NEUROBIOLOGY OF SUICIDAL BEHAVIOUR

J. John Mann

About one million suicides and ten million suicide attempts occur worldwide each year. Suicide is not simply a response to stress, but generally a complication of a psychiatric disorder. A proposed stress–diathesis model is described in clinical and neurobiological terms. Neurobiological correlates of the diathesis for suicidal acts point to the involvement of the serotonergic and noradrenergic systems, and the ventromedial prefrontal cortex. Some treatments seem to reduce suicide risk independently of an effect on the primary psychiatric disorder, perhaps by reducing the diathesis.

BORDERLINE PERSONALITY DISORDER
According to the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV), this is a pervasive pattern of instability of interpersonal relationships, self-image, affects and marked impulsivity, which begins by early adulthood and is present in various contexts.

ANTISOCIAL PERSONALITY DISORDER
According to the DSM-IV, this is a pervasive pattern of disregard for and violation of the rights of others, occurring from the age of 15 years.

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Suicidal behaviour refers to the occurrence of suicide attempts, which I define here as self-directed injurious acts with at least some intent to end one's own life. Suicidal behaviour ranges from fatal acts (completed suicide), to highly lethal and failed suicide attempts (where high intention and planning are evident, and survival is fortuitous), and to low-lethality attempts (usually impulsive attempts that are triggered by a social crisis, seem to be ambivalent and contain a strong element of an appeal for help)[1,2]. Intent and lethality are correlated positively, and are related to biological abnormalities that mostly involve the serotonergic system[1,3–6]. The clinical and neurobiological study of failed suicides can inform us about completed suicide because the two populations are similar, clinically and demographically.

The scope of the problem

Suicide is currently the eleventh leading cause of death in the United States, and it accounted for 29,350 deaths in 2000. In 20 years, the total number of yearly suicides has changed little; there were 27,596 suicides in 1981. The age-adjusted suicide rate has dropped 10.9% in 20 years (see http://www.cdc.gov/ncipc/wisqars). Males commit suicide over four times more frequently than females, and suicide risk is twice as high for white males and females than for African-American males and females, respectively. Rates reported by other countries vary widely, ranging from fewer than 1/100,000 suicides per year in Syria, Egypt and Lebanon to over 40/100,000 in some countries that were formerly part of the Soviet Union (see http://www.who.int/whosis). There are 10–20 suicide attempts for every completed suicide.

A clinical model of suicidal behaviour

Over 90% of suicide victims or suicide attempters have a diagnosable psychiatric illness, most commonly a mood disorder[7–9]. About 60% of all suicides occur in relation to mood disorders[9], and the rest are related to various other psychiatric conditions, including schizophrenia, alcoholism[10], substance abuse[11] and personality disorders[8,12,13]. Suicide frequency in discharged hospital populations ranges from about 20% in people with manic depression or bipolar disorder, to 5–10% in people with BORDERLINE and ANTISOCIAL PERSONALITY DISORDERS[13–16], and is lower in outpatient psychiatric populations[17,18]. Even in the psychiatric groups at the highest risk, most patients never attempt suicide, indicating the importance of a DIATHESIS or predisposition to suicidal behaviour that is independent of the main psychiatric disorder.

Other clinical features that increase the risk for suicidal behaviour include aggressive/impulsive traits, hopelessness or pessimistic traits, co-morbidity for substance abuse and alcoholism[10,11,16,17,19,20], a history of physical or sexual abuse during childhood, a history of head injury or neurological disorder[21–23], and cigarette smoking[24,25]. These risk factors are not

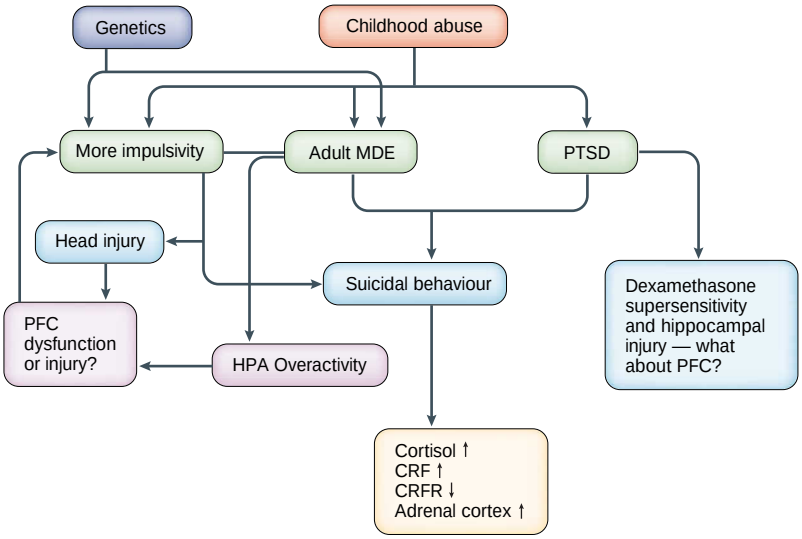

Figure 1 | **Effects of genetics, head injury and childhood abuse on mood disorders and impulsivity in relation to suicidal behaviour.** Impulsivity in combination with a mood disorder or post-traumatic stress disorder (PTSD) increases the risk of suicidal behaviour. CRF, corticotrophin releasing factor; CRFR, CRF receptor; HPA, hypothalamic pituitary adrenal; MDE, major depressive episode; PFC, prefrontal cortex.

independent (FIG. 1). For example, there is a relationship between aggressive/impulsive traits, substance abuse, depression and cigarette smoking[24,26,27]. Also, head injuries occur more frequently in aggressive, impulsive subjects and in people with a history of alcohol and substance abuse. This particular relationship is bidirectional because alcoholism, substance abuse and aggressive behaviours can follow head injuries[28,29]. My colleagues and I have found that head injuries in childhood are more common in aggressive children, and that the impact of the head injury on future aggression is greater in children who were more aggressive before the head injury (M. Oquendo *et al.*, unpublished data). As aggressive behaviours and alcoholism are more common in males than in females[10,30], this might partly explain the higher suicide rates that are reported in males.

Illnesses that affect the brain have a greater effect on suicide risk compared with other medical conditions. Potentially fatal illnesses such as cancer carry a relatively modest 2–4-fold increased risk of suicide over the general population unless there is a co-morbid psychiatric disorder[31]. A higher relative risk for suicide is seen in people with brain disorders, such as epilepsy[21,22], AIDS[32], Huntington's disease[23], head injury and cerebrovascular accidents. Pathologies that involve the nervous system might trigger both depression and suicidal ideation, and impair the inhibition of the desire to act on such thoughts[28,29,33], therefore explaining the greater relative risk of suicide.

Many explanatory and predictive models of suicidal behaviour have been hypothesized[34]. Here I will present a stress–diathesis model[25]. A typical stressor includes the acute worsening of a psychiatric disorder, but often an acute psychosocial crisis seems to be the most proximal stressor or 'the straw that broke the camel's back', leading to suicidal behaviour. Pessimism and aggression/impulsivity are components of the diathesis for suicidal behaviour[25]. Sex, religion, familial/genetic factors, childhood experiences and various other factors, including cholesterol levels (BOX 1), influence the diathesis[25]. The neurobiological correlates of the stressors and the diathesis are described later (FIG. 2).

Psychosocial correlates of suicidal behaviour

Rural areas, high rates of gun ownership, poverty, unemployment and social isolation have all been implicated in suicide[35,36]. These factors are clearly not independent from each other or from psychiatric illness. Psychiatric disorders can lead to job loss, to breakup of marriages or relationships, or to the failure to form such relationships. Moreover, psychiatric illness and psychosocial adversity can combine to increase stress on the person and, thereby, potentially increase the risk for suicidal behaviour. So, it is difficult to separate the impact of psychosocial adversity from that of psychiatric illness.

Suicide risk, particularly in adolescents, is affected by imitation and by glamorous, sensational reporting by the press[37]. Recently, television viewing has been associated with aggressive behaviour in adolescents and adults[38]. The occurrence of 3–5 violent acts per hour during prime time television, and 20–25 violent acts per hour during children's programmes might explain such a finding[38].

Neurochemical correlates of suicidal behaviour

Post-mortem brain tissue has been used to examine indices of the serotonergic, noradrenergic and dopaminergic neurotransmitter systems, signal transduction and cellular morphology in suicide victims. Such studies have the advantage that completed suicide is the most severe form of suicidal behaviour, and that the brain can be directly examined. By contrast, limitations include their reliance on medical records and a PSYCHOLOGICAL AUTOPSY for clinical data, the confounding effects of ante-mortem drug treatment, and the possibility of examining the brain only at one point in time.

The serotonergic system. Most post-mortem studies of suicide have examined the serotonergic system, because two seminal studies[39,40] identified abnormalities of the serotonin (5-HT, 5-hydroxytryptamine) system in prefrontal cortex in suicide victims. In these people, there are fewer presynaptic serotonin transporter sites in the prefrontal cortex (FIG. 3a), hypothalamus, occipital cortex and brainstem[41]. AUTORADIOGRAPHIC STUDIES of

DIATHESIS
In the medical literature, it is a constitution of the body that makes it react in specific ways to extrinsic stimuli, thereby tending to make the person more susceptible than normal to certain diseases.

STATINS
Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A, which are commonly used to reduce the amount of low-density lipoprotein cholesterol.

PSYCHOLOGICAL AUTOPSY
Interviews with friends and next-of-kin of a subject who committed suicide, trying to establish the reasons for suicidal behaviour.

Box 1 | Effect of cholesterol on suicidal behaviour

There is a small increase in the rate of suicide, and perhaps suicide attempts and ideation, in people with very low cholesterol levels and after lowering of cholesterol through the diet (see REFS 180–182 for reviews). In non-human primates, a high cholesterol diet is associated with higher serotonergic activity, and less impulsivity and aggressive behaviour[181,183]. Such a relationship has yet to be shown in humans but, if present, it might explain how cholesterol levels influence suicide risk. Why the effect of low cholesterol might be greater after cholesterol lowering by diet compared with treatment with STATINS is unknown[182].

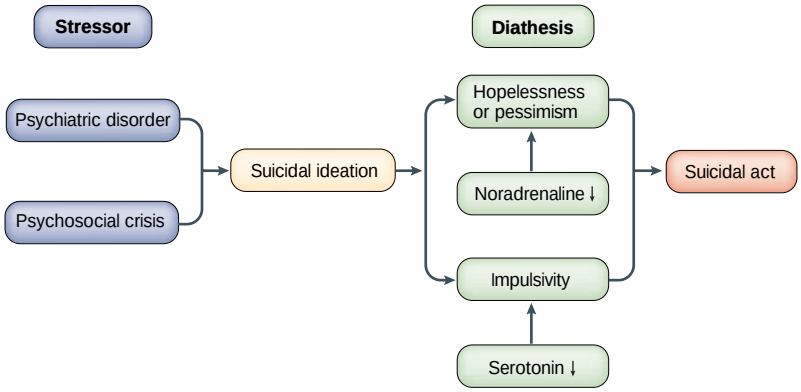

Figure 2 | **A stress–diathesis model of suicidal behaviour.** Components of the diathesis include pessimism and impulsivity, and biological correlates are hypothesized.

AUTORADIOGRAPHIC STUDIES
Technique in which a specimen that has been labelled with a radioactive molecule (usually the ligand of a receptor) is placed on a photographic emulsion. Its subsequent development reveals the localization of radioactivity, and therefore the localization of the molecule of interest, as a pattern of silver grains.

BRODMANN AREAS
Korbinian Brodmann (1868–1918) was an anatomist who divided the cerebral cortex into numbered subdivisions on the basis of cell arrangements, types and staining properties. Modern derivatives of his maps are commonly used as the reference system for discussion of brain-imaging findings.

prefrontal cortex in suicide victims localize this abnormality to the ventromedial prefrontal cortex[42]. This effect is related to suicide and is independent of a history of major depression[43]. Less serotonin transporter-binding extends across all cortical layers, therefore only partly reflecting the reported reduction in the length of serotonin transporter-positive axons, which is confined to layer 6 of BRODMANN AREA 46 in prefrontal cortex[44]. Ono *et al.*[45] found no alteration in the immunoreactivity of tryptophan hydroxylase (TPH; the rate-limiting enzyme in the synthesis of serotonin) and in 5-HT_{2A}-binding in suicide victims in dorsolateral prefrontal cortex, indirectly indicating that impaired serotonin input in suicide affects ventromedial prefrontal cortex.

Postsynaptic serotonin 5-HT_{1A} and 5-HT_{2A} receptors are reported by some studies to be upregulated in the prefrontal cortex of suicide victims (see REF. 46 for a review). Postsynaptic serotonin receptor upregulation might be a compensatory response to the low activity of serotonin neurons. In the case of 5-HT_{2A} receptors, this upregulation involves increased gene expression[47].

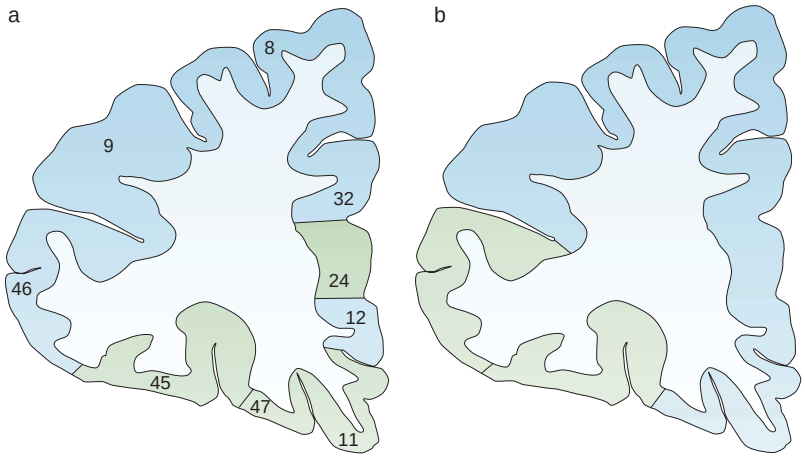

Figure 3 | **Serotonin and suicidal behaviour.** Post-mortem binding differences (green arrows) in serotonin transporter (**a**) and serotonin receptor 5-HT_{1A} (**b**) in the prefrontal cortex of people who committed suicide. Whereas serotonin transporter binding was decreased in these subjects, 5-HT receptor binding was increased. The numbers correspond to the different Brodmann areas. (Image courtesy of V. Arango and M. Underwood.)

Notably, 5-HT_{1A} receptor upregulation in association with suicide seems to be localized to the ventral prefrontal cortex[42] (FIG. 3b). The anatomical convergence of fewer serotonin transporter sites and upregulation of the 5-HT_{1A} receptor in the ventral prefrontal cortex indicates a role for this brain region in suicide.

The ventral prefrontal cortex is also involved in behavioural and cognitive inhibition[48]. Injury to this brain area can result in disinhibition[49], and low serotonergic input might contribute to impaired inhibition, creating a greater propensity to act on suicidal or aggressive feelings. Aggression is associated with suicidal behaviour, and both are independently associated with low serotonergic function (see REF. 50 for a review). So, the ventromedial prefrontal cortex seems to be part of a restraint mechanism, the function of which modulates the probability of suicidal behaviour and aggression.

Hypofunction of the serotonin system in suicide is indicated in most studies of brainstem levels of serotonin or its main metabolite, 5-hydroxyindole acetic acid (5-HIAA) — modestly lower levels of these compounds have been reported in suicide victims[51]. Brainstem results are consistent with the cortical receptor findings and with reports of low levels of 5-HIAA in the cerebrospinal fluid (CSF) of people with a history of serious suicide attempts[52]. Paradoxically, there is no deficiency in the number of serotonin neurons[53], and TPH immunoreactivity is higher in the dorsal raphe nucleus of suicide victims with a history of major depression[54] (FIG. 4). Only the type 2 or neuronal TPH[55] is found in the brainstem, and we hypothesize that its catalytic activity is low in suicide victims to account for less brainstem serotonin or 5-HIAA. The increase in TPH immunoreactivity might be a homeostatic feedback effect of low intrasynaptic concentrations of serotonin. Other evidence of dysfunctions of the serotonergic system includes reduced expression of the serotonin transporter and altered 5-HT_{1A}-receptor binding[56,57]. However, most post-mortem studies of brainstem serotonin changes have examined suicide victims with a history of major depression and therefore cannot separate the effects of mood disorder from those of suicide.

Low CSF 5-HIAA has been reported in suicide attempters with major depression[3], schizophrenia[58] and personality disorders as compared to people who do not attempt suicide but have the same psychiatric diagnosis. A biochemical trait — low CSF 5-HIAA — predicts future suicide attempts and suicide completions[58,59], and is consistent with low post-mortem brainstem levels of serotonin or 5-HIAA in suicide victims, independent of psychiatric diagnosis.

Prolactin levels after the acute administration of the serotonin reuptake inhibitor fenfluramine have been used as a probe of serotonergic activity. The relationship between low serotonergic function and suicidal behaviour is also indicated by a blunted prolactin response to serotonin that is released by fenfluramine in suicide attempters with major depression[60] or personality disorders[61] compared with controls. The more lethal the suicide attempt, the lower the CSF levels of 5-HIAA and the prolactin response to fenfluramine[60,62].

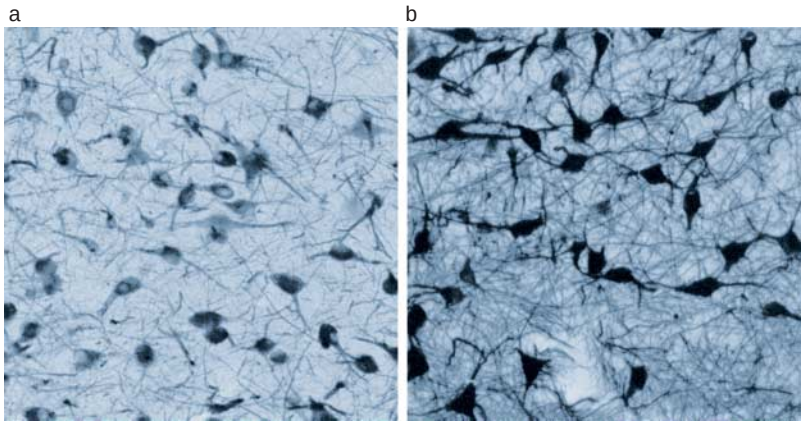

Figure 4 | **Serotonin and suicidal behaviour.** Photomicrographs of brainstem sections stained with an antibody against tryptophan hydroxylase at the rostral level of the dorsal raphe nucleus from a control subject and a suicide victim. Note the higher immunoreactivity in the suicide victim. (Images courtesy of V. Arango and M. Underwood.)

Genetic factors, a deprived upbringing or childhood abuse, low cholesterol, cigarette smoking and substance abuse are associated with or induce lower serotonergic activity and suicidal behaviour. Depletion of serotonergic function in animals and humans increases aggressive behaviour and impulsivity, whereas serotonergic enhancement decreases such behaviours[50]. It remains to be seen whether raising serotonergic activity reduces the risk of serious suicidal behaviour. The serotonergic input to ventromedial prefrontal cortex of suicide victims might modulate the diathesis or predisposition to suicidal behaviour, independently of the psychiatric illness that might have triggered the suicidal act[43]. Imaging studies in suicide attempters also identify the ventromedial prefrontal cortex as a region related to impulsivity and suicidal behaviour, as I discuss later in this review.

The noradrenergic system. Alterations in post-mortem noradrenergic indices in suicide victims have been the subject of fewer studies in comparison with the serotonergic system[63]. There are fewer noradrenergic neurons in the locus coeruleus in suicide victims with major depression[64], but non-specific illness or stress effects cannot be ruled out. In addition, noradrenaline levels seem to be lower in the brainstem of suicide victims, whereas α_2-adrenergic receptor numbers are higher, perhaps upregulated secondary to lower noradrenaline levels[65]. Immunoreactivity for tyrosine hydroxylase (TH, the rate-limiting enzyme in the biosynthesis of noradrenaline) is reported to be higher in one study[66], but we and others[67] have found it to be reduced. TH immunoreactivity increases as a compensatory mechanism under conditions in which increased noradrenaline release leads to transmitter depletion[68]. So, the TH immunoreactivity could be state-dependent, explaining the discrepant results in the literature. α_2-Adrenergic receptor upregulation might also occur because noradrenaline is depleted. So, more TH and α_2-adrenergic binding could indicate noradrenergic depletion.

In the prefrontal cortex, β-adrenergic receptor binding is generally reported to be higher in suicide victims[69]. We have found that the high-affinity component of β_1-adrenergic binding is lower (V. Arango, M. Underwood and J.J.M., unpublished data), indicating a possible shift to the low-affinity state of β_1-adrenergic receptors. To account for the reports of higher β-adrenergic binding, it would be necessary to postulate that β_2-adrenergic binding is greater in suicidal behaviour. We have also reported that noradrenaline levels in the prefrontal cortex are higher and that α-adrenergic binding is lower[70], indicating cortical noradrenergic overactivity. Such overactivity might have resulted in depletion of noradrenaline from the smaller population of noradrenergic neurons that is found in suicide victims.

Increased noradrenergic and cortisol-dependent stress responses are reported in depression[71]. Moreover, humans exposed to adverse childhood experiences can show exaggerated sympathetic responses in adulthood in response to stress[72], and such an effect would further deplete noradrenaline function[68] (FIG. 5). So, the TH upregulation in the locus coeruleus of suicide victims could potentially be a response of the noradrenergic system to excessive noradrenaline release in response to the stress that is associated with impending suicide.

Studies of suicidal behaviour and the noradrenergic system *in vivo* have been limited. The urinary secretion of adrenaline is lower in suicide attempters, but there is no correlation between the CSF levels of noradrenaline, adrenaline or their metabolites, and suicidal behaviour[73,74]. Challenge with the α_2-adrenergic agonist clonidine in suicide attempters produces a blunted response, indicating that α_2-adrenergic receptor binding or activity might be low. Post-mortem studies indicate the latter to be the case. Severe anxiety or agitation is associated with noradrenergic overactivity, higher suicide risk[75] and overactivity of the hypothalamic–pituitary–adrenal (HPA) axis[76]. Pathological anxiety might therefore give greater valence to suicidal feelings.

The dopaminergic system. Few post-mortem studies have examined the dopaminergic system in suicide vicitims. No alteration of mRNA for the dopamine D_1 and D_2 receptors was found in the caudate nucleus of suicide victims[77]. The available studies are too few to determine confidently whether there are changes in dopamine or homovanillic acid (HVA), its main metabolite, in either the prefrontal cortex or brainstem of victims[63,78]. Dopamine D_4-receptor binding in the caudate is not altered in suicide victims with major depression[79]. Subsets of GABA (γ-aminobutyric acid) interneurons and pyramidal glutamatergic neurons in the prefrontal cortex, which receives significant dopaminergic input, contain the neuropeptide cholecystokinin, which has been implicated in anxiety and psychosis. Cholecystokinin mRNA levels are elevated in the prefrontal cortex in suicide victims[80]. Although the dopaminergic system is abnormal in depression, there are too few studies to determine whether it can be implicated in suicide.

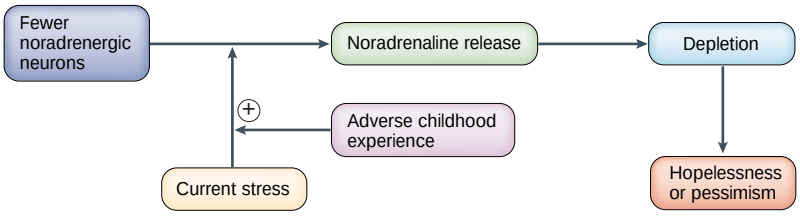

Figure 5 | **Stress sensitivity and hopelessness.** Adverse childhood experiences might lead to stress sensitivity that is manifested in excessive noradrenaline release and the hypothesized depletion that might underlie the excessive hopelessness that is seen in association with suicidal behaviour.

Low CSF HVA is found in suicide attempters that have been diagnosed with major depression[81], and the dopamine system seems to be hypofunctional in major depression[82]. Neuroendocrine studies of dopamine function and suicidal behaviour are inconclusive[83]. Psychostimulants increase impulsiveness in rodents[84,85], although some reports show a decrease[86]. In healthy volunteers, acute challenge with low doses of amphetamine reduces impulsiveness[87], an effect that has been ascribed to presynaptic dopamine receptor activation and inhibition of dopamine function. Because amphetamine causes a massive release of dopamine, postsynaptic effects will predominate in situations of amphetamine abuse. But in low doses, enhanced alertness or signal discrimination might outweigh the drive to respond[88]. This drive presumably leads to more aggression, as reported in clinical studies of stimulant abuse.

Abnormalities of signal transduction in suicide. The activity of protein kinase C (PKC), part of the signal transduction pathway for 5-HT_{2A} receptors, is low in the prefrontal cortex of suicide victims[89]. The levels of the cyclic-AMP-responsive element (CRE)-binding protein (CREB, a transcription factor), its DNA-binding activity, and the cAMP-dependent activity of protein kinase A (PKA) are low in the hippocampus and prefrontal cortex of suicide victims[90]. A deficiency of selective G-protein α-subunits is associated with suicide, independently of psychiatric diagnosis[91]. So, the effects of receptor upregulation might be offset by impaired signal transduction. Some of this biochemical deficit might be due to a loss of cortical target neurons in depression[92]. People with major depression who commit suicide also have abnormalities in the activity of the mitogen-activated protein (MAP) kinase[93], which might reduce its neurotrophic activity and other physiological actions in the brains of suicide victims with major depression. A crucial issue is the relationship of these changes to the number of cortical neurons, which might be fewer in people with mood disorders.

Genes, environment and stress responses. There seems to be a significant interaction between genes and environment in relation to the function of the serotonergic and noradrenergic systems. An example is provided by the finding that peer-reared monkeys have lower serotonergic activity in comparison to maternally raised monkeys[94]. This lower activity persists into adulthood and is reflected in greater impulsivity and aggression. Extrapolating from this study and given that a history of child abuse is associated with a greater risk for suicidal behaviour in adult life, it is possible to hypothesize that adverse rearing sets serotonergic function at a lower level. This effect might persist into adulthood, contributing to the increased risk for suicidal behaviour.

In the case of the noradrenergic system, cortisol and the HPA axis constitute an important stress-response system, and major depression, particularly if severe or associated with psychomotor agitation, might be associated with hyperactivity of the HPA axis[95]. Moreover, some suicide victims have HPA axis abnormalities[96,97]. Studies of the HPA axis and brain noradrenergic indices in suicide victims point to biological stress responses that might reflect the risk for suicide. Relief of stress effects might enhance the efficacy of therapeutic interventions.

Non-genetic familial factors that might contribute to suicide risk include the impact of parenting. Adverse parenting can involve neglect, but physical or sexual abuse has been more commonly studied. Adults reporting childhood abuse experiences have a higher rate of suicidal behaviour and greater impulsivity, consistent with findings in peer-reared monkeys. We have observed familial transmission of impulsivity: greater parental impulsivity and/or greater provocation from an impulsive child can increase the probability of physical or sexual abuse[98]. Overactivity of the HPA axis and the alteration in some neuropeptide systems, including neuropeptide Y and corticotropin-releasing factor (CRF), which have been reported in abused populations, might be related to the neurobiological consequences of abuse and neglect, as shown by animal studies of maternal separation[72,99–101]. Abuse can result in post-traumatic stress disorder (PTSD). Major depression and PTSD are associated with higher suicide rates[102]; their symptoms overlap and both are associated with HPA axis dysfunction. Remarkably, PTSD and major depression have different patterns of abnormal HPA axis function[103,104]. PTSD is associated with low 24-hour urinary cortisol levels[105], low plasma cortisol[106], hypersuppression of cortisol by the glucocorticoid dexamethasone[103,107,108] and decreased responsivity of the adrenal glands[106]. Heim *et al.*[109] found that depressed women who reported a history of abuse in childhood had higher rates of PTSD and lower cortisol responses to adrenocorticotrophin than non-abused depressed women did. By contrast, major depression is characterized by hypercortisolaemia[76,103,110] and impaired suppression of cortisol secretion after dexamethasone[76,95]. Subjects in which major depression and PTSD are co-morbid have lower plasma cortisol levels compared with people with major depression alone or healthy volunteers, and have a higher rate of suicide attempts[111].

Although the studies do not universally agree[112], suicide seems to be associated with hyperactivity of the HPA axis. Higher cortisol levels after dexamethasone suppression and HPA axis hyperactivity at baseline might increase the odds of eventual suicide as much as 14-fold[76,112]. Suicide is associated with larger adrenal glands and less prefrontal cortical CRF binding. The HPA

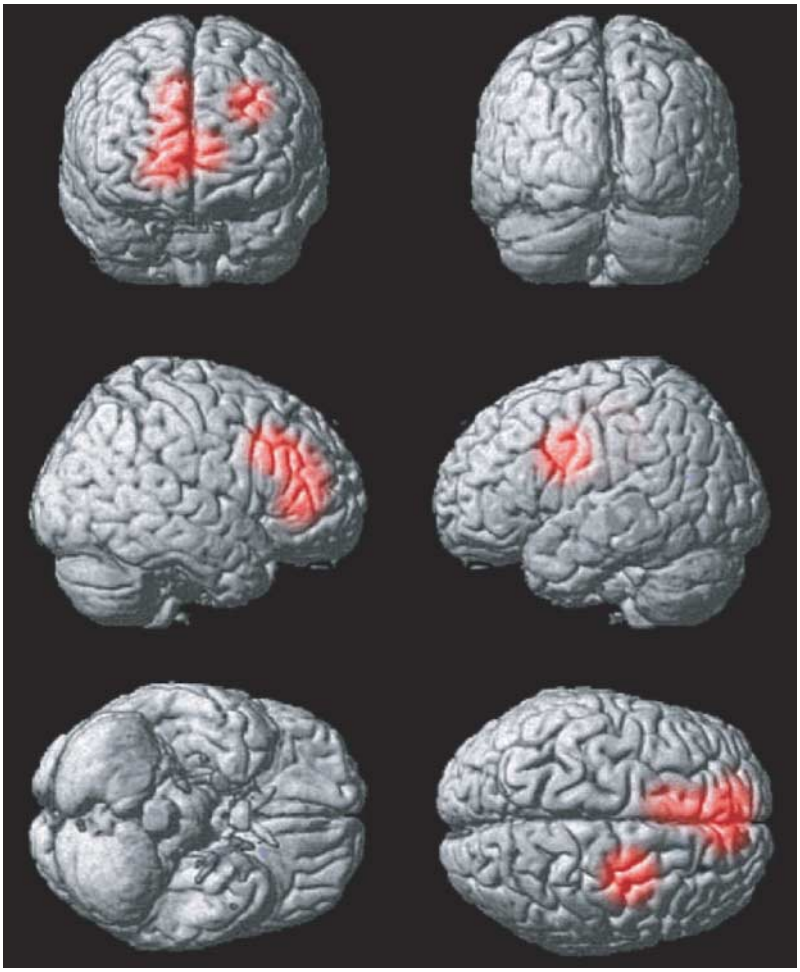

Figure 6 | **Differences in anterior cingulate and lateral prefrontal cortex brain activity after serotonin release related to suicide attempt behaviour.** Correlations are formed with impulsivity and intent, explaining some of the variance in lethality of suicidal behaviour.

axis has a bidirectional relationship with the serotonergic system (see REF. 113 for a review). We and Ono *et al.*[45] have reported more TPH immunoreactivity in the brainstem and prefrontal cortex from suicide victims. This could be a stress effect, as dexamethasone and stress raise TPH immunoreactivity in the raphe nuclei[114,115]. Alternatively, higher TPH levels could be a response to low intra-synaptic levels of serotonin because of impaired catalytic activity or less serotonin release. Other potential stress-related effects are lower mRNA levels of mineralocorticoid and 5-HT_{1A} receptors in temporal cortex[116], and 5-HT_{2A}-receptor upregulation in the prefrontal cortex.

Genetic factors in suicidal behaviour

People who commit suicide or make suicide attempts have a higher rate of familial suicidal acts[117]. CONCORDANCE rates for suicide[118] and suicide attempts[119] are higher in monozygotic versus dizygotic twins. Adoption studies[120] have shown a higher reported rate of suicide in the biological parents of adoptees who commit suicide compared with biological relatives of control adoptees, even after controlling for rates of psychosis and mood disorders. Parents of young suicide victims have higher rates of suicidal behaviour, independently of the presence of a major psychiatric disorder[121]. HERITABILITY of suicide and suicide attempts is comparable to the heritability of other psychiatric disorders, such as bipolar disorder and schizophrenia[122].

The specific genes that contribute to suicide risk independently of associated psychiatric disorders are unknown. As serotonin activity is related to suicidal behaviour and is under partial genetic control, investigators have examined the relationship between genetic variation in serotonin-related genes, and both suicidal behaviour and impulsive aggression. I briefly review the findings with regard to six candidate genes — TPH, the serotonin transporter (*SERT*), three serotonin receptors (*HTR1A*, *HTR2A* and *HTR1B*) and the monoamine oxidase promoter (*MAOA*).

There are two TPH genes that are located on different chromosomes, and the gene that has been the focus of all genetic studies published so far — *TPH1* — is not expressed in the brain. By contrast, the recently discovered *TPH2* gene, which is expressed in the brain, has not been the subject of published genetic studies. Although *TPH1* is not expressed in the brain, the less common A218 and A779 alleles are associated with a blunted prolactin response to fenfluramine[123] and low CSF levels of 5-HIAA in healthy volunteers[124]. Moreover, suicidal behaviour is associated with altered platelet serotonin functions that could potentially reflect serotonin gene alterations outside the nervous system. *TPH1* has two POLYMORPHISMS in tight LINKAGE DISEQUILIBRIUM — A779C and A218C. These have been the subject of 39 reports on mood disorders and suicidal behaviour (see REF. 125 for a review and meta-analysis of their association with suicidal behaviour). There is no agreement on the association of these polymorphisms with suicidal behaviour, mood disorders or other psychiatric disorders. So, discovering a role for *TPH2* on suicidal behaviour is the subject of much current interest.

The *SERT* promoter region has two allelic variants, long and short, which differ in a 44-base pair stretch. The long form is associated with greater gene expression in a transformed lymphoblastoid cell line[126]. In mood disorders, alcoholism and suicide attempters, associations have been reported between the short form and violent suicide attempts[127–129]. We found an association of this form with major depression, but not with suicide[43]. Du *et al.*[130] found an association between the long variant and suicide in people with major depression, but the association could be with either depression or suicide, as the controls had neither condition.

The *HTR1A* gene deserves attention because there is altered 5-HT_{1A} binding in the midbrain and ventral prefrontal cortex of depressed suicide victims[42,57,131]. In addition, anxiety-like behaviour has been reported in mice that are deficient in 5-HT_{1A} receptors[132]. A common polymorphism (C1018G) has been reported, as well as several other amino-acid substitutions or insertions[133]. We have found associations of the C1018G polymorphism with psychosis, substance abuse and panic disorder, but no relationship to mood disorders or

CONCORDANCE
The occurrence of a trait in two related individuals, such as twins or siblings.

HERITABILITY
The proportion of variability in a particular characteristic that can be attributed to genetic influences. This is a statistical description that applies to a specific population and might change if the environment is altered.

POLYMORPHISM
The simultaneous existence in the same population of two or more genotypes in frequencies that cannot be explained by recurrent mutations.

suicidal behaviour, or to prefrontal cortex 5-HT_{1A} binding[134]. Perhaps this polymorphism is associated with differential signal transduction but no binding differences.

The T102C polymorphism in the *HTR2A* gene has been examined in at least seven studies of suicidal behaviour, and some studies have also reported on other polymorphisms (H452Y and A1438G). Most studies have found no association between the T102C allele and suicide attempt[130,135–139]. Similar to the findings of Turecki and colleagues in post-mortem brain[137], we have found an *in vivo* relationship between the genotype and 5-HT_{2A} binding in platelets, but not to suicidal behaviour or depression (V. Khait *et al.*, unpublished data).

HTR1B is of interest because 5-HT_{1B}-knockout mice are impulsive, aggressive and more susceptible to self-administer cocaine and possibly alcohol[140,141]. Conversely, 5-HT_{1B} agonists decrease both instigated and frustration-heightened aggression in mice with no effect on motor behaviour[142]. Pharmacological challenges indicate that 5-HT_{1B}-receptor stimulation might enhance cocaine reinforcement[143], suggesting that knocking out the gene might exert a more complex developmental effect that results in a cocaine-preferring phenotype. Two polymorphisms have been identified — C129T and G861C. In our case-control study, the C129T and G891C alleles were associated with 20% fewer receptors in the post-mortem brain, although these polymorphisms were found in the same frequency in suicides and control subjects[144]. The latter allele was also associated with antisocial alcoholism[145], and we found an association with non-alcohol-related substance abuse, but not with mood disorders or suicidal acts[146].

The *MAOA* gene has at least four variants that are identified by the number of tandem repeats in the promoter region. Although the relationship of these variants with suicide attempt has hardly been studied, the alleles with 2–3 tandem repeats have been associated with impulsive aggression in males and with lower levels of MAOA expression[147]. Failure to express the gene in males has been associated with pathological aggressive behaviour in a study of an extended Dutch pedigree[148]. Consistent with a recent report[149], we found that the low-expressing form of the gene is associated with childhood abuse, and with more aggression in adult males reporting childhood abuse, indicating a gene–environment interaction.

Candidate-gene association findings are inconsistent, highlighting the limitations of this approach. Some inconsistencies in the results could be due to sample differences, failure to take sex or ethnicity effects into consideration, or not assessing dimensional traits. The candidate-gene approach is not likely to bear fruit without directly sequencing candidate genes, in combination with more basic behavioural and neurochemical ENDOPHENOTYPES that are likely to have a closer biological relationship, which might therefore be more detectable[150].

Neuroanatomical studies

Bechara *et al.*[151] have proposed a somatic marker hypothesis that provides a neuroanatomical and cognitive framework for decision-making, which is relevant to suicidal behaviour. Ingvar[152] has proposed a similar model for volitional acts. Both models implicate the ventromedial prefrontal cortex, as well as its connections with the amygdala and somatosensory/insular cortices, and the underlying white matter. Damage to the ventromedial prefrontal cortex results in defects of social behaviour, including a failure to observe social conventions and to make poor decisions, although learning, memory, attention, language and many other cognitive functions are normal. In a gambling task, people with lesions in the ventromedial prefrontal cortex persist in selecting cards from losing decks (incurring a net loss despite occasional bigger payouts) long after healthy controls had learned to avoid such decks[153]. Skin conductance responses are blunted in lesioned subjects during the phase that normal subjects learn to avoid decks of cards with poorer odds of winning, indicating that an emotional response is required to make the switch. Subjects with frontal lobe lesions are impulsive and make poor decisions[154], but are not necessarily risk-taking[155].

Ingvar[152] argues that the prefrontal cortex becomes activated during imagined actions (also see REF. 156) as part of the process of carrying out wilful acts. So, the prefrontal cortex provides insight into consequences of future actions and as such, when defective, might contribute to an increased risk for suicidal and other impulsive acts. Davidson *et al.*[157] described an anatomical circuitry of emotion and aggression. In their model, anger involves the activation of the orbital prefrontal and anterior cingulate cortices as part of an effort to suppress emotions[158], including an inhibitory projection to the amygdala[157]. Lesions of the prefrontal cortex interfere with the extinction of a conditioned aversive response[159,160], indicating a loss of inhibitory input. Imaging studies using positron emission tomography (PET) also indicate an inverse relationship between the activity of the prefrontal cortex and the amygdala[161].

We and others have linked prefrontal cortical activity on PET and the response to serotonin release by fenfluramine[162] to suicidal acts and impulsivity[6] (FIG. 6). A reduced cortical response is associated with suicidal and aggressive behaviours[163]. Structural and functional abnormalities are related to impulsive homicide[30,164]. Inferior frontal white matter microstructural defects, as shown by lower fractional ANISOTROPY, have been found in association with aggressive impulsivity in males with schizophrenia[165]. Our receptor autoradiographic studies of suicide victims have also localized the reduction in SERT binding and the increase in 5-HT_{1A}-receptor binding to the ventromedial prefrontal cortex. Serotonin activity can modulate aggressive behaviour[166], an idea that is also supported by the finding that rats reared in isolation show impaired release of serotonin by amphetamine in the prefrontal cortex[167]. Such rats are more impulsive and display impaired REVERSAL LEARNING, PERSEVERATION and hyperactivity in the open field[168,169], resembling animals with frontal cortex lesions[170–172]. Less behavioural restraint can lead to aggressive or suicidal behaviour, depending on the affective state of the subject.

LINKAGE DISEQUILIBRIUM
A condition in which the frequency of a particular haplotype for two loci is significantly greater than that expected from the product of the observed allelic frequencies at each locus.

ENDOPHENOTYPES
The physiological traits that are related to a disease; for example, blood pressure, angiotensin levels or salt sensitivity are endophenotypes of hypertension.

ANISOTROPY
When the physical properties of a given medium have different values, when measured along axes orientated in different directions, it is said to be anisotropic.

REVERSAL LEARNING
A situation in which a subject is trained to respond differentially to two stimuli, and is subsequently trained under reversed reward values.

PERSEVERATION
The persistent use of a specific strategy to solve a problem, despite the fact that the strategy is wrong or the rule of the task has changed.

DIALECTICAL BEHAVIOUR THERAPY
A cognitive–behavioural approach that was originally developed to treat people with borderline personality disorder, especially those with chronic patterns of suicidal behaviour. As people with this disorder lack interpersonal skills and have an impaired self-image, the dialectical strategy aims to help the patients accept the way they are while simultaneously helping them to change.

HAPLOTYPE
A combination of alleles at different sites on a single chromosome.

MODIFIER GENE
A gene that influences the phenotypic expression of another gene.

Implications for patient management

The management of the suicidal patient potentially involves three components (see REF. 173 for a review). First, the diagnosis and treatment of existing psychiatric disorders. Second, the assessment of suicide risk and limiting access to the most lethal methods for suicide. Third, specific treatment to reduce the diathesis or propensity to attempt suicide.

Reducing the diathesis for suicidal behaviour might be possible as evidenced by the clinical effects of lithium, the atypical antipsychotic drug clozapine and a form of psychotherapy known as DIALECTICAL BEHAVIOUR THERAPY.

Lithium seems to reduce the rate of suicidal behaviour independently of its mood-stabilizing effects in patients with bipolar disorder and in patients with unipolar disorder who have recurrent depressions (for review see REFS 174,175). Clozapine also reduces suicidal behaviour in schizophrenia independently of its antipsychotic action[176–178]. The mechanisms that underlie the anti-suicidal effects of lithium and clozapine are not known, but both medications affect the serotonergic system: lithium enhances serotonergic activity and clozapine is a potent 5-HT_{2A} antagonist. Aggression levels and suicide correlate positively with prefrontal cortical 5-HT_{2A} binding[69,179]. So, blockade of these receptors might be therapeutic in terms of antisuicidal and anti-aggressive effects.

Conclusions

Suicide is a complication of all existing psychiatric disorders. The probability of suicidal behaviour depends in part on a diathesis that includes more hopelessness and more impulsivity, which are partly related to impaired serotonergic input into the ventromedial prefrontal cortex. The diathesis is a potential therapeutic target.

Future directions of suicide research include genetic and neurochemical studies of *TPH2*, efforts to identify a genetic HAPLOTYPE that constitutes a risk for suicidal behaviour, and the development of imaging and neuropsychological tests of decision-making to measure risk of attempting suicide when depressed. Similarly, as antidepressants and antipsychotic medications take several weeks to have a beneficial effect, the development of treatments to ameliorate the risk of suicidal acts while waiting for those drugs to work would be an important step forward. Another promising direction is the use of animal models of impulsive and aggressive behaviours in the identification of candidate MODIFIER GENES, the investigation of genetic and rearing effects, and testing pharmacological treatments to ameliorate aggressive/impulsive behaviour that, by extrapolation, might reduce the probability of suicidal behaviour.

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Online links

DATABASES

The following terms in this article are linked online to:

LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/

5-HT_{1A} | 5-HT_{2A} | *HTR1A* | *HTR1B* | *HTR2A* | *MAOA* | *SERT* | *TPH1* | *TPH2*

FURTHER INFORMATION

Encyclopedia of Life Sciences: http://www.els.net/mood disorders

National Center for Injury Prevention and Control: http://www.cdc.gov/ncipc/

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