence promote impulsive suicidal acts in a depressive state [28]. Cortical thickness has also been examined in suicide. Dorsolateral and ventrolateral regions of the PFC (DLPFC and VLPFC) and the ACC have been implicated in emotional and behavioural control processes. Significantly thinner cortical thickness in these regions is demonstrated in suicide attempters with MDD and schizophrenia [25,32]. These findings are compatible with the suggestion of lack of inhibitory control and increased impulsivity in suicidal behaviour.

Despite structural neuroimaging research into suicide has mainly focused on mood disorders, a number of studies that examine neuroanatomical differences in suicidal patients with other psychiatric diagnoses are also worth mentioning. In terms of psychotic disorders, structural differences were observed in neural circuitries that mediate inhibition, impulsivity and emotion, visceral perception, and visual and auditory processing in suicide attempters. Attempters

with psychotic disorders have decreased GM density in the left superior temporal lobe and left OFC and GM volumes in bilateral temporal cortices, the left superior parietal cortex, thalamus, right insula, and several frontal regions; while enlarged right amygdala and bilateral inferior frontal WM volumes are noted [33–36]. Neuroanatomical correlates of suicidality in individuals with BPD have been attracting suicide researchers on the field. Larger pituitary gland volume and decreased GM densities in the ventral cingulate gyrus and several medial temporal lobe regions were found to be associated with suicidal and parasuicidal acts among teenagers and adults [36,37]. These abnormalities may be involved in the dysregulation of impulse and affect in BPD as well [13]. In an epileptic pediatric group, suicidality was associated with smaller right orbitofrontal gyrus WM volumes and larger left temporal lobe GM volumes [38].

Diffusion tensor imaging (DTI) is a recently developed MRI technique that can measure structural connectivity and macroscopic axonal organization in the brain. DTI studies demonstrate presence of WM lesions, which are suggested to contribute to self-aggression and impulsivity in suicidal behaviour [17]. DTI is sensitive to water movements and diffusions in neuronal fibres in WM of specific brain regions. Fractional anisotropy (FA), a diffusivity measure that used by DTI, reflects the directional coherence of diffusion within WM bundles, their architecture, or structural integrity [17]. In panic disorder patients, increased fractional anisotropy (FA) values for the internal capsule and thalamic radiations are found significantly correlated with suicidality supporting that aberrant WM integrity in these areas is a contributing factor for the suicidal behaviour [39]. Other DTI studies have shown low FA in the left anterior limb of the internal capsule, the dorsomedial PFC, the left cingulum, and anterior thalamic radiation in suicide attempters with mood disorders and traumatic brain injury [40–43]. Decreased FA within the orbitofrontal WM is associated not only with a history suicidal attempt, also with higher overall impulsivity in bipolar patients [44]. Abnormal projections to the OFC and thalamus are linked to disrupted affective and cognitive functions representing an elevated vulnerability for suicidal behaviour [45]. Conversely, higher FA values are found in fronto-temporo-limbic circuits among suicide attempters diagnosed with schizophrenia or schizophreniform disorder [46]. In a younger study population with bipolar disorder, decreased WM integrity in the uncinate fasciculus, ventral frontal and right cerebellum regions; the CC and amygdala is associated with suicide attempts [18,47]. Diffusion or integrity deficits in those brain regions may be related not only to negative cognitive inference that leads to suicidal behaviour but also to the abnormalities in WM connections are associated with impulsivity [17].

Functional MRI

Researchers frequently employ quantitative neuropsychological measurement tools to examine cognitive functions related to suicidality. For instance, Raust et al. have found diminished executive function in suicidal individuals, using a variety of neuropsychological assessment instruments [48]. Such studies serve to elucidate the cognitive correlates of suicidal thoughts and behaviours; however, they are criticized due to inability for revealing the underlying neuronal pathophysiology. Researchers on this field can only hypothesize which parts of the brain are responsible for cognitive and behavioural pathologies. Some authors have speculated that structural brain abnormalities may represent a trait factor and lead to functional changes that represent state factors; however, functional alterations in particular brain circuits without overt neuroanatomical changes could provide a basis for cognitive and emotional characteristics, such as in suicidal thoughts and acts [5]. Functional neuroimaging techniques have been employed in order to resolve this conflict and to establish relationships between dysfunctional patterns in emotional/cognitive/behavioural correlates and neural activation in suicide. To date, the most commonly used functional neuroimaging tool is represented by functional MRI (fMRI). The fMRI allows monitoring the neural activity in specific brain regions which are involved mainly in appraisal, mood regulation, and particularly decision-making, more specifically, the prediction of reward and punishment to examine directly the diathesis for suicidal behaviour [6]. It uses blood oxygenation levels (representing metabolic demand) in specific brain regions as a measure of neural activity at rest or while individuals perform cognitive and other particular cognitive tasks [1].

Neurocircuitries involved in impaired decision-making and emotional regulation have been frequently implicated in fMRI research into suicidal behaviour. Task-based fMRI has been used to examine the neural substrates of specific cognitive and emotional intermediate phenotype of suicide. For instance, Van Heeringen et al. performed a meta-analysis of functional neuroimaging studies comparing suicidal individuals with psychiatric disorders and healthy controls and demonstrated increased functional activations during emotional tasks and decreased functional activations during cognitive tasks particularly in the rostral and dorsal ACC in association with a history of suicide attempt. They also linked functional overactivity in the ACC and the PCC to a vulnerability to suicidal behaviour [5]. A study with emotion-based tasks using angry faces showed increased activity in the ACC-dorsolateral PFC attentional control circuitry in attempters compared to non-attempters [49]. In a well-designed fMRI work with an emotional challenge

task in suicidal patients, Jollant et al. measured neural activity in response to angry and happy versus neutral faces in a group of MDD patients with and without a history of suicide attempt [50]. They found that suicide attempters showed greater activity in the right lateral OFC and decreased activity in the right superior frontal gyrus in response to prototypical angry versus neutral faces. Suicidal patients also responded greater activity in the right ACC and in the right cerebellum to mild happy and mild angry faces, respectively. These findings suggested that suicide attempters have increased sensitivity to others' disapproval, higher propensity to act on negative emotions, and decreased attention to mildly positive stimuli [13]. Two years later, the same authors tested a group of suicidal and non-suicidal MDD patients with Iowa Gambling Task during fMRI scanning. This test, which is a decision-making task, was employed to measure risk liability and executive control, in particular. Among suicide attempters, poorer performance in risk-taking under conditions of uncertainty was associated with the left OFC dysfunction, which could explain the lack of decision-making observed in them [51].

Disruption in the OFC was also demonstrated among suicide attempters with BPD, during a task involving recall of the aversive autobiographical memories [52]. Recall of the past suicide action was associated with increased activation in the regions of emotional control circuitry, such as in the medial PFC, the ACC, and the hippocampus; while recall of the experienced mental pain when committing suicide was associated with frontal cortical deactivation [53]. It is suggested that frontal deactivation in a state of mental pain inhibits the emotional control circuitry; leading the patients toward suicidal behaviour to resolve the pain they are suffering. Once fixated on suicide, the brain regions involved in goal-directed behaviour, medial PFC and ACC specifically, are activated to complete the action. Additionally, the activation of goal-directed suicidal act may be related with a decrease in mental pain [53]. In other words, goal-directed suicidal act may be pursued to decrease mental pain. Psychic pain itself was identified as a risk factor for suicide and was considered to be related with neurocircuitries that modulate reward processing, emotional regulation, and hopelessness [49]. Besides mental pain, feeling of guilt, another associated risk factor for suicidal behaviour was found to be in relation with altered functionality in left dorsal cingulate cortex [54]. In an fMRI study of responses to facial expressions, greater OFC and ventrolateral PFC activation in response to angry faces was found among suicidal patients and inadequate risk processing was associated to dorsal PFC hypoactivation [55]. The outcomes of the fMRI studies with responses to facial expressions suggest that emotional dysregulation is based on the OFC and the ACC in suicidal patients. In another study combining emotional responses and decision-making tasks, suicide attempters showed an increased response to angry faces in the left OFC and ventrolateral PFC; increased response to wins in the right OFC, dorsal PFC, and ACC; decreased response to risky choices in the left dorsal PFC; and decreased response to sad faces in the right ACC [55]. In a very recent fMRI study, disrupted neural responses to potential wins and losses in the subgenual ACC, insular cortex, and left amygdala; the brain regions involved in valuation, emotion reactivity, and emotion regulation, were shown in MDD patients with a history of suicide attempt. Just et al. has examined the neural representations of the emotional concepts among youth population with and without suicidal ideation. They have demonstrated that suicidal group had more clusters of stable voxels in the left inferior parietal region, while had the control group in the anterior frontal regions with the evoked emotions. Those emotions were particularly evoked with the concepts of "death," "cruelty," "trouble," "carefree," "good," and "praise" [56]. The outcomes may be attributed to the heightened negative valuation in decision-making under risk, and impaired emotion processing in suicidal patients [57].

Emotional processing and decision-making have also been examined in adolescent population with suicide attempts plus MDD. In this cohort, high-risk decisions were associated with the right thalamus hypoactivation and increased activity in the left dorsal PFC, right ACC, middle temporal gyrus, and sensory cortices was seen in the response to mildly angry faces [58,59]. These indicated regions may also reinforce higher impulsivity in younger suicide attempters with MDD. It is also argued that adolescents with a history of suicide attempt have relatively normal cognitive performance and show rapid and fixed responses to cognitive problems; however, they exhibit greater abnormalities in processing negative emotions [60]. In elderly patients with MDD, altered paralimbic reward signal was linked with a history of impulsive suicidal act. In addition, older MDD patients have a behavioural oversensitivity to punishment, which is related to disrupted corticostriatothalamic encoding of unpredicted rewards, and predispose a suicidal behaviour as a self-punishment [61]. Excessive coupling in both ventral striatum and other striatal network structures has been associated with suicidality during loss *vs.* reward trials in depressive patients, which is another implication for the role of striatal function in the suicide aetiopathogenesis [62]. Exaggerated response to angry faces in the frontal operculum was shown in the older patients with a history of highly impulsive and/or unplanned suicide attempts [63]. In a reward-delay fMRI study, premeditated and highly planned suicide attempts were associated with less activation in the lateral PFC, while longer delays to reward

were correlated with less parahippocampal and occipital activation [64]. It was assumed that impulsive suicidal behaviour was associated with a less tolerance to reward delay; however, both impulsive and premeditated behaviours were consequences of impaired decision-making processes. A group of women with MDD and a history of suicide attempt, responded with a hypoactivation in the left insula and supramarginal gyrus when experiencing social exclusion related to the task which may have suggested that suicide attempters with MDD do not have intact social perception and failed to tolerate mental pain and were unable to form an accurate social cognition [65].

Resting-state functional imaging

The fMRI also provides an index of resting-state neural activity that is when the subject is not performing any task. In a recent study, increased resting-state functional connectivity of the right amygdala with the left middle temporal area was shown in suicide attempters with MDD [66]. Abnormal baseline brain activity such as increased amplitude of low-frequency fluctuation in the right superior temporal gyrus was also shown in suicide attempters with depression [67]. In a younger sample with MDD, increased resting-state activity was seen in the right superior and left middle temporal, and left middle occipital gyri; while decreased functional connectivity was seen in left superior and middle frontal gyri in suicide attempters. In light of these findings, it could be argued that disruptions in the fronto-limbic or fronto-parietal-cerebellar pathways lead to poor executive functioning, lack of impulse control, cognitive flexibility, and impaired decision-making in in suicide attempters with depression [68].

The default mode network (DMN), a collection of brain regions including the posterior cingulate cortex (PCC) and precuneus, shows reliable inter-regional functional connectivity at resting-state. The association between DMN and negative affective states and ruminative thoughts in MDD has been previously studied [69]; however, research on DMN activity in suicidal population is relatively lack. In one of the two studies investigating the association between the DMN and suicidality, Zhang and collaborators have examined selected DMN regions and found increased connectivity in the right PCC and the left lingual gyrus and decreased connectivity in the right precuneus in depressed adolescents with suicidal behaviour [70]. In the second study, Chase et al. have demonstrated impaired functional connectivity between the dorsal PCC and dorsal ACC, and the ventral PCC and dorsal ACC in suicidal ideators; while increased functional connectivity between the left inferior frontal gyrus and the dorsal PCC was shown in attempters [65]. The DMN's involvement in the suicide pathogenesis was also implicated in the presence of neurostructural abnormalities. For instance, anatomical deficits in the rectal gyrus, in the other parts of the orbital-cingulate network or in the DMN, might lead maladaptive affective responses during cognitive and emotional processing, which may precipitate a vulnerability to suicidal behaviour [5].

Both task-activated and resting-state neuroimaging studies suggest that suicidal ideation could be explained with abnormalities in particular neurocircutries. More specifically, the left putamen hypoactivation during motor activation task and hyperactivation in the ACC and PFC during error-processing task were demonstrated [71,72]. Intrinsic functional connectivity between certain regions including the dorsal/ventral PCC, the rostral ACC, the orbitomedial PFC, and the right middle temporal pole were found to be decreased among suicidal ideators [65,73]. Resting-state disconnection within the fronto-limbic circuits and the DMN might have an impact on decision-making and emotional processing in the context of suicidal thoughts. Among schizophrenia patients with past suicidal ideation, the PFC-based circuit dysfunction during goal-representation task was revealed [74]. In addition, in a task performance study, past suicidal ideation and suicidal behaviour were associated with the higher control-related activation in right brain regions including the ventrolateral PFC and insula and relatively lower activation in cuneus and precuneus in patients with mood disorders [75].

In sum, there seems to be an increased prefrontal activation – may be as a compensatory mechanism – while engaging emotional processing tasks, a decreased activation during risk assessment, reward evaluation, and decision-making on risky conditions, reflecting impaired top-down control [1]. All the aforementioned brain regions studied by using fMRI have been also shown to play a role in different psychopathological domains such as modulation of physiological responses to emotions, emotional dysregulation, abnormal coupling of the self to negative emotions, and self-processing, which in turn are also supposed to play a role in the emergence of suicidal behaviour [69]. In a novel study that examines association of epigenetic alterations with functional neural connectivity in suicidal patients, the methylation degree of several GpC sites, specified gene promoter zones, were in positive correlation with signal intensity in response to particular emotional stimuli in brain regions such as the left frontal gyrus and left thalamus [76]. Elucidating the functional deficits associated with specific network disturbances combining with other neurobiological substrates, such as genetic, epigenetic or neuroinflammatory mechanisms, may aid to clarify the pathophysiological mechanisms underlying suicidal behaviour and assist in identifying high-risk individuals in clinical settings.

Molecular neuroimaging using PET and SPECT

Positron-emission tomography (PET), single-photon emission computed tomographies (SPECT) are radiotracer-based non-invasive imaging techniques that provide quantitative binding information on specific brain target areas of interest. These modalities have been proven to be particularly valuable for imaging targets in the central nervous system, enabling receptor occupancy and metabolic activity measurements, and dose selection for clinical candidates. PET uses positron emitting tracers, likes of manifold fluor [F] and carbon [C] radioisotopes, while SPECT utilizes gamma tracers, such as iodine [I] radioisotopes. PET provides better imaging for the brain's molecular and metabolic architecture with a higher contrast and spatial resolution; however, SPECT is advantageous with its lower cost [77].

The serotonergic system plays a key role in the regulation of mood and emotion. Under the serotonin hypothesis, reduced activity or bioavailability of this neurotransmitter linked to MDD or other associated mood disorders [6]. The serotonin system and its associated transporter (5-HTT or SERT) and receptors (5-HT1A and 5-HT2A) have assumed well-documented roles in the aetiology of suicidal behaviour [13]. Therefore, most molecular imaging studies regarding suicide neurobiology have focused on this neurotransmitter and its metabolites and on the transporter and receptors. Such studies have rooted their hypotheses to the previous post-mortem findings as the deficits in serotonin-transporter and receptor expression, and in molecular binding potential. Involvement of dopamine transporter (DAT) was also asserted in the aetiopathogenesis of suicide in several lines. However, two molecular imaging studies were not able to demonstrate a significant relationship between DAT binding potential and suicidal behaviour [78,79].

Molecular imaging studies on serotonin transporter (5-HTT/ SERT)

5-HTT is a membrane bound transporter which is responsible for recycling serotonin by returning it to presynaptic serotonergic neurons [80]. With regard to suicide, a series of landmark post-mortem studies have demonstrated either lower expression of the serotonin transporter gene 5HTTLPR or reduced 5-HTT density in several brain regions including the thalamus, PFC, ACC, hippocampus, putamen, and hypothalamus among suicide victims when compared to non-suicidal controls [81–86]. Arango et al. reported low 5-HTT binding capacity (a product of receptor binding x region volume that is more analogues to PET outcome measures) and fewer neurons expressing 5-HTT mRNA in the dorsal raphe nuclei in depressed suicide patients [87]. Therefore, existed molecular neuroimaging work has postulated reduced 5-HTTT as a potential correlate for suicidal behaviour. In 2004, Lindström collaborators used SPECT and [^{123}I]-β-CIT, a cocaine analog radioligand used to examine monoamine transporters to examine 5-HTT and the DAT and they reported no significant differences in monoamine transporters between suicidal and control groups. However, they found a linkage between low 5-HTT and impulsivity [77]. Two years later, Ryding et al. replicated this study with the same method. Although they did not find a systematic relationship between 5-HTT binding potential and suicidality, there was a negative correlation between the 5-HTT and impulsiveness/initiative among suicide attempters were noted [78]. Parsey et al. were able to find a significant correlation between the 5-HTT binding potential and MDD in the amygdala and the midbrain; even though, they failed to establish a consistent association of transporter binding and suicide [88]. However, the results of a 2013 work by Nye et al. employed [^{11}C]-ZIENT, a selective SERT radioligand, using PET imaging and found reduced SERT binding potential in the midbrain, pons, and putamen of MDD patients with a history of suicide attempt compared to MDD patients without suicidal history and healthy controls [89]. Three PET studies using superior radiotracers, [^{11}C]-DASB and 4-[^{18}F]-ADAM, demonstrated lower 5-HTT binding in the midbrain of the suicide attempters with MDD and bipolar disorder [90–92]. Overall, current evidence suggested that SERT deficit in the midbrain might be a reliable biomarker for suicidal behaviour rather than for MDD [91]. These findings further implicated the serotonin system in the pathophysiology of suicide.

Molecular imaging studies on serotonin receptors

There has been a number of evidence on the link between certain 5-HT receptor subtypes and suicidal behaviour. In a recent meta-analysis, Wang et al. implicated that reduced 5-HT1A receptor binding was associated with the pathology of depression in various brain regions that might be related to suicidal behaviour [93]. In a post-mortem autoradiography study, Arango et al. have demonstrated increased 5-HT1A receptor binding potential in several brain regions, pronounced mostly in ventrolateral PFC, among suicide victims [82]. In other three post-mortem studies, increased 5-HT1A in the dorsal raphe nuclei and several frontal regions in suicide victims have been shown [84,94,95]. Evidence from in vitro studies led researchers to argue that increased 5-HT1A receptor binding would favour lower serotonin neuron firing and less serotonin release in the suicide

aetiopathogenesis. Therefore, several in vivo molecular neuroimaging studies have focused on 5-HT1A receptor binding potential in suicidal population. Two recent PET studies using [^{11}C]-WAY-100635 have examined the association between 5-HT1A receptor binding potential and lethality grade of the suicide attempts. Oquendo and collaborators have shown that greater raphe nuclei 5-HT1A binding potential predicted higher suicidal ideation and more lethal suicidal behaviour in their prospective two-year-observational study [96]. Similarly, Sullivan et al. argued that elevated 5-HT1A binding potential particularly in raphe nuclei might have indicated higher lethality of past and future suicide attempts in depressed individuals, and so, it did not appear to be a consequence of suicidal behaviour [97].

Alterations in the 5-HT2A-receptor subtype have been reported in suicidal behaviour [13]. In post-mortem studies, results have generally reported an increased 5-HT2A in suicide decedents compared to healthy controls [13]. In a PET study, Meyer et al. were not able to establish a significant correlation between 5-HT2A binding and depression or past suicide attempt [98]. In 2001, Audenaert and colleagues conducted a [^{123}I]-5-[I]-R91150, a 5-HT2A-specific ligand, SPECT study in medication-free recent suicide attempters compared to healthy controls. The authors reported that the suicide attempter group

Table 1. Studies of structural neuroimaging in suicidal populations.

Authors and year	Subjects	Methods	Major Findings
Ahearn et al. (2001)	40 MDD patients (20 with vs. 20 without suicide attempts)	MRI: hyperintensities	Significantly more subcortical and periventricular grey matter hyperintensities in attempters
Aguilar et al. (2008)	37 patients with schizophrenia (13 with suicide attempts)	MRI: voxel-based morphometry	Reduced grey matter density in the left superior temporal lobe and left orbitofrontal cortex in suicidal patients
Pompili et al. (2008)	99 patients with mood disorders (44 suicide attempters)	MRI: white matter hyperintensities	Increase prevalence (x8) of periventricular white matter hyperintensities in attempters
Rüsch et al. (2008)	55 schizophrenia patients (10 suicide attempters) vs. 55 controls	MRI: voxel-based morphometry	Larger inferior frontal white matter volumes in attempters with schizophrenia
Caplan et al. (2010)	51 pediatric subjects with epilepsy (11 with suicidal ideation)	MRI: voxel-based morphometry	Smaller right orbitofrontal gyrus white matter volumes and larger left temporal cortex grey matter volumes is related to suicidal thoughts
Jia et al. (2010)	52 MDD patients (16 suicidals) vs. 52 healthy controls	MRI: DTI	Decreased FA in the left anterior limb of the internal capsule in attempters
Spoletini et al. (2011)	50 schizophrenia patients (14 suicide attempters) vs. 50 controls	MRI: volumetric analysis	Increased amygdala volume in schizophrenia patients with past suicide attempts
Cyprien et al. (2011)	Elder groups of 21 suicide attempters vs. 180 mood disordered subjects vs. 234 healthy controls	MRI: volumetric analysis	Smaller posterior third of the corpus callosum in attempters
Dombrovski et al. (2012)	Elder patient groups: 13 MDD (suicidal) vs. 20 MDD (non-suicidal) vs. 19 healthy controls	MRI: voxel-based morphometry	Decreased putamen grey matter in suicidal patients
Soloff et al. (2012)	68 individuals with borderline personality disorder (44 attempters) vs. 52 controls	MRI: voxel-based morphometry	Diminished left insular grey matter volume in attempters
Wagner et al. (2012)	15 MDD patients (10 suicidal) vs. 30 healthy matches	MRI: cortical thickness analysis	Reduced cortical thickness in the left in dorsolateral prefrontal, ventrolateral prefrontal and anterior cingulate cortices in suicidal patients
Olvet et al. (2014)	52 MDD patients (13 with attempts) vs. 46 healthy participants	MRI: DTI	Low FA in the dorsomedial prefrontal cortex is associated with suicidal behaviour
Lijffijt et al. (2014)	93 bipolar patients (51 attempters)	MRI: voxel-based morphometry	Various prefrontal cortex volume alterations in suicidal bipolar patients depending on illness course and treatment
Jia et al. (2014)	63 MDD patients (23 attempters) vs. 46 controls	MRI: DTI	Reduced projections through the left anterior limb of the internal capsule to the left medial frontal cortex, OFC, and thalamus
Colle et al. (2015)	63 MDD patients (24 attempters)	MRI: volumetric analysis of the hippocampus	Smaller hippocampal volumes in the attempter group
Kim et al. (2015)	44 panic disorder patients (20 with suicide attempts)	MRI: DTI and voxel-based morphometry	Increased FA values for the internal capsule and thalamic radiations in attempters
Pan et al. (2015)	59 adolescents with MDD (28 attempters) vs. 41 health controls	MRI: volumetric analysis	Reduction in right superior temporal gyrus grey matter volumes in attempter group
Lee et al. (2016)	56 patients with schizophrenia/ schizophreniform disorder (15 attempters)	MRI: DTI	Higher FA values in various parts of the fronto-temporo-limbic circuits in attempters
Besteher et al. (2016)	37 schizophrenia patients (14 attempters) vs. 50 healthy controls	MRI: cortical thickness analysis	Significant cortical thinning in the right DLPFC and the superior temporal cortex
Lee et al. (2016)	38 MDD patients (19 with suicide history)	MRI: voxel-based morphometry	Reduced grey matter volumes in the left angular gyrus and right cerebellum in attempters
Cyprien et al. (2016)	91 patients with mood disorders (45 attempters) vs. 30 healthy controls	MRI: DTI	Significantly lower FA value of the splenium part of the corpus callosum in attempters
Johnston et al. (2017)	68 bipolar adolescents and young adults (26 suicide attempters)	MRI: volumetric, DTI, functionality	Decreased grey matter volumes in OFC, hippocampus, and cerebellum. Decreased white matter integrity in the uncinate fasciculus, ventrofrontal, and right cerebellum regions; and amygdala in suicidal patients
Duarte et al. (2017)	39 bipolar-I patients (20 attempters) vs. 20 controls	MRI: voxel-based morphometry	Increased grey matter volumes of anterior cingulate cortex is related to suicide attempts and severity

Table 2. Studies of functional neuroimaging in suicidal populations.

Authors and year	Subjects	Methods	Major Findings
Jollant et al. (2008)	27 euthymic MDD patients (13 suicidal) vs. 16 controls	fMRI: Response to facial expressions	Greater activity in the right lateral OFC and decreased activity in the right superior frontal gyrus in response to prototypical angry versus neutral faces in attempters
Jollant et al. (2010)	25 euthymic MDD patients (13 suicidal) vs. 15 controls	fMRI: Iowa Gambling Task	Left OFC hypoactivation during risky choices among attempters
Reisch et al. (2010)	8 MDD patients with suicide attempt	fMRI: Recall of the mental pain and suicidal episode vs. neutral activity	Increased activation in the medial prefrontal cortex, the ACC, and the hippocampus during recall of suicidal episode; frontal cortical deactivation while recall of the experienced mental pain related past suicidal act
Marchand et al. (2012)	22 MDD patients (5 with suicide attempt)	fMRI: Motor activation task	Decreased activation in the left putamen and altered functional connectivity in the striatal motor-sensory network during motor task in attempters
Matthews et al. (2012)	26 combat exposed-war veterans with MDD or PTSD or TBI (13 with suicidal ideation)	fMRI: Error-processing task	Increased activation in the ACC and PFC during error-processing task in suicidal ideators
Pan et al. (2013)	29 adolescents with MDD (15 suicide attempters) vs. 13 healthy controls	fMRI: Iowa Gambling Task	Hypoactivation in the thalamus and hyperactivation in the caudate during high-risk decisions
Pan et al. (2013)	29 adolescents with MDD (14 suicide attempters) vs. 15 healthy controls	fMRI: Response to facial expressions	Greater reactivity to angry faces in the right dorsal ACC and left dorsolateral PFC, decreased functional connectivity between the right ACC and bilateral posterior insulae
Dombrovski et al. (2013)	33 elder patients with MDD (15 attempters) vs. 20 healthy controls	fMRI: Reward learning using a reinforcement learning model	Weakened expected reward signal in the paralimbic cortex is associated with suicidal behaviour and impulsivity
Fan et al. (2013)	37 MDD patients (10 suicide attempters) vs. 57 healthy controls	fMRI: Resting-state activity	Amplitude of low-frequency fluctuation increased in the right superior temporal gyrus in attempters
Marchand et al. (2013)	20 MDD patients (7 attempters) vs. 21 healthy controls	fMRI: Motor activation task	Striatal motor circuit functional connectivity is significantly associated with past suicidal behaviour in remitted depressive disorder
Minzenberg et al. (2014)	35 schizophrenia patients (18 suicidal ideators)	fMRI: Cognitive control task	Lower activation with goal representation demands in multiple PFC regions
Minzenberg et al. (2015)	30 patients with psychotic mood disorders (8 attempters)	fMRI: Cognitive control task	Past suicidal behaviour was associated with higher control-related activation in right-hemisphere rostrolateral PFC regions; and relatively lower activity in midline parietal regions
Zhang et al. (2016)	53 MDD patients (35 attempters) vs. 47 healthy controls	fMRI: Resting-state activity (DMN)	Increased connectivity in the left cerebellum and the left lingual gyrus and decreased connectivity in the right precuneus associated with suicide attempts
Vanyukov et al. (2016)	26 MDD patients (13 attempters) vs. 22 healthy controls	fMRI: Reward delay discounting task	Longer reward delays were associated with decreased parahippocampal responses. Deactivation of the lateral PFC in response to value difference favouring the immediate option was seen in patients with a history of premeditated attempt.
Cao et al. (2016)	53 MDD patients (35 attempters) vs. 47 health controls (young adults)	fMRI: Resting-state activity	Increased activity in the right superior temporal, left middle temporal, and left middle occipital gyri; decreased activity in the left and middle superior frontal gyri in attempters
Silvers et al. (2016)	60 individuals with borderline personality disorder (46 attempters)	fMRI: Recall of the aversive personal memories task	Elevated activity in the lateral OFC, reduced recruitment of the precuneus during recall of the negative memories in attempters
Du et al. (2017)	48 MDD patients (28 suicidal ideators) vs. 30 healthy controls	fMRI: Resting-state activity	Ideators exhibited decreased functional connectivity between the rostral ACC, the orbitomedial PFC and the right middle temporal pole
Chase et al. (2017)	34 patients with various diagnoses (18 suicide attempters) vs. 40 healthy controls	fMRI: Resting-state activity (DMN)	Increased functional connectivity between the left inferior frontal gyrus and the dorsal PCC in attempters
Johnston et al. (2017)	68 bipolar adolescents and young adults (26 suicide attempters)	fMRI: Response to facial expressions (plus volumetric analysis; DTI)	Lower functional connectivity in the left ventral PFC in response to fearful expression among attempters
Kang et al. (2017)	38 MDD patients (19 attempters)	fMRI: Resting-state activity of the amygdala	Attempters showed an increased resting-state functional connectivity of the left amygdala with the right insula and left superior OFC; the right amygdala with the left middle temporal area
Kim et al. (2017)	14 suicide attempters (various diagnoses) vs. 22 healthy controls	fMRI: facial expressions/suicidal means, DNA methylation status	Methylation degree of CpG site 4 and site 6 was positively correlated with signal intensity in response to negative emotional stimuli in the left middle (site 4) and inferior frontal gyri (site 4), and left thalamus (site 4 and 6). signal intensity in left middle and inferior frontal gyri in attempters.
Baek et al. (2017)	92 MDD patients (45 attempters) vs. 75 health controls	fMRI: Monetary risk and loss aversion tasks	Disrupted neural responses to potential gains and losses in the subgenual ACC, insular cortex and left amygdala.
Just et al. (2017)	17 suicidal ideators with various psychiatric diagnoses vs. 17 controls	fMRI: Neurosemantic analyses	The suicidal group had more clusters of stable voxels in the left inferior parietal region, while had the control group in the anterior frontal regions with the evoked emotions

had significantly decreased 5-HT2A binding. Even greater decrease in 5-HT2A receptors in self-injurious attempters was pronounced compared to those who attempted self-poisoning [98]. Van Heeringen et al. employed the same method in their study and they found that compared to normal controls, attempted

Table 3. Studies of molecular neuroimaging in suicidal populations.

Authors and year	Subjects	Methods	Major findings
Arango et al. (1995)	22 suicide victims with MDD vs. 22 non-suicidal decedents	Autoradiography ([^{3}H]-8-OH-DPAT and [^{3}H]-Cyanoimipramine): 5-HT$_{1A}$ and 5-HTT binding potentials	Increased 5-HT$_{1A}$ receptor and decreased 5-HTT binding potentials in several brain regions, pronounced mostly in ventrolateral PFC, among suicide victims
Stockmeier et al. (1998)	10 suicide victims with MDD vs. 10 non-suicidal decedents	Autoradiography ([^{3}H]-8-OH-DPAT): 5-HT$_{1A}$ binding potential	Increased 5-HT$_{1A}$ receptor binding potential in the dorsal raphe nuclei
Meyer et al. (1999)	14 patients with MDD (3 attempters) vs. 19 healthy controls	PET: ([^{18}F]-setoperon): 5-HT$_{2A}$ binding potential	No significant correlation between 5-HT2A binding and depression or past suicide attempt
Mann et al. (2000)	82 suicide victims with different diagnoses vs. 138 non-suicidal decedents	Autoradiography ([^{3}H]-Cyanoimipramine): 5-HTT binding potential; 5-HTTLPR polymorphism genotyping	Binding to 5-HTT was lower in the ventral PFC of suicides compared with nonsuicides, the 5-HTTLPR genotype was associated with major depression but not with suicide or 5-HTT binding
Audenaert et al. (2001) [99]	9 attempters with various diagnoses vs. 12 healthy controls	SPECT ([^{123}I]-5-[I]-R91150): 5-HT$_{2A}$ binding potential	Suicide attempter group had significantly decreased 5-HT2A binding potential
Arango et al. (2001)	10 suicide victims with MDD vs. 10 non-suicidal decedents	Autoradiography ([^{3}H]-8-OH-DPAT and [^{3}H]-Cyanoimipramine): 5-HT$_{1A}$ and 5-HTT binding potentials; 5-HTT mRNA determination	Low 5-HTT binding capacity and fewer neurons expressing 5-HTT mRNA in the dorsal raphe nuclei in depressed suicides
Audenaert et al. (2002)	20 MDD patients with attempt vs. 20 controls	SPECT ([^{99M}Tc]-ECD) with a verbal fluency task: rCBF measurement	Attempters showed a blunted increase in perfusion in the PFC during neuropsychological activation
Oquendo et al. (2003)	25 MDD patients with a history of suicide attempt	PET ([^{18}F]-FDG) resting-state plus fenfluramine challenge: rCMRglu measurement	Lower metabolism in superior and inferior frontal regions and the ACC in high-lethality attempters relative to low-lethality attempters. This difference was more pronounced after fenfluramine challenge.
Van Heeringen et al. (2003)	9 attempters with various diagnoses vs. 12 healthy controls	SPECT ([^{123}I]-5-[I]-R91150): 5-HT$_{2A}$ binding potential	Attempters had a significantly lower binding potential of frontal 5-HT$_{2A}$ receptors
Lindström et al. (2004)	12 attempters with various diagnoses vs. 12 healthy controls	SPECT ([^{123}I]-β-CIT): 5-HTT and DAT binding potentials	No significant 5-HTT difference between suicidal and non-suicidal groups; a correlation between low 5-HTT and impulsivity among attempters
Oquendo et al. (2006)	37 suicide victims with various diagnoses vs. 73 non-suicidal decedents	Autoradiography ([^{3}H]-ketanserin): 5-HT$_{2A}$ binding potential	Lifetime aggression was found to be positively correlated with higher 5-HT2A binding among suicide victims
Parsey et al. (2006)	25 MDD patients (9 attempters) vs. 43 healthy subjects	PET ([^{11}C]-McN-5652): 5-HTT binding potential	No significant 5-HTT difference between suicidal and non-suicidal groups; correlation between 5-HTT binding potential and MDD in the amygdala and the midbrain
Leyton et al. (2006)	10 attempters with various diagnoses vs. 16 healthy controls	PET (α-[^{11}C]-methyl-L-tryptophan): Tryptophan trapping	Attempters had reduced tryptophan trapping in the orbital and ventromedial PFC
Cannon et al. (2006)	18 bipolar depressed patients (8 attempters) vs. 37 healthy controls	PET ([^{11}C]-DASB): 5-HTT binding potential	Subjects with a history of suicide attempt showed significantly reduced 5-HTT binding in the midbrain and increased binding in the ACC
Ryding et al. (2006)	12 attempters with various diagnoses vs. 12 healthy controls	SPECT ([^{123}I]-β-CIT): 5-HTT and DAT binding potentials	No significant transporter differences between groups No significant transporter differences between groups; a correlation between low 5-HTT and impulsivity/initiative among attempters
Boldrini et al. (2008)	10 suicide victims with MDD vs. 10 non-suicidal decedents	Autoradiography ([^{3}H]-8-OH-DPAT): 5-HT$_{1A}$ binding potential	Increased 5-HT$_{1A}$ receptor binding potential in the dorsal raphe nuclei
Amen et al. (2009)	12 suicide completers with MDD vs. 12 controls	SPECT ([^{99M}Tc]-exametazime) with a continuous performance test: rCBF measurement	A prospective study. Significant perfusion deficits in the medial prefrontal cortex and subgenual areas, and the ventral tegmentum
Willeumier et al. (2011)	21 suicide completers with MDD vs. 27 controls	SPECT ([^{99M}Tc]-HMPAO) with a continuous performance test: rCBF measurement	A prospective study. Significant hypoperfusion in the superior frontal lobes, the subgenual cingulate cortex, the right precuneus, and the rolandic operculum.
Underwood et al. (2012)	15 suicide victims with various diagnoses vs. 15 non-suicidal decedents	Autoradiography ([^{3}H]-8-OH-DPAT, [^{3}H]-Cyanoimipramine, and [^{3}H]-ketanserin): 5-HTT, 5-HT$_{1A}$, and 5-HT$_{2A}$ binding potentials	Lower SERT binding index and higher 5-HT$_{1A}$ receptor binding index in dorsal and ventral PFC in depressed suicides. No differences were observed in 5 HT$_{2A}$ binding or in 5-HT$_{2A}$ binding index.
Miller et al. (2013)	51 MDD patients (15 attempters) vs. 32 healthy controls	PET ([^{11}C]-DASB): 5-HTT binding potential	Lower 5-HTT binding in the midbrain of the suicide attempters with MDD
Sublette et al. (2013)	29 patients with MDD or bipolar (13 attempters)	PET ([^{18}F]-FDG) plus fenfluramine challenge: rCMRglu measurement	Lower rCMRglu in the right dorsolateral PFC among suicide attempters; while hypometabolic area differences became bilateral with fenfluramine challenge.
Nye et al. (2013)	11 suicide attempters with MDD vs. 10 controls	PET ([^{11}C]-ZIENT): 5-HTT binding potential	Reduced 5-HTT binding potential in the midbrain, pons, and putamen of MDD patients with a history of suicide attempt
Soloff et al. (2014)	33 individuals with borderline personality disorder (21 attempters) vs. 27 healthy controls	PET: ([^{18}F]-altanserin): 5-HT$_{2A}$ binding potential	No significant relationship between 5-HT2A receptor function and suicidality

(*Continued*)

Table 3. Continued.

Authors and year	Subjects	Methods	Major findings
Ballard et al. (2015)	20 MDD patients (12 suicidal ideators)	PET ([^{18}F]-FDG) resting-state activity plus ketamine infusion: rCMRglu measurement	Baseline suicidal ideation and regional cerebral glucose metabolism in the infralimbic cortex were significantly correlated
Sullivan et al. (2015)	91 MDD patients (29 with a history of suicide attempt)	PET ([^{11}C]-WAY-100635): 5-HT$_{1A}$ binding potential	Elevated 5-HT$_{1A}$ binding potential particularly in raphe nuclei may indicate higher lethality of past and future suicide attempts in depressed individuals
Pu et al. (2015)	67 MDD patients (31 suicidal ideators) vs. 67 healthy controls	Near-infrared spectroscopy with verbal fluency task: regional cerebral oxy-hemoglobin measurement	Smaller hemodynamic changes during the task in the right dorsolateral PFC, the OFC, and the frontopolar cortex in the MDD patients with suicidal thoughts
Yeh et al. (2015)	17 MDD patients (8 attempters) vs. 17 healthy controls	PET (4-[^{18}F]-ADAM): 5-HTT binding potential	Lower 5-HTT binding in the midbrain, the thalamus and the striatum of the suicide attempters with MDD
Oquendo et al. (2016)	100 MDD patients (51 with a history of suicide attempt)	PET ([^{11}C]-WAY-100635 and [^{11}C]-DASB): 5-HT$_{1A}$ and 5-HTT binding potentials	Greater RN serotonin1A binding potential predicted higher suicidal ideation and more lethal suicidal behaviour during a two-year period. The midbrain serotonin transporter binding potential did not predict future attempts
Van Heeringen et al. (2017)	40 MDD patients (17 suicide planners) vs. 20 healthy controls	PET ([^{18}F]-FDG) resting-state activity: rCMRglu measurement	Depressed individuals with suicide plans showed relative hypometabolism in the right middle frontal gyrus and the right inferior parietal lobe
Jollant et al. (2017)	25 MDD patients (15 attempters) vs. 33 healthy controls	Proton magnetic resonance spectroscopy: Resting-state measurement of biomarkers	Neuronal and glial functioning was indirectly examined with measuring biochemical markers in MDD patients and lower *N-acetylaspartate* levels, and higher glutamine levels were noted in suicide attempters
Tsuji et al. (2017)	68 MDD patients (30 attempters) vs. 40 healthy controls	Near-infrared spectroscopy with verbal fluency task: regional cerebral oxy-hemoglobin measurement	Smaller hemodynamic changes during the task in the left precentral gyrus in the attempters

suicide patients had a significantly lower binding potential of frontal 5-HT2A receptors, a higher level of hopelessness, a higher score on the temperament dimension of harm avoidance and lower scores on the character dimensions self-directedness and cooperativeness per Cloninger's personality model [100]. In a group of individuals with BPD, Soloff et al. failed to demonstrate a significant relationship between 5-HT2A receptor function and suicidality [101]. Despite limited molecular imaging work on 5-HT2A, this receptor subtype is regarded more important target for future research and perhaps further molecular imaging studies will elucidate a role for this receptor in suicidal behaviour.

Other molecular neuroimaging studies

In addition to the serotonin transporter and receptor investigations in suicidal population, Leyton and colleagues indirectly examined capacity of serotonin synthesis, using PET and α-[^{11}C]-methyl-L-trytophan trapping in patients with high-lethality suicide attempt. Compared to control group, attempters had reduced tryptophan trapping in the orbital and ventromedial PFC which may reflect the hypothesis that low serotonin synthesis in the PFC lowers the threshold for suicidal behaviour [102]. Involvement of the PFC impairment in suicidality was also pronounced in two studies measuring regional cerebral blood flow (rCBF) with SPECT. It was found that rCBF was significantly decreased in the medial PFC, subgenual areas, and the ventral tegmentum in the suicidal group. Perfusion deficits in these areas were implicated to be in relation with impaired impulse control and limbic dysregulation that predisposing to suicidal behaviour [103,104]. Besides examination of serotonergic system's involvement in the aetiopathogenesis of suicide, various works with different measurements, such as glucose uptake ratio were also conducted. Oquendo and colleagues categorized suicidal MDD patients into two; patients with a history of a high-lethality suicide attempt and patients with a low-lethality suicide attempt. They compared two groups with respect to relative regional rates of glucose metabolism (rCMRglu) using [^{18}F]-FDG PET and identified lower metabolism in superior and inferior frontal regions and the ACC in high-lethality attempters relative to low-lethality attempters. This difference was more pronounced after fenfluramine challenge, which causes massive serotonin release [105]. Another study using PET with MDD and bipolar patients has revealed lower rCMRglu in the right dorsolateral PFC among suicide attempters; while hypometabolic area differences became bilateral with fenfluramine challenge [106]. In a study with SPECT, Audenart et al. examined regional cortical activation during a neuropsychological task, Verbal Fluency Test, by measuring a radiotracer's ([^{99M}Tc]-ECD perfusion quotient among suicide attempters with MDD. They have found that attempters showed a blunted increase in perfusion in the PFC during neuropsychological activation. They speculated that blunted increase in

prefrontal blood perfusion during the task may indicate a possible biological reason for reduced drive and loss of initiative in suicide attempters [107]. Two other studies replicated this one using near-infrared spectroscopy and found smaller hemodynamic changes in the right dorsolateral PFC, the OFC, the frontopolar cortex, and the left precentral gyrus in MDD patients with suicidality [108,109]. Infralimbic dysfunction, and hypometabolism in the right middle frontal gyri and the right inferior parietal lobe were also implicated in the aetiopathogenesis of the suicidal ideation [110,111]. In a recent proton magnetic resonance spectroscopy study, neuronal and glial functioning was indirectly examined with measuring biochemical markers in MDD patients and lower N-acetylaspartate levels and higher glutamine levels were noted in suicide attempters [112].

Conclusions

Neuroimaging has fundamentally transformed the way psychiatric researchers study the pathophysiology of suicidal behaviour in the living brain. It has provided many different quantitative measures including morphometry, functional activity, and metabolism. Tables 1 –3 illustrate the key studies of structural, functional, and molecular neuroimaging in the field and summarized the major findings described throughout this article. This review highlights the value of imaging in this field of research. Many of the postulated theories on neurobiological dysfunction in suicide and its related disorders can be thoroughly vetted through the use of any of the imaging technologies mentioned above. As can be seen, earlier attempts at studying suicidal behaviour were largely dominated by MRI techniques. Nevertheless, in recent years, the use of molecular imaging, particularly PET and SPECT, has greatly increased as a result of academic centres equipping high-resolution scanners and investing larger resources into novel ligand development. On the other hand, structural and functional MRIs were expected to resume playing an essential role in the investigation of all psychiatric conditions, including suicide. However, it may be assumed that future work will be led by combined molecular neuroimaging modalities due to its unique ability to examine neurobiochemical systems with greater specificity in vivo. It is clear that neuroimaging will continue to play a critical role in suicide research and much uncovered still exists to be figured out by future studies. As such novel brain-imaging studies provide crucial information on the neural circuitry associated with suicide risk, we assume that pharmacologic and behavioural interventions would be more influential in suicide risk reduction.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Yasin Hasan Balcioglu http://orcid.org/0000-0002-1336-1724
Samet Kose http://orcid.org/0000-0003-0841-004X

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