Evidence of an association between a vulnerability to suicidal behaviour and neurobiological abnormalities is accumulating. Post-mortem studies have demonstrated structural and biochemical changes in the brains of suicide victims. More recently, imaging techniques have become available to study changes in the brain in vivo. This systematic review of comparative imaging studies of suicidal brains shows that changes in the structure and functions of the brain in association with suicidal behaviour are mainly found in the orbitofrontal and dorsolateral parts of the prefrontal cortex. Correlational studies suggest that these changes relate to neuropsychological disturbances in decision-making, problem solving and fluency, respectively. As a consequence, the findings from these studies suggest that suicidal behaviour is associated with (1) a particular sensitivity to social disapproval, (2) choosing options with high immediate reward and (3) a reduced ability to generate positive future events. Further study is needed to elaborate these findings and to investigate to what extent changes in the structure and function of suicidal brains are amenable to psychological and/or biological interventions.
public health problem, and costs at societal and individual levels are huge. In addition, suicidal behaviour poses a major challenge to clinicians, health care workers and policy makers due to its limited predictability (Hawton and van Heeringen, 2009). Problems in predicting and thus preventing suicidal behaviour are due to the multiplicity of possible causes and a limited insight in predisposing mechanisms.

Based upon the current state of knowledge a stress-diathesis model of suicidal behaviour has been proposed to describe the interaction between proximal risk factors and such predisposing mechanisms (Hawton and van Heeringen, 2009). The vast majority of suicidal behaviours are associated with depression, but indeed require the presence of an additional diathesis or predisposition. In vivo brain imaging is a promising tool for the investigation of the diathesis predisposing to suicidal behaviour, and the last decade has witnessed a steady increase in the number of such studies (Mann, 2005). A first advantage of using brain-imaging techniques is to confirm post-mortem findings of involved brain areas and neurobiological systems such as the serotonin system. Second, brain imaging provides a possibility to demonstrate a biological substrate for neuropsychological changes in relation to suicidal behaviour, thus providing support of a causal interpretation of this relation.

The findings from brain-imaging studies have not been systematically reviewed yet. Imaging studies of suicidal behaviour fall into two broad categories, i.e. the study of the neural correlates of suicidal behaviour directly, and studies addressing clinical traits typically associated with suicidal behaviour, such as aggressive and impulsive behaviours. The current review focuses on the first category of studies and therefore aims at the identification, synthesis and appraisal of structural and functional neuroimaging studies of suicidal behaviour.

2. Methods

A comprehensive literature search yielded the set of relevant articles for this review. First, we did an electronic search using the Web of Science, MEDLINE, PsycINFO (and PubMed) databases for articles published in English, from 1990 onward. Search terms were suicidal, suicide, suicide attempt, and imaging, CT, MRI, SPECT, PET, fMRI, DTI. Unpublished studies, case reports or conference abstracts were not included in this review. Second, the reference lists of relevant papers were checked manually for additional relevant publications not previously identified. Studies, for which electronic full text was available, were selected if based on commonly used...
imaging techniques and if individuals were included with a history of suicidal behaviour.

2.1. Selection criteria

Inclusion of studies in this review was based on three criteria. First, studies needed to report neuroanatomical differences between study groups composed of individuals with a history of suicide attempts (suicide attempters; SA) and those without a history of such behaviour. Studies comparing two groups of SA with different characteristics were also included. Second, taking into account the heterogeneity of definitions of suicidal behaviour, studies in order to be included needed to provide clear definitions of suicidal behaviour. Third, studies were included only if Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI) or Diffusion Tensor Imaging (DTI) were used as imaging techniques.

3. Results

As shown in Fig. 1, the search produced 550 publications. Twenty-two articles met the inclusion criteria and were thus included in this review, categorized as ‘structural imaging studies’ (CT, MRI, DTI) or ‘functional imaging studies’ (SPECT, PET, fMRI).

In the following part of the paper, studies will be reviewed in chronological order; studies from the same research group are reported together. Table 1 summarizes the sample characteristics and detailed results of the reported studies. Figs. 2–5 summarize the main results in a visual manner.

Good quality of included studies has been ensured by the use of strict criteria. Among the selected articles, the good quality of the studies by Audenaert et al. (2002), Meyer et al. (2003), Ehrlich et al. (2005), Monkul et al. (2007), Jovev et al. (2008), Pompili et al. (2008) and Jollant et al. (2008, 2010) is noteworthy due to the control for comorbidity, specifically for depression.

3.1. Structural imaging studies

3.1.1. CT

No studies of suicidal behaviour using CT and meeting the selection criteria were found.

3.1.2. MRI

Structural imaging, using MRI, within the suicide research can be divided into two main fields.

3.1.2.1. White matter hyperintensities. A substantial number of studies have demonstrated an association between suicidal behaviour and white matter hyperintensities (WMH), i.e. deep WMH (DWMH), periventricular hyperintensities (PVH) or subcortical gray matter hyperintensities (SCH).

Ahearn et al. (2001) were the first to demonstrate hyperintensities associated with a history of SA. As noted in Table 1, SA had significantly more SCH and tended to have more PVH than controls. Ehrlich et al. (2004) reported an increased prevalence of WMH (particularly PVH) in (psychiatrically hospitalized) children and youth with unipolar depression and a history of SA. Unipolar depressed subjects with WMH were 18.6 times more likely to have a history of SA than subjects with unipolar depression or another psychiatric disorder with no evidence of WMH. There was no significant
Table 1  
Neuroimaging of suicidal behaviour—key features of brain-imaging studies of suicide attempters.

<table>
<thead>
<tr>
<th>Study^a</th>
<th>Design^b</th>
<th>Targeted brain region^c</th>
<th>Subjects^d</th>
<th>Results^e</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahearn et al. (2001)</td>
<td>MRI: hyperintensities</td>
<td>Whole brain</td>
<td>40 unipolar depressed patients (M + F): 20 patients have attempted suicide (mean 66.0 yr) and 20 patients have not attempted suicide (mean 66.4 yr)</td>
<td>Significantly more SCH and PVH in the patients who attempted suicide</td>
<td>Small sample size; age of first suicide attempt and severity of each depressive episode not available</td>
</tr>
<tr>
<td>Ehrlich et al. (2004)</td>
<td>MRI: hyperintensities</td>
<td>Whole brain</td>
<td>153 patients with a primary DSM-III-R or IV Axis I diagnosis (M + F), 6–21 yr</td>
<td>Patients with unipolar depression and white matter hyperintensities have increased prevalence of suicide attempts</td>
<td>No comparison group; no assessment of comorbidity; small sample size; unclear causality</td>
</tr>
<tr>
<td>Ehrlich et al. (2005)^f</td>
<td>MRI: T2 hyperintensities</td>
<td>Whole brain</td>
<td>102 young adult patients with MDD (M + F), mean 26.7 yr</td>
<td>Significant increase in prevalence of PVH (not DWMH) in patients who attempted suicide</td>
<td>Possible selection bias; age and severity of suicide attempt not taken into account; unclear causality</td>
</tr>
<tr>
<td>Monkul et al. (2007)^g</td>
<td>MRI: fronto-limbic brain abnormalities</td>
<td>OFC amygdala cingulate hippocampus</td>
<td>34 unipolar depressed patients (F): 7 patients have attempted suicide (mean 31.4 yr), 10 patients have not attempted suicide (mean 36.5) and 17 subjects did not attempt suicide or have a unipolar depression (mean 31.3 yr)</td>
<td>Smaller bilateral OFC gray matter volume and larger right amygdala volume in patients who attempted suicide</td>
<td>Possible wrong evaluation of severity of depressive episode; small sample size; study limited to women</td>
</tr>
<tr>
<td>Pompili et al. (2007)</td>
<td>MRI: White matter hyperintensities</td>
<td>Whole brain</td>
<td>65 patients with a diagnosis of MDD or BD, without an additional Axis I diagnosis of schizophrenia or psychosis (M + F): 29 patients have attempted suicide (mean 42.17 yr) and 36 patients have not attempted suicide (mean 44.61 yr)</td>
<td>Significantly increased prevalence (4.7 times) of WMH in patients who attempted suicide</td>
<td>Selection bias; retrospective assessment of suicide attempts; not able to disclose effects of medication on suicidality; significant age difference between experimental groups; no differentiation between subtypes of WMH</td>
</tr>
<tr>
<td>Aguilar et al. (2008)</td>
<td>MRI: Whole brain structural abnormalities</td>
<td>Whole brain OFC Amygdala</td>
<td>37 patients meeting the DSM-IV criteria for schizophrenia (M): 13 patients have attempted suicide (mean 37.12 yr) and 24 patients have not attempted suicide (mean 42.65 yr)</td>
<td>Gray matter density reduction in the left superior temporal lobe and left OFC in patients who attempted suicide. No amygdala volume differences between patients who attempted suicide and who did not attempt suicide</td>
<td>Only male schizophrenic subjects; age difference between experimental groups; No healthy subjects included</td>
</tr>
<tr>
<td>Jovev et al. (2008)^g</td>
<td>MRI: pituitary gland volume</td>
<td>Pituitary gland</td>
<td>20 patients meeting the DSM-IV criteria for BPD (M + F), mean 17.3 yr</td>
<td>Age and number of parasuicidal behaviours are significant predictors of pituitary gland volume</td>
<td>Small sample size; retrospective data collection of parasuicide history</td>
</tr>
<tr>
<td>Pompili et al. (2008)^g</td>
<td>MRI: deep white matter hyperintensities and periventricular white matter hyperintensities</td>
<td>Whole brain</td>
<td>99 patients with a diagnosis of MDD, BD-I or BD-II (M + F): 44 patients have attempted suicide (mean 45.57 yr) and 55 patients have not attempted suicide (mean 42.27 yr)</td>
<td>Patients who attempted to commit suicide are more likely to have higher PVH. The presence of PVH makes the risk for suicidal behaviour 8 times higher</td>
<td>Small sample sizes; DWMH not discriminated by location; influence of medication not taken into account; unclear causality</td>
</tr>
<tr>
<td>Riessch et al. (2008)</td>
<td>MRI: gray and white matter volumetric differences</td>
<td>Whole brain</td>
<td>105 subjects (M + F): 10 patients had a DSM-IV diagnosis of schizophrenia and have not attempted suicide (mean 30.3 yr), 45 patients had a DSM-IV diagnosis of schizophrenia and have not attempted suicide (mean 37.3 yr), 50 healthy controls were matched with the patients (mean 36.0 yr)</td>
<td>Significantly larger bilaterally inferior frontal white matter volumes in patients who attempted suicide, with significant positive correlation between current self-aggression (in past 6 months) and white matter volume</td>
<td>Small suicidality sample size; significant differences between groups on substance abuse; no general psychiatric comparison group</td>
</tr>
<tr>
<td>Matsuo et al. (2010)</td>
<td>MRI: white matter of the anterior medial regions of the corpus callosum</td>
<td>Corpus callosum</td>
<td>47 subjects (F): 10 patients with BD who attempted suicide (mean 36.2 yr), 10 patients with BD who have not attempted suicide (mean 44.2 yr) and 27 healthy subjects (mean 36.9 yr)</td>
<td>(1) Suicidal BD patients have an inverse partial correlation between the anterior genu area and the total score on the Barratt Impulsivity Scale (2) Smaller anterior corpus callosum predicts higher impulsivity in suicidal BD patients (3) No difference in size of the anterior corpus callosum areas between suicidal BD patients and the control groups</td>
<td>Small sample size; purely female sample; psychiatric medication; lack of comparison between patients with or without comorbid cluster B disorder; lack of comparison between patients with or without family history of risk factors for suicidality</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Targeted brain region</td>
<td>Subjects</td>
<td>Results</td>
<td>Limitations</td>
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</table>
| Lo et al. (2007)      | DTI: hyperintensities                 | Centrum semiovale     | 12 subjects (M+F): 6 patients with carbon monoxide intoxication (suicide attempt) and 6 matched healthy subjects | (1) Suicidal patients have hyperintensities in the centrum semiovale, next to PVH
(2) 4 patients have bilateral globi pallid necrosis                      | Small sample size                                                             |
<p>| Audenaert et al. (2001) | SPET: Serotonin-2A-receptor functioning | Frontal cortex        | 21 subjects, mean 30.4 yr (M+F): 9 patients who have attempted suicide and 12 healthy subjects | Significant decrease in bilateral frontal 5-HTA binding index in patients who attempted suicide | 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 (&lt;7 days) attempted suicide (19–49 yr) and 20 healthy subjects | Blunted perfusion in the left inferior PFC (during a category fluency task), bilateral gyrus temporalis medius (during a letter fluency task) and the AC (while performing both a letter fluency and a category fluency task) | 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 yr) and 12 healthy subjects (mean 28.9 yr) | Binding potential in the prefrontal 5-HTA receptors is decreased in patients who attempted suicide, next to higher levels of hopelessness, harm avoidance and self-transcendence and lower scores on self-directedness and cooperativeness. In patients who attempted suicide, prefrontal 5-HTA binding potential correlates negatively with hopelessness and harm avoidance and positively with self-directedness and cooperativeness. Also, hopelessness correlates positively with harm avoidance and negatively with cooperativeness and self-transcendence. | Small sample size; composition of patient sample; possible effect of physical trauma on binding index; effects of alcohol and medication |
| Lindström et al. (2004) | SPECT: brain serotonin and dopamine transporters | Whole brain      | 24 subjects, mean 38.8 yr (M+F): 12 patients who attempted suicide (5 violent and 7 non-violent) and 12 healthy matched subjects | No significant 5-HTT or DAT binding potential differences were found. A significant correlation between 5-HTT and DAT, next to a significant positive correlation between 5-HTT and impulsiveness, is found in patients attempting suicide | 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 yr) and 12 matched healthy subjects | Patients, who have attempted suicide, show a significant correlation between whole brain 5-HTT BP and impulsiveness in the right inferior frontal, bilateral temporal, midbrain, thalamic bilateral basal ganglia and left cerebellar regions. These patients also show significant negative correlation between whole brain DAT BP and mental energy in the bilateral basal ganglia regions |                                                                  |
| Amen et al. (2009)    | SPECT: In vivo brain differences       | Wholebrain 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 yr), 12 patients meeting DSM-IV criteria for depression who did not commit suicide and 12 healthy subjects | Patients who attempted suicide, compared to non-attempter patients, had higher rCBF at rest in the right insular cortex, dorsal AC gyrus and inferior parietal lobule. Patients who attempted suicide, compared to non-attempter patients, had perfusion deficits in the left frontal lobe, the right thalamus and part of the right medial temporal lobe during concentration. Areas of high rCBF were noticed in the right ACC and the left cerebellar pyramid. Patients who attempted suicide have general lower rCBF at rest than healthy subjects | Heterogeneous sample; lack of data for all subjects; medication |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>PET: serotonergic function</th>
<th>Targeted brain region</th>
<th>Subjects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al. (2003)</td>
<td>PET: serotonin agonism</td>
<td>PFC</td>
<td>69 subjects: 22 patients with MDD (mean 31.0 yr), 18 patients with self-injurious behaviour (mean 31.0 yr) and 29 healthy subjects (mean 31.0 yr)</td>
<td>No significant differences in 5-HT&lt;sub&gt;2&lt;/sub&gt; BP are found between patients with self-harm behaviour and healthy subjects</td>
</tr>
<tr>
<td>Oquendo et al. (2003)</td>
<td>PET: regional brain serotonergic function</td>
<td>Whole brain</td>
<td>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 yr), 9 patients had a history of low-lethality suicide attempts (mean 30.4 yr)</td>
<td>rCMR glucose uptake in PFC, ACC and superior frontal gyri is associated with high lethality of suicide attempt; lower ventromedial prefrontal activity associated with lower lifetime impulsivity, higher suicidal intent and higher-lethality suicide attempts; rCMR glucose uptake in right midcingulate and superior frontal gyri correlated negatively with executive functions, memory and attention, and positively with language fluency</td>
</tr>
<tr>
<td>Leyton et al. (2006)</td>
<td>PET: [11 C]MTrp trapping</td>
<td>PFC</td>
<td>26 subjects (M + F): 10 patients have attempted suicide (mean 37.7 yr) and 16 healthy subject (mean 35.5 yr)</td>
<td>High-lethality suicide attempters have significantly reduced serotonin synthesis in the OFC and ventromedial PFC (BA 11), next to an elevation in the right paracentral lobule, the left thalamus, the left middle occipital cortex and the hippocampal gyrus</td>
</tr>
<tr>
<td>Jollant et al. (2008)</td>
<td>fMRI: neural activity</td>
<td>Whole brain</td>
<td>42 subjects (M): 13 patients with a past history of MDD and suicidal behaviour, 14 patients with a history of MDD and no suicidal behaviour and 16 healthy subjects</td>
<td>(1) Prototypical faces: patients with suicidal behaviour, compared to patients without such behaviour, have greater activity in the right lateral OFC and lower activity in the right superior frontal gyrus in response to angry (versus neutral) faces (2) Mild faces: patients with suicidal behaviour, compared to patients without such behaviour, have greater activity in the right ACC and the right cerebellum to mild happy versus neutral faces (3) Neutral faces: healthy subjects, compared to the patients, have greater activity in the right cerebellum to neutral faces versus fixation baseline</td>
</tr>
<tr>
<td>Jollant et al. (2010)</td>
<td>fMRI: whole brain and orbitofrontal cortex activity</td>
<td>Whole brain</td>
<td>40 subjects: 13 patients with a past history of MDD and suicidal behaviour (mean 38 yr), 12 patients with a history of MDD and no suicidal behaviour (mean 43 yr) and 15 healthy subjects (mean 30 yr)</td>
<td>(1) Significantly poorer decision-making in suicide attempters, compared with healthy subjects and patients without a history of a suicide attempt (2) Suicide attempters, compared with patients without a history of suicidal behaviour, have decreased activation during risky versus safe choices in the left lateral OFC (BA47) and left orbitofrontal cortex (BA19)</td>
</tr>
</tbody>
</table>

**a** Study: *Study of good methodological quality.*  
**c** Targeted brain region: AC(C) = anterior cingulate (cortex); DLPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; 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.  
**e** Results: 5-HT = Serotonin; 5-HT<sub>2</sub> = Serotonin-2; 5-HT<sub>2A</sub> = Serotonin-2A; 5-HTT = the serotonin transporter; BA = Brodmann area; BF = binding potential; DAT = dopamine transporter; DWMH = deep white matter hyperintensities; PVH: periventricular white matter hyperintensities; rCBF = regional cerebral blood flow; rCMR = regional cerebral glucose metabolism; SCH = subcortical gray matter hyperintensities; WMH = white matter hyperintensities.
increase in a history of SA in patients with WMH and other psychiatric disorders. With regard to localization, DWMH in the right parietal lobe, but not in the frontal lobe, appeared to be associated with a significantly higher prevalence of a history of SA. In their sample of young adults with major depressive disorder (MDD), Ehrlich et al. (2005) showed a significantly increased prevalence of PVH, most commonly located in the right hemisphere, in patients with a history of SA as compared to those without such a history.

Pompili et al. (2007) found a significantly increased prevalence of WMH in adults with MDD/bipolar disorder (BD) with a history of attempted suicide and elevated suicide risk, compared to similar patients without such a history. There was no significant difference in the frequency of previous suicide or WMH between subjects with MDD and BD. In a subsequent study, Pompili et al. (2008) investigated whether WMH are associated with suicidal behaviour in patients with a mood disorder. Attempters and non-attempters differed only in the presence of PVH, with a more common presence of PVH in attempters than in non-attempters. Study groups did not differ with regard to the presence of DWMH.

3.1.2.2. Gray matter volume and density. Monkul et al. (2007) compared fronto-limbic brain structures between females diagnosed with a unipolar mood disorder and a history of one or more SA and unipolar females without such a history, to those of female healthy controls. As indicated in Table 1, the presence of a history of SA was associated with volumetric changes in the bilateral OFC gray matter and the right amygdala. There were no differences in gray matter volumes between unipolar patients without a history of SA and healthy controls.

Two studies investigated gray and white matter in the brains of patients suffering from schizophrenia according to suicidal behaviour. Male patients with a history of SA, compared to those without such a history, showed a significant reduction in gray matter density in specific left hemispheric areas (see Table 1) (Aguilar et al., 2008). Rüsch et al. (2008) found significantly larger white matter volumes in patients with a history of SA as compared to patients without such a history and to healthy controls (Table 1). No other significant white or gray matter volume differences were observed.

The study of Jovev et al. (2008) showed a correlation between number of suicidal behaviours and pituitary gland volume in young patients diagnosed with borderline personality disorder and with minimal exposure to treatment.

Matsuo et al. (2010) specifically studied the association between a history of SA and anterior corpus callosum volumes, but found no differences between bipolar patients with a history of SA and those without such a history.

3.1.3. DTI

One study by Lo et al. (2007) showed bilateral PVH and centrum semiovale hyperintensities after deliberate carbon monoxide intoxication.

3.2. Functional imaging studies

3.2.1. SPECT

Compared to normal controls, patients with a recent history of suicide attempts showed a significantly lower 5-HT2A binding index (reflecting a decrease in the number and/or in the binding affinity of 5-HT2A receptors) (Audenaert et al., 2001). The decrease was more marked in dorsolateral than in orbitofrontal regions. The decrease was also significantly more marked among patients who
used violent methods to attempt suicide (self-injury) than among those who attempted suicide by means of self-poisoning. Further analysis revealed a significant negative correlation between 5-HT2A-receptor binding and levels of hopelessness, one of the most important clinical predictors of suicidal behaviour (van Heeringen et al., 2003).

Audenaert et al. (2002) used a neuropsychological split-dose activation paradigm to assess brain perfusion in SA. They presented a verbal fluency task to depressed patients who had recently attempted suicide and to healthy controls. When compared to the controls, SA showed a blunted increase in perfusion in the left inferior PFC, in the gyrus temporalis medius bilaterally, and in the anterior cingulate during specific verbal fluency tasks (see Table 1) (Audenaert et al., 2002).

Two studies assessed the binding potential of the serotonin transporter (5-HTT) and dopamine transporter (DAT) using the 123I-β-CIT ligand (Lindström et al., 2004; Ryding et al., 2006). In both studies binding potentials were compared between patients with a recent SA and healthy controls, and between violent and non-violent SA. The findings from both studies were negative.

Amen et al. (2009) compared regional cerebral blood flow (rCBF) in the brains of psychiatric patients who committed suicide, with brain rCBF in groups of healthy and non-suicidal depressed individuals. In the baseline condition, i.e. at rest, rCBF in the suicide group differed from that in the non-suicidal depressed control group through a significantly higher perfusion in the right hemisphere. During the Continuous Performance Test, the suicide group showed perfusion deficits in the left frontal lobe, in addition to a deficit in the right thalamus and part of the right medial temporal lobe, compared with depressed non-suicidal patients, while clusters of high rCBF were noted in the right anterior cingulate cortex (ACC; BA 32) and the left cerebellar pyramid. In comparison with healthy subjects, the suicide group showed a generally lower rCBF throughout the cortex during the baseline condition.

3.2.2. PET

Meyer et al. (2003) found that depressed subjects with extremely dysfunctional attitudes had higher 5-HT2 binding potential, compared to healthy subjects, particularly in BA 9.

By measuring relative regional cerebral uptake of fludeoxyglucose F 18 (rCMRglu), Oquendo et al. (2003) showed that depressed high-lethality suicide attempters had lower rCMRglu in ventral, medial, and lateral PFC compared with low-lethality attempters. This difference was more pronounced after fenfluramine administration, particularly in the anterior cingulate and the medial frontal gyri (BA 32 and 8) bilaterally, and the right midcingulate and superior frontal gyri (BA 24 and 6). Lower ventromedial PFC activity was associated with different characteristics (Table 1). Verbal fluency correlated positively with rCMRglu in the same regions.

Leyton et al. (2006) compared high-lethality SA with healthy controls with regard to the level of their $\alpha-[^{11}C]$ methyl-l-tryptophan ($\alpha-[^{11}C]$MTrp) trapping, an index of serotonin (5-HT) synthesis. High-lethality SA had significantly reduced normalized $\alpha-[^{11}C]$MTrp trapping values in parts of the PFC, while an elevation in $\alpha-[^{11}C]$MTrp trapping was seen in more posterior parts of the brain (see Table 1). A significant association between ventromedial $\alpha-[^{11}C]$MTrp trapping and suicidal intent was found.

3.2.3. fMRI

Jollant et al. (2008) investigated neural reactivity following exposure to angry and happy versus neutral faces in currently
euthymic men with a history of major depressive disorder, whether or not with suicidal behaviour (SA and affective comparison subjects) and male healthy comparison subjects. The main results of this study are summarized in Table 1. In a subsequent study, Jollant et al. (2010) not only confirmed their earlier findings of a comparatively poor performance on a decision-making task in SA (Jollant et al., 2005), but they also demonstrated a change in activation in the orbitofrontal cortex and the occipital cortex during disadvantageous versus safe choices in SA (Table 1).

4. Discussion

Suicidal behaviour constitutes an important public health problem and poses a major challenge to health care because of difficulties in its prediction and thus prevention. This paper reviews studies of the association between structural or functional brain characteristics and suicidal behaviour. Such a review is relevant as knowledge of neural characteristics may contribute to our understanding, and thus to the prediction and prevention of suicidal behaviour.

The findings from this review can be summarized as follows. White matter hyperintensities, whether or not in the periventricular area, appear to be associated with the occurrence of suicide attempts in depressed children, adolescents and adults. Limbic gray matter hyperintensities are more commonly found in case of a history of suicide attempts than if such a history is not present.

With regard to inferior frontal and orbitofrontal areas white matter volumes are increased, while gray matter volumes of the orbitofrontal cortex of suicide attempters appear to be reduced. Tryptophan trapping, an index of serotonin synthesis, is reduced in significant correlation with suicidal intent. In persons with a history of depressive episodes, a history of attempted suicide is associated with greater activity in the right orbitofrontal cortex in response to angry (versus neutral) faces than in such persons without a history of suicidal behaviour. In normothymic suicide attempters a reduction in activation in the left lateral orbitofrontal cortex during disadvantageous (versus safe) choices is found, when compared to normothymic subjects without a history of suicide attempt and healthy controls.

Regarding the ventral and medial prefrontal cortex the findings point at a reduction in tryptophan trapping and glucose uptake, both correlating negatively with suicidal intent. Ventromedial glucose uptake also correlates negatively with lethality of suicide attempts but positively with impulsivity.

Several findings point at a role of the dorsolateral and superior frontal areas in the development of suicidal behaviour. Suicide attempters show a significant reduction in 5-HT2A-receptor binding in the prefrontal cortex, particularly in the dorsolateral area. The reduction is significantly more marked among violent attempters than among non-violent attempters. Depressed suicide attempters show a blunted increase in perfusion during activation using a verbal fluency task. High-lethality attempters show less glucose uptake than low-lethality-attempters and verbal fluency appears to be related to glucose metabolism in these areas. Following exposure to angry faces the right superior frontal gyrus shows less activation in individuals with a history of depression and attempted suicide than in those with a history of depression but not attempted suicide.

Regarding limbic areas, a history of suicidal behaviour is associated with larger right amygdala volumes. Suicidal behaviour is also associated with increased activity in the right insular cortex, dorsal anterior cingulate cortex... and with increased tryptophan trapping in the hippocampal gyrus and left thalamus. Lethality of the most serious lifetime suicide attempt correlates negatively with glucose uptake after fenfluramine administration in the anterior cingulate gyrus. Increased activity in the right anterior cingulate gyrus is found following exposure to mild happy (versus neutral) faces in case of a history of suicidal behaviour.

Finally, suicidal behaviour appears to be associated with changes in structural and functional characteristics of the parieto-occipito-temporal areas. Studies have indeed shown decreased gray matter density in the left superior temporal gyrus, increased activity in the inferior parietal lobule, and increased tryptophan trapping in the left middle occipital cortex.

Preceding a discussion of these findings, methodological issues need to be addressed. The comparability of findings from different studies is limited because of variations in imaging and analytic techniques (Cannon et al., 2007). Radioligands differ in their binding specificity, and, in spite of the use of Statistical Parametric Mapping in many studies, anatomical localization of findings is often imprecise. Small sample sizes, whether or not due to high dropout rates, limit the power of studies to detect small group differences (Soloff et al., 2007) or can tend to amplify individual differences due to biological heterogeneity (Soloff et al., 2003). Other potential biases may be due to the lack of (e.g. healthy or psychiatric) comparison groups.

Studies, which control for comorbidity, offer the possibility to distinguish between predispositions for comorbid disorders such as depression and suicide (Audenaert et al., 2002; Meyer et al., 2003; Ehrlich et al., 2005; Monkul et al., 2007; Jovev et al., 2008; Pompei et al., 2008; Jollant et al., 2008, 2010). In some studies, however, patients and controls are not matched for potentially biasing characteristics, such as demographic variables, psychiatric (co-)morbiditity, nature and severity or chronicity of associated disorders, treatment, and exposure to risk and protective factors (Pompeii et al., 2007; Aguilar et al., 2008; Rüsch et al., 2008). Alcohol dependence, which may lead to changes in brain areas such as the cerebellum, was an exclusion criterion in the majority of reviewed studies.

Generalizability of findings may be limited due to inclusion of only male or female individuals or patients with particular disorders such as schizophrenia. In the majority of studies, assessment of imaging is not blind to behavioural history.

The possibility of publication bias cannot be ruled out and may therefore limit the interpretability of the current results.

Taking these methodological limitations in mind, the question as to what extent the findings from this review may help to understand the development of suicidal behaviour needs to be answered. Many of the areas involved in suicidal behaviour, as described in this review, are part of emotion-regulating circuits in the brain. Such circuits comprise the prefrontal cortex, the amygdala–hippocampus complex, the thalamus, the basal ganglia and the extensive connections between these areas (Soares and Mann, 1997). Lesions in one specific part or disruption of interconnections may thereby result in malfunctions in other areas. Those abnormalities may trigger the onset of mood disorder and confer a biological vulnerability, which, in combination with environmental stressors, may result in suicidal behaviour (Ehrlich et al., 2004, 2005).

The possibility to study clinical and/or neuropsychological correlates of brain characteristics constitutes an important advantage of imaging studies over post-mortem studies, and may help to find an answer to this question by the identification of clusters of disturbed brain functions, neuropsychological and/or clinical characteristics, and suicidal behaviour. The identification of a biological substrate for neuropsychological and/or clinical characteristics related to suicidal behaviour thereby supports a causal interpretation of this relationship.

First, the results from this review point at the involvement of the orbitofrontal cortex in the development of suicidal behaviour. Early studies in relation to suicidal behaviour have focused on the association between orbitofrontal dysfunction and impulsive-aggressive
traits. Findings have, however, not been equivocal, which may be due to the multifaceted nature of the impulsivity construct. Behavioural indices of impulsivity, such as response inhibition, are more basic constructs and thus quantifiable in a more reliable way (Mann, 2005). Response inhibition has not yet been studied in relation to suicidal behaviour, but functional imaging in healthy volunteers indeed shows involvement of the (right) orbitofrontal cortex, the cingulate cortex and the inferior parietal lobe (Horn et al., 2003). As described in this review these areas are also involved in suicidal behaviour.

With regard to the orbitofrontal cortex, attention has more recently been drawn to the association between orbitofrontal cortex dysfunctioning, disturbances in decision-making and suicidal behaviour. A first study showed that violent suicide attempters differed 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., 2005). 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 behaviour. Taken together with the findings of increased orbitofrontal activation following exposure to angry faces in suicide attempters (Jollant et al., 2008), these findings suggest that suicidal behaviour is correlated with disturbances in the attribution of importance to stimuli, i.e. undue importance to signals of others’ disapproval and insufficient importance to risky choices. The development of unbearable emotional pain following perception of signals of others’ disapproval may be associated with a choice for immediate reward (i.e. alleviation of pain). The association between mental pain and risk of suicidal behaviour has indeed recently been demonstrated in depressed individuals (van Heeringen et al., 2010). While decision-making in general is associated with the activation of ventromedial prefrontal regions, it appears that the orbitofrontal cortex could be related with deciding between advantageous and disadvantageous choices following exposure to particular stimuli, such as angry faces in suicide attempters. A number of reviewed studies point at a correlation between orbitofrontal functioning and suicidal intent or lethality of suicide attempts. In addition, decision-making appears to be disturbed more in violent than in non-violent attempters. The interpretation of these correlational findings requires further study.

A second potential cluster of findings concerns the role of the dorsolateral prefrontal cortex in the development of suicidal behaviour. Prefrontal, and in particular dorsolateral 5-HT_2A-receptor binding correlates significantly with levels of hopelessness, a strong clinical predictor of suicidal behaviour (van Heeringen et al., 2003). Prefrontal (i.e. superior frontal) serotonergic activity also correlates with verbal fluency (Oquendo et al., 2003). It is of particular interest that dysfunctional attitudes, which correlate with hopelessness, are associated with prefrontal 5-HT_2A-receptor binding (Meyer et al., 2003). A negative correlation between fluency and hopelessness has been described previously (MacLeod et al., 1993). Taken together these findings point at a possible role of the dorsolateral prefrontal cortex in the development of suicidal behaviour: findings of reduced activity, reduced 5-HT_2A-receptor binding, reduced fluency and increased hopelessness appear to cluster in attempted suicide patients. The reduced fluency thereby particularly concerns a reduced ability to generate positive future events.

Among particular functional and structural characteristics of suicidal brains this review of studies thus identifies two clusters of findings, which involve changes in the functions of the orbitofrontal cortex and the dorsolateral prefrontal cortex, associated with increased preference for immediate reward and decreased ability to generate positive events in the future, respectively. Research outside the domain of suicidology has demonstrated that the ability to select an action by considering delays and amount of reward outcome is critical for survival and wellbeing (Schweighofer et al., 2007).

In daily life, people indeed make decisions based on prediction of rewards at different time scales. In many instances the choice for a longer-term positive outcome is more appropriate than a choice for immediate reward. However, the vulnerability to suicidal behaviour appears to be associated with choosing immediate reward (possibly the alleviation of emotional pain) in the absence of the ability to generate future rewards. We have recently indeed demonstrated an association between emotional pain and suicide risk in depressed individuals (van Heeringen et al., 2010).

It has recently been shown that the prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops (Tanaka et al., 2004a, 2004b). More specifically, it appears that the orbitofrontal cortex is involved in predicting immediate reward, while the dorsolateral prefrontal cortex is involved in future reward prediction. Taking into account the clearly demonstrated role of serotonin in the vulnerability to suicidal behaviour, it is worthy to note that serotonin appears to be involved in action selection by modulating the evaluation of delayed rewards. More particularly, experimental data show that delayed rewards have a low value with low serotonin levels leading agents to choose immediate over delayed rewards (Schweighofer et al., 2007). The availability of serotonin thus appears to correlate with the extent to which future events are taken into account when choosing between behavioural options.

Further research is clearly needed to assess the applicability of such neuropsychological models to suicidal behaviour. Attention should thereby be given to functional neuroimaging studies of decision-making and reward prediction.

Conflicts of interest

The authors have neither financial interest in, nor financial support for writing this review.

References


