Functional Brain Imaging of Suicidal Behavior

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Abstract

This chapter provides a review of the literature on positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging studies of suicidal thoughts and behavior. Main findings from the review include a reduced prefrontal perfusion or metabolism in association with a history of suicide attempts or with suicidal ideation. Studies in resting conditions but especially studies using activation paradigms point at a basal hypofunction with a blunted increase in activation when challenged. Moreover, impairment of the prefrontal serotonergic system in association with suicidal behavior is demonstrated in a number of studies. A substantial number of methodological issues however hamper the interpretation of findings. Future neuroimaging studies need to take these issues into account in order to contribute to our understanding of the neurobiological mechanisms underlying suicidal behavior and thus to the prediction, treatment, and prevention of this important public health problem.

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Abbreviations

BP	Binding potential
DAT	Dopamine transporter
MDD	Major Depressive Disorder
PET	Positron Emission Tomography
rCMRglu	Regional cerebral metabolic rate of glucose uptake
SERT	Serotonin transporter
SPECT	Single Photon Emission Computed Tomography

6.1 Introduction

The World Health Organization estimates that one million people die from suicide each year, which reflects a global annual suicide rate of 16 per 100,000 or one death every 40 s. Suicide is among the three leading causes of death in people aged 15–44 years. These figures do not include suicide attempts, which are estimated to occur up to 20 times more frequently than completed suicide. The individual and socioeconomic costs are enormous, so prevention programs have been developed in many countries worldwide.

Difficulties in predicting suicidal behavior, even among individuals at high risk, pose however a major challenge to adequate prevention. Limited knowledge of predisposing characteristics contributes to these difficulties. It has become clear that depressed suicidal patients can be distinguished from depressed non-suicidal individuals based on trait-dependent characteristics, which constitute their predisposition for suicidal behavior. Based on current knowledge, a stress-diathesis model has therefore been proposed to explain the interactions between proximal risk factors (such as depression) and these predisposing characteristics (Hawton and van Heeringen 2009).

Neuroimaging studies of depression are discussed in detail elsewhere in this book. This chapter will focus on the use of neuroimaging techniques to study the vulnerability to suicidal behavior. Neuroimaging studies have many advantages over the postmortem studies, which were, until recently, the only approach to the study of changes in brain functions in association with suicidal behavior. In vivo functional neuroimaging of the suicidal brain not only avoids the many methodological drawbacks of postmortem research but also provides the possibility of assessing personality-related, cognitive, and emotional characteristics of suicidal individuals in order to study correlations between cerebral dysfunctions and their cognitive and emotional manifestations, which may contribute to the vulnerability to suicidal behavior (Desmyter et al. 2011).

6.2 Methods

The literature on PET and SPECT imaging studies of the brain in individuals with a history of nonfatal suicidal behavior was reviewed. Literature searches were performed with the search engines “Pubmed” and “Web of Science” using the following

keywords: single photon emission tomography, single photon emission computed tomography, SPET, SPECT, positron emission tomography, PET, and suicide. The first selection was made through an inspection of the abstracts. Although most studies were published in the last decade, the search was performed without a time limit. The reference lists of the selected articles were also checked for additional publications.

6.3 Results/Review of the Literature

The studies in which PET or SPECT brain imaging techniques were used to examine differences between suicidal and non-suicidal subjects will be described in chronological order, starting with PET studies. Table 6.1 summarizes the sample characteristics and limitations of the reported studies.

6.3.1 PET Studies

Oquendo and colleagues published an interesting study in 2003, in which they investigated the brains of 16 high-lethality and 9 low-lethality suicide attempters having a depressive episode. The patients were scanned in resting condition with ^{18}F-FDG PET imaging in order to estimate regional brain activity in conditions where external activation is minimized or standardized. Subjects were scanned after a single-blind placebo and after fenfluramine hydrochloride administration on a second day. Fenfluramine is a serotonin agonist that provokes an increase in the presynaptic release of serotonin. Secondary and proportional to this postsynaptic receptor stimulation, the anterior pituitary gland releases prolactin in the circulation. If the serotonergic system is impaired, a blunted increase in prolactin is found (Malone et al. 1996; Correa et al. 2000). Besides an increase in prolactin, fenfluramine also increases frontal cortex metabolism (Soloff et al. 2003). The authors found that depressed high-lethality suicide attempters showed relative hypometabolism compared to low-lethality attempters in the ventral, medial, and lateral prefrontal cortex. This difference was more pronounced after fenfluramine administration. Lethality of the attempt appeared to be inversely correlated with metabolism in the ventromedial prefrontal cortex after challenge with fenfluramine. A lower mean regional cerebral metabolic rate of glucose uptake (rCMRglu) correlated with higher lethality of suicidal behavior. The authors also demonstrated that higher verbal fluency correlated positively with rCMRglu in the same regions of the prefrontal cortex and that lethality of the suicide attempt inversely correlated with prolactin after challenge. They found a lower CMRglu in high- versus low-lethality suicide attempters. This hypometabolism in frontal cortex structures was related to the degree of suicide intent and impulsivity and not to depression (Oquendo et al. 2003).

Leyton and coworkers (2006) measured regional serotonin synthesis in the brain with PET and α-(^{11}C)-methyl-L-tryptophan trapping in ten patients who had made a high-lethality suicide attempt and in 16 healthy controls. Suicide attempters showed reduced serotonin synthesis in the orbital and ventromedial prefrontal cortices. α-(^{11}C)-methyl-L-tryptophan trapping in these regions correlated negatively with

Table 6.1 Functional neuroimaging of suicidal behaviour – key features of PET and SPECT studies of suicide attempters

Study[a]	Design[b]	Targeted brain region[c]	Subjects[d]	Limitations
PET				
Oquendo et al. (2003)	PET: Regional brain serotonergic function	Whole brain	25 patients (M+F) meeting DSM-III-R criteria of a major depressive episode and who have attempted suicide: 16 patients had a history of high-lethality suicide attempts (mean 42.9 years), 9 patients had a history of lo-lethality suicide attempts (mean 30.4 years)	Small sample size; direct brain injuries not ruled out
Leyton et al. (2006)	PET: α[^{11}C]MTrp trapping	PFC	26 subjects (M+F): 10 patients have attempted suicide (mean 37.7 years) and 16 healthy subject (mean 35.5 years)	Effects of drugs on 5-HT transmission; small sample size; imaging technique possibly not the best to assess 5-HT neurotransmission
SPECT				
Audenaert et al. (2001)	SPET: Serotonin-$_{2A}$ receptor functioning	Frontal cortex	21 subjects, mean 30.4 years (M+F): 9 patients who have attempted suicide and 12 healthy subjects	Impact of alcohol and medication on clearance of the ligand; possible effect of physical trauma on binding index
Audenaert et al. (2002)*	SPECT: Binding potential	Whole brain PFC	40 subjects (M+F): 20 depressed patients who recently (< 7 days) attempted suicide (19–49 years) and 20 healthy subjects (18–50)	Influence of medication; selection bias; at random division of subgroups
van Heeringen et al. (2003)	SPECT: Serotonin-$_{2A}$ receptor functioning	PFC	21 subjects (M+F): 9 patients who have attempted suicide (mean 32.4 years) and 12 healthy subjects (mean 28.9 years)	Small sample size; composition of patient sample; effects of alcohol and medication; possible effect of physical trauma on binding index
Lindström et al. (2004)	SPECT: Brain serotonin and dopamine transporters	Whole brain	24 subjects, mean 38.8 years (M+F): 12 patients who attempted suicide (5 violent and 7 non violent) and 12 healthy matched subjects	Possible type 2 error

Ryding et al. (2006)	SPECT: Serotonin transporter and dopamine transporter	Whole brain	24 subjects (M + F): 12 patients who attempted suicide (mean 38.8 years) and 12 matched healthy subjects	
Amen et al. (2009)	SPECT: In vivo brain differences	Whole brain PFC Subgenual cingulate	36 subjects (M + F): 12 patients meeting DSM-IV criteria for depression who committed suicide since the brain imaging (mean 33.8 years), 12 patients meeting DSM-IV criteria for depression who did not commit suicide and 12 healthy subjects	Heterogeneous sample; medication; lack of data for all subjects
Willeumier et al. (2011)	SPECT: Technetium-99 m hexamethylpropylene amine oxime brain uptake	Whole brain	84 subjects (M + F): 21 patients meeting DSM-IV criteria for depression who committed suicide since the brain imaging (mean 36 years), 36 matched non-suicidal depressed subjects (mean 36 years) and 27 matched healthy subjects (mean 35 years)	Follow-up study of Amen et al. (2009), with only 9 additional patients who committed suicide
van Heeringen et al. (2010)	SPECT: Regional cerebral blood flow under resting conditions	Whole brain	39 subjects (M + F): 39 admitted patients, treated for a depressive episode according to DSM-IV-TR criteria, subdivided in 3 groups according to level of mental pain	Impact of medication

[a] *Study*: *Study of good methodological quality
[b] *Design*: *PET* Positron Emission Tomography, *SPECT* Single Photon Emission Computed Tomography, *SPET* Single Photon Emission Tomography, *α[11C]MTrp* α-[11C]methyl-l-tryptophan
[c] *Targeted brain region*: *PFC* prefrontal cortex
[d] *Subjects*: *BD* bipolar disorder, *BD-I* bipolar depression type I, *BD-II* bipolar depression type II, *BPD* borderline personality disorder, *F* Female, *M* Male, *MDD* major depressive disorder

suicide intent. Elevated α-(^{11}C)-methyl-L-tryptophan trapping was seen in the left thalamus, right paracentral lobule, and the left middle occipital cortex. The investigators concluded that low serotonin synthesis in the prefrontal cortex might lower the threshold for suicidal behavior.

6.3.2 SPECT Studies

A few studies used SPECT imaging to study functional changes in brain functions. Audenaert and coworkers (2001) studied nine patients who had recently (1–7 days) attempted suicide and compared these to 12 age-matched healthy controls using ^{123}I-5-I-R91150 SPECT. They found a significantly reduced binding index in the frontal cortex in the patient group. The binding index was significantly lower in the deliberate self-injury patients compared to the deliberate self-poisoning subjects. The results indicate a decrease in the number and/or in the binding affinity of 5-HT_{2A} receptors. Further analysis revealed a significant negative correlation between 5-HT_{2A}-receptor binding and levels of hopelessness, a very important clinical predictor of suicidal behavior (van Heeringen et al. 2003).

In a split-dose ^{99m}Tc-ECD SPECT activation paradigm, Audenaert and colleagues (2001) included 20 depressed patients who had recently attempted suicide and compared them to 20 healthy volunteers. The neuropsychological activation consisted of a verbal fluency test. When compared to healthy volunteers, patients showed a blunted increase in perfusion in the prefrontal cortex during specific verbal fluency tasks. When comparing the activated brain regions between healthy volunteers and patients in the category fluency paradigm, a statistically significant blunting of the perfusion was observed in the patient group in the left gyrus frontalis inferior, right gyrus parietalis inferior, and bilateral gyrus cinguli anterior. There were no regions with significantly increased perfusion in the patient group compared to the controls. When comparing the activated brain regions between healthy and depressed subjects in the letter fluency paradigm, the authors found a statistically significant blunting of the perfusion in the depressed group in the left and right gyrus temporalis medius, right gyrus cinguli anterior, and hypothalamic region. There were no regions with significantly increased perfusion in the patient group compared to control subjects. The authors suggest that the blunted increase in prefrontal blood perfusion might be a biological reason for reduced drive and loss of initiative in attempted suicide patients.

Serotonin and dopamine transporter binding in association with suicidal behavior was assessed in two SPECT studies using the mixed monoamine transporter tracer ^{123}I-β-CIT. Lindström and colleagues (2004) measured the whole brain binding potential (BP) of the serotonin transporter (SERT) and dopamine transporter (DAT) in 12 patients after a serious suicide attempt and in 12 matched healthy controls. No significant differences in BP between study groups were found. In patients, but not in controls, there was a significant correlation between whole brain 5HTT and DAT BP. In suicide attempters, high impulsiveness was significantly correlated with low SERT BP, which was not found in controls. Ryding and coworkers

(2006) further analyzed the measurements of the previous study, examining regional serotonin reuptake (5HTT) and dopamine reuptake (DAT) capacity (binding potential, BP). They observed no significant difference concerning the regional levels of SERT or DAT binding potential. However, they found regional significant negative correlations between SERT BP and impulsiveness among suicide attempters but not in controls. Significant correlations between solidity (the level of initiative or impulsivity) and local 5-HTT BP in suicide attempters were found in the right inferior frontal (orbital) and bilateral temporal cortical regions, subcortically in the midbrain, thalamic and bilateral basal ganglia regions, and in the left cerebellar hemisphere. Moreover, the patients showed a significant negative correlation between whole brain DAT BP and mental energy. Regional significant correlations were found solely in bilateral basal ganglia regions. These correlations were not found in controls.

Amen and colleagues (2009) carried out a study using brain ^{99m}Tc HMPAO SPECT imaging at rest and during a cognitive activation task. They compared the brain scans of 12 psychiatric inpatients, who committed suicide between 10 days and 36 months after the scan, with 12 non-suicidal depressed subjects and 12 healthy controls. Comparing the suicide versus the control group in resting condition, they noted generally lower regional cerebral blood flow in the suicide patients throughout the cortex, with no clusters of high activity. Reduced perfusion was found in the premotor and primary motor cortex, corpus callosum, cingulate, and anterodorsal cortex. A significant area of low activity was the nucleus accumbens, extending into the ventromedial prefrontal cortex, into the left and right putamen. When comparing the suicide group with the non-suicidal depressed group, hemispheric asymmetries were found with the suicide patients showing significantly higher perfusion in the right hemisphere with no relative regional cerebral blood flow deficits. The largest cluster of increased perfusion centered in the right insular cortex. Subjects were additionally challenged with Conner's Continuous Performance Test, a 15-min computerized go/no go task measuring omissions, commissions, and reaction time. The perfusion deficits present at baseline were attenuated in the depressed group but exacerbated in the suicide group during concentration. The authors noted that deficits in the middle and frontal gyri were better perfused in non-suicide depressed patients, but degraded in suicide subjects during concentration. The authors generally concluded that the results were consistent with prior imaging studies on depression and were indicative of impaired impulse control and limbic dysregulation, including significant perfusion deficits in the medial, prefrontal, and subgenual areas and ventral tegmentum.

In an extension of the previous study, the study group included nine additional patients who committed suicide after the SPECT scan. When the scanning data of these 21 patients were compared with those from a group of 27 healthy subjects and another control group of 36 non-suicidal depressed persons, global decreases in blood flow and activity patterns in the suicide group versus the healthy control group were found. This decrease was most pronounced in the precuneus and the prefrontal cortex. Other deficits were found in the rolandic operculum, postcentral

gyrus, the caudate, thalamus, and insular cortex. When comparing the suicide group and the matched non-suicide depressed patients, more subtle, global decreases in blood flow and activity patterns were observed. In the cohort of completed suicides, the subgenual cortex appeared to be hypoperfused in 18 patients as compared with the healthy control group (Willeumier et al. 2011).

The functional neuroanatomy of mental pain in depression was investigated by Van Heeringen and colleagues (2010) in a group of depressed individuals using ^{99m}Tc-ECD SPECT. They found that, when compared with patients with low levels of mental pain, those with high levels of mental pain showed relatively increased perfusion in the right dorsolateral prefrontal cortex, occipital cortex and inferior frontal gyrus, and in the left inferior temporal gyrus and relatively decreased perfusion in the medulla. The findings point at an association between mental pain in depressed patients and an increased risk of suicide and between high levels of mental pain and changes in perfusion in brain areas that are involved in the regulation of emotions.

6.4 Discussion

The findings from this review of the literature on PET and SPECT imaging studies of suicidal behavior can be summarized as follows. Overall, a reduced prefrontal perfusion or metabolism in association with a history of suicide attempts or with suicidal ideation is the most robust finding from these perfusion and metabolism studies of the brain of patients vulnerable to suicidal behavior. Studies in resting conditions but especially studies in activation conditions support a basal hypofunction with a blunted increase in activation when challenged. Moreover, impairment of the prefrontal serotonergic system of these patients was demonstrated in a number of studies.

Before drawing any conclusions concerning the impact of this research on our knowledge of the suicidal brain and thus on the prediction and prevention of suicidal behavior, several methodological issues need to be addressed. The comparison of findings from different studies is hampered by differences in techniques of imaging and analysis. Moreover, the description of anatomical localizations of findings is not identical between the study groups. The definitions of suicidal behavior also differ ranging from a history of suicide attempts or thoughts to current suicidal ideations or intentions. Clear descriptions of the study populations were rather scarce and imprecise. Moreover, the studies that have been carried out with PET and SPECT were done in small sample size groups, which limit the power to detect small group differences or which can amplify individual differences due to biological heterogeneity. In some studies, patients and controls were not matched for potential biasing characteristics such as demographic variables, psychiatric comorbidity, and treatment. Finally, the study population used in more recent studies all consist of patients with a history of suicide attempts, while the studies dated from before 2006 generally studied recent severe suicide attempts, limiting the comparability between these studies.

Taken together, these methodological issues raise the question to what extent the current findings from PET and SPECT studies of suicidal behavior may help to understand the neurobiological basis of this behavior.

At this point, the application of PET and SPECT imaging to the problem of suicidal behavior is research oriented, and there is currently no indication for routine functional neuroimaging in the diagnosis of suicide risk. The significant correlation between decreased binding potential of prefrontal 5-HT_{2A} receptors and increased levels of hopelessness in patients vulnerable to suicidal behavior is one of the most clinically relevant findings. There was consistence in reports of a reduced prefrontal blood perfusion during verbal fluency tasks in suicidal patients. High levels of mental pain are associated with changes in perfusion in brain areas that are involved in the regulation of emotion.

Our review of neuroimaging studies of suicidal behavior published between 1990 and 2010 (van Heeringen et al. 2011) led to the conclusion that many brain areas appear to be involved, including the prefrontal cortex, the limbic system, the basal ganglia, and extensive connections between these areas. A more recent review (Desmyter et al. 2013), which includes a substantial number of more recent studies, narrows the focus of attention by suggesting that suicidal behavior is associated particularly with changes in a fronto-cingulo-striatal network. Recent neurobiological research outside the suicidological domain has clearly demonstrated the major role of this network in decision-making.

Most probably not coincidentally, recent neuropsychological studies in suicide attempters have also identified changes in decision-making processes as crucial characteristics of the predisposition to suicidal behavior. Violent suicide attempters differ from affective controls in their performance on a decision-making task in that suicide attempters make more disadvantageous choices, i.e., choose options with high immediate reward (Jollant et al. 2008). A subsequent functional neuroimaging study indeed showed that suicide attempters (1) performed worse on a decision-making task than affective controls and (2) showed reduced activation in the orbitofrontal (and occipital) cortex for the contrast between risky (disadvantageous) and safe (advantageous) choices (Jollant et al. 2010). The insufficient contrast between risky and safe choices prevents advantageous guiding of long-term behavior.

Taken together with the results from recent functional MRI studies, these findings suggest, first, that suicidal behavior is associated with disturbances in the attribution of importance to stimuli, i.e., undue importance to signals of others disapproval and insufficient importance to risky choices. Secondly, changes in the prefrontalstriatal network are associated with changes in the representation of value to different outcome options, which may lead to the choice of immediate reward over abstract and delayed reward in the process of decision-making. The development of unbearable emotional pain following perception of signals of others' disapproval may be associated with a choice for immediate alleviation of pain, not taking into account the possibility of a better future. Disturbed intertemporal reward discounting may thus play an important role in the vulnerability to suicidal behavior. As the serotonergic neurotransmission system is involved in the modulation of this process of delay discounting (Schweighofer et al. 2007), this may explain

the demonstrated association between prefrontal serotonergic dysfunctioning and levels of hopelessness in suicide attempters.

Further research is necessary, and functional neuroimaging will help us to better understand the underlying neurobiological mechanisms of suicidal behavior.

Future research with PET and SPECT should clearly describe study populations and study targets, i.e., suicidal behavior, history, and/or thoughts. These targets may indeed be characterized by different underlying neurobiological mechanisms. Moreover, it is of great importance to have an affective control group (e.g., depressed patients without a history of suicide) next to healthy controls to rule out the effects of this psychiatric disorder on the imaging results of suicidal behavior. In addition, the increasing use of functional magnetic resonance imaging, which already has provided promising results (Jollant et al. 2008, 2010; Reisch et al. 2010; Dombrovski et al. 2012), will further broaden our knowledge particularly in the context of multimodal imaging, i.e., the combination of different imaging techniques in one study.

Future neuroimaging studies can be expected to contribute to a greater understanding of the mechanisms underlying suicidal behavior by studying associations between relevant characteristics (e.g., hopelessness, impulsivity, interpersonal sensitivity) and brain functions, thereby targeting particular brain areas such as the prefrontal-striatal network. Such studies may well facilitate the development of neurocognitive biomarkers for suicidal behavior, which will be of great clinical importance by increasing the possibilities to predict the occurrence of suicidal behavior. The growing knowledge of the neurobiological mechanism underlying suicidal behavior can be expected to help the clinician in detecting and preventing suicidal behavior. Moreover, brain imaging has promising prospects concerning the evaluation of the effect of treatments such as medication, psychotherapy, and neuromodulation techniques.

Conclusion

In spite of the substantial impact of suicidal behavior at individual, social, and public health levels, relatively few neuroimaging studies have been carried out using PET or SPECT in suicidal populations. Overall, the most robust findings in suicidal patients are a relative hypometabolism and impairment of the serotonergic system in the prefrontal cortex. Several methodological issues make it difficult to come to conclusions at this point. Further neuroimaging research is necessary to elucidate the neurobiological mechanisms underlying suicidal behavior in order to increase possibilities of prediction, treatment, and prevention.

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