

# The Neurobiology of Suicide and Suicidality

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**Objective:** To investigate the current state of knowledge regarding the neurobiology of suicide and suicidality.

**Method:** The literature on the neurobiology of suicidality and suicide was reviewed.

**Results:** There is clear evidence that the activity of 3 neurobiological systems has a role in the pathophysiology of suicidal behaviour. This includes hyperactivity of the hypothalamo-pituitary-adrenal axis, dysfunction of the serotonergic (5-HTergic) system, and excessive activity of the noradrenergic system. While the first and the last system appear to be involved in the response to stressful events, dysfunction of the serotonergic system is thought to be trait-dependent and associated with disturbances in the regulation of anxiety, impulsivity, and aggression. It can be hypothesized that neurobiological dysfunctions mediate the occurrence of suicidal behaviour through the disturbed modulation of basic neuropsychological functions.

**Conclusion:** Increasing insight into the neurobiological basis of suicidal behaviour suggests that serotonin (5-HT) agonists have an important role in the treatment and prevention of suicidal behaviour. Studies of the efficacy of such drugs have, however, been disappointing. Because suicidal behaviour continues to be a major public health problem, further study is clearly needed, including research on the effect of combined pharmacologic and psychotherapeutic approaches.

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## Highlights

- At least 3 neurobiological systems are involved in the neurobiology of suicidal behaviour.
- These systems appear to be involved in state-dependent (the noradrenergic system and the hypothalamo-pituitary-adrenal axis) and trait-dependent (the serotonergic system) risk factors.
- Increasing evidence points to an overlap between neurobiological and cognitive psychological approaches to understanding suicidal behaviour.
- State- and trait-dependent characteristics should be included in risk assessment and treatment to prevent suicidal behaviour.
- Further study is needed of the effects of psychopharmacological and psychotherapeutic treatment, particularly in combination, on the occurrence of suicidal behaviour.

**Key Words:** *suicide, neurobiology, serotonin, genetics, cortisol, norepinephrine*

Suicide and attempted suicide rarely occur outside a context of a psychiatric disorder. Despite advances in treating and preventing these disorders, recent epidemiologic research indicates that suicide and attempted suicide still constitute a major public health problem. Reasons for the apparent failure of improved treatments to reduce suicide have been identified and include simplistic explanatory models of suicidal behaviour that portray suicide as simply a logical response to ex-

treme stress (1). It is also commonly suggested that adequate treatment of a psychiatric disorder is sufficient to prevent suicide. This approach, however, does not take into account the heterogeneous symptomatology of psychiatric disorders (for example, sleep, appetite, mood, cognition) and outcome, including suicide. Moreover, such a simplistic approach implies no attention to the fact that a completed suicide is commonly preceded by a suicidal process—a process that may become

manifest through suicidal communications or suicide attempts, or both. The propensity to respond with suicidal behaviour when confronted with psychosocial adversity (including psychiatric disorders) thus reflects an underlying trait-dependent predisposition or diathesis. To increase accuracy of predicting and efficacy in preventing suicidal behaviour, this predisposition has to be taken into account in addition to the manifest psychiatric disorder, when treating suicidal patients.

This paper reviews recent findings from biological studies of suicidal behaviour (Table 1 lists abbreviations for terms used throughout the paper). First, definitions and models of suicidal behaviour are discussed in terms of their relevance for understanding (inconsistencies in) the results of biological research. Following an overview of recent biological findings, the paper then considers the cognitive, behavioural, and emotional correlates of biological dysfunctions. Based on these considerations, implications for the treatment, prevention, and further study of suicidal behaviour are discussed.

### Definitions and Models of Suicidal Behaviour

The term “suicidality” refers to the occurrence of suicidal thoughts (or suicidal ideation) or suicidal behaviour. Suicidal behaviour may include acts of self-harm with a fatal (suicide) or a nonfatal (attempted suicide) outcome. By definition, the term “attempted suicide” does not refer to habitual forms of self-destructive behaviour such as self-mutilation, cigarette smoking, sensation seeking, or alcohol abuse. Nevertheless, the definition of attempted suicide is complex because this behaviour is characterized by several dimensions. These dimensions include degree of medical damage, lethality of methods used, and level of suicidal intent and may or may not be incorporated in the definition. For example, in the US it is common to include at least some intent to end one’s life in the definition of attempted suicide (1), but this is not the case in most European studies. The European approach to defining attempted suicide can be justified by the finding that several divergent intentions may lead to an act of self-harming behaviour (2). It is currently not clear whether or to what extent differences in defining attempted suicide contribute to discrepancies among research findings.

Several different models have been developed to explain the occurrence of suicidal behaviour. The most commonly applied models include the stress–diathesis model (3) and the process model (4). The stress–diathesis model usefully explains why one person commits suicide during a depressive episode and another does not. The risk of suicide does not correlate with the objective severity of the psychiatric disorder but appears to depend on variations in the diathesis or predisposition. Typical stressors associated with suicidal behaviour include adverse life events, such as interpersonal or social

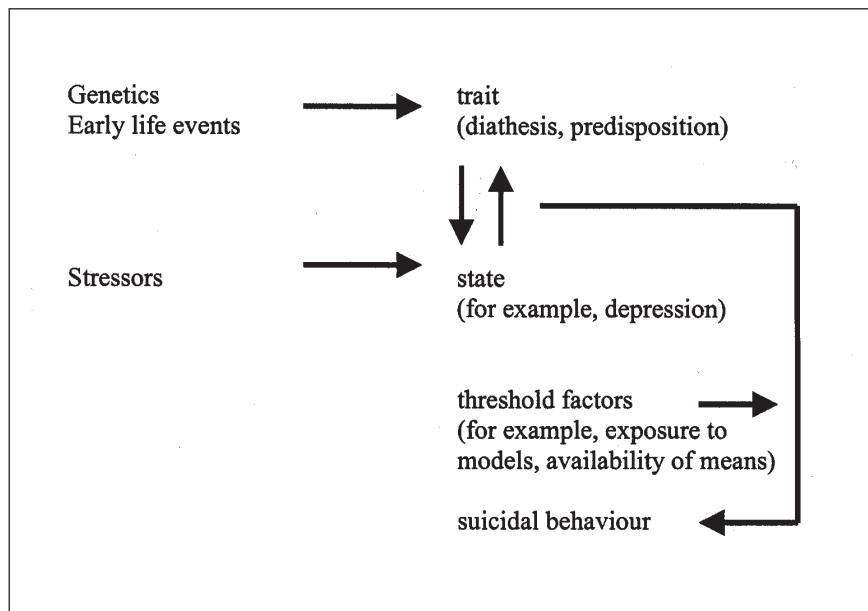
**Table 1 List of abbreviations appearing in this article**

(DL)PFC	(dorsolateral) prefrontal cortex
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
5-HTergic	serotonergic
5-HTT	serotonin transporter gene
A	amygdala
ACTH	adrenocorticotrophic hormone
AMT	autobiographical memory test
AVP	arginine vasopressin
cAMP	cyclic adenosine monophosphate
CRH	corticotropin-releasing hormone
CSF	cerebrospinal fluid
Dex/CRH	dexamethasone suppression CRH test
dopa	dopamine
DRN	dorsal raphe nucleus
DST	dexamethasone suppression test
FTC	frontotemporal cortex
HA	harm avoidance
HC	hippocampus
HPA axis	hypothalamo-pituitary-adrenal axis
HVA	homovanillic acid
MAO-A	monoamine oxidase inhibitor A
MRNA	messenger ribonucleic acid
NE	norepinephrine
RD	reward dependence
SERT	serotonin transporter
SPECT	single photon emission computerized tomography
Stroop	The Stroop Test
TPH	tryptophan hydroxylase

problems, and the acute intrinsic psychiatric illness. Currently recognized causes of the diathesis include genetic influences, rearing and early traumatic life experiences, chronic illness, chronic substance or alcohol abuse, and dietary factors leading to low cholesterol levels (1).

The process model of suicidal behaviour is also based on a state–trait interaction approach but incorporates as well the effect of this interaction on the gradual evolution of suicidality over time. The suicidal process concept describes the development and progression of suicidality as a process occurring within individuals and in interaction with their surroundings. The process may evolve from thoughts about taking one’s life, which may grow through often-recurrent suicide attempts with increasing lethality and suicidal intent and end with completed suicide (4). As shown in Figure 1, the state–trait interaction approach describes 3 levels of risk factors: trait-dependent factors, state-dependent factors, and threshold factors. Recent research findings indicate that the trait-dependent and the state-dependent factors can be described in psychological and biological terms. The findings from biological studies of suicidal behaviour are reviewed below. Studies in the cognitive psychological domain have shown that 3 characteristics constitute the trait-dependent predisposition to

**Figure 1** The state–trait interaction component of the process model



suicidal behaviour. These are, first, perceptions of “defeat” (a tendency to perceive oneself as a loser when confronted with a psychosocial stressor); second, perceptions of “no escape” (associated with autobiographical memory impairment and problem-solving deficits leading to perceived entrapment); and third, perceptions of “no rescue” (the tendency to develop feelings of hopelessness) (5).

### The Neurobiology of Suicide and Suicidality

Neurobiological characteristics that are potentially associated with suicidality have been studied using several methods (for example, in divergent body fluids, in blood platelets, and in the brains of individuals who completed or attempted suicide). This section reviews relevant findings according to the research method used and the biological system under study (that is, cortisol, serotonin [5-HT], norepinephrine, or others).

Elevated 24-hour urinary cortisol production was found in patients who recently attempted suicide, compared with patients who did not have a history of suicidal behaviour (6). Depression patients who attempted or reattempted suicide had a significantly smaller 24-hour urinary output of the dopamine metabolite homovanillic acid (HVA) than did depression patients who had not attempted suicide (7). In studies comparing plasma cortisol levels in suicidal and nonsuicidal individuals following the administration of 1 mg dexamethasone (dexamethasone suppression test [DST]), the results have been contradictory. Recently, however, Coryell and Schlessler showed that baseline dexamethasone nonsuppression was associated with a fourteenfold increase in the likelihood of suicide during 15 years of follow-up (8). Arginine vasopressine (AVP) and corticotropin-releasing hormone (CRH) are both localized in the parvicellular

neurons of the hypothalamic paraventricular nucleus. Because AVP is an important corticotropin secretagogue, AVP concentrations in plasma and cerebrospinal fluid (CSF) have been studied. Inder and others found higher AVP concentrations in the plasma of suicide attempters suffering from depression (9). Conversely, Brunner and others did not (10). Both studies showed a correlation between AVP and cortisol concentrations. However, with regard to adrenocorticotrophic hormone (ACTH) and cortisol responses in the dexamethasone suppression CRH (Dex/CRH) test, the Brunner and others study found no difference between depression patients who attempted suicide and depression patients who did not attempt suicide, possibly owing to small sample sizes.

Recently, there have been indications for increased suicide risk with decreasing cholesterol levels, whether they occur spontaneously or whether they are attributable to drugs or diet. The increase may be greater when cholesterol is reduced through diet, compared with drug treatment (11).

Elevated levels of CRH in the CSF of suicide victims also indicate increased activity of the hypothalamic-pituitary-adrenal (HPA) axis associated with suicidal behaviour (12). However, not all studies have shown a similar association, and patients who made repeated suicide attempts have been found with even lower CSF CRH concentrations than nonrepeaters (13). No differences in CSF AVP concentrations could be demonstrated between depression patients who attempted suicide and depression patients who did not attempt suicide (10). Studies of the 5-HT metabolite 5-HIAA in the CSF have provided the first indication that the 5-HT neurotransmission system has a role in the pathogenesis of suicidal behaviour. Indeed, Marie Åsberg and her coworkers showed an association between 5-HIAA levels and serious suicide attempts (14). Subsequent studies have confirmed this finding in patients suffering from major depression, schizophrenia, and personality disorders and have indicated a negative correlation between CSF 5-HIAA and lethality of the suicide attempt. Moreover, it has been shown that low CSF 5-HIAA predicts future suicide attempts and completed suicide (15), indicating that this biochemical marker reflects a stable trait, analogous to the association between low brain-stem levels of 5-HT or 5-HIAA in suicide victims, independent of psychiatric diagnosis (1). Some, but not all (10,16), CSF studies have indicated that the dopamine

neurotransmission system is involved in the pathophysiology of suicidal behaviour and that autoimmune mechanisms may be responsible in cases of deficient functioning (17).

A blunted prolactin response to a challenge with the 5-HT-releasing drug fenfluramine has been shown in patients who suffer from major depression or personality disorders and who have a history of attempted suicide. As with CSF 5-HIAA, there appears to be a negative correlation between the prolactin response to fenfluramine and the lethality of the suicide attempt (18).

Reduced 5-HT uptake, fewer serotonin transporter (5-HTT) sites, and increased density of 5-HT<sub>2A</sub> receptors have been found in platelets of suicidal subjects with depression. In addition, a positive correlation between a (possibly compensatory) upregulation of 5-HT<sub>2A</sub> platelet receptors and severity of the most recent suicide attempt has been found (19,20). However, it is currently unclear to what extent changes in serotonergic (5-HTergic) platelet functions reflect altered 5-HTergic activity in the brain. For instance, prolactin response to fenfluramine was found to correlate with CSF 5-HIAA levels, but platelet 5-HT<sub>2</sub> indexes were not: the number of platelet 5-HT<sub>2</sub> receptors and the prolactin response to fenfluramine correlated only in patients aged 30 years or over (21).

Reduced binding sites for CRH have been found in post-mortem brains of suicide victims (22). Further, post-mortem brain receptor mapping studies suggest that 5-HTergic input to the orbital prefrontal cortex may be deficient in persons who are at risk for suicidal behaviour. Some, but not all, studies indicate that 5-HT receptor populations are altered in the brains of suicide victims: there are decreases in presynaptic binding sites in the prefrontal cortex (for example, reduced 5-HTT binding) and increases in postsynaptic receptors such as the 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors. Pandey and coworkers recently studied post-mortem brains of teenage suicide victims (23) and found that a greater number of active 5-HT<sub>2A</sub> receptor binding sites was not the consequence of more binding sites alone: gene expression contributes to this greater number, as indicated by a higher gene expression of 5-HT<sub>2A</sub> receptors and the cognate protein in the prefrontal cortex and the hippocampus. The quantitative changes in receptors appear to be associated with suicide independent of psychiatric diagnosis (24). However, it has recently been argued that the increased density of postsynaptic 5-HT<sub>2</sub> receptors in the brains of suicide victims, especially in Brodmann's area 9, is related more to major depression, and particularly to the dysfunctional attitudes associated with depression (see below), than to suicide (25). As discussed below, however, it is possible that such dysfunctional attitudes delineate a subgroup of depression patients with a particularly increased risk of suicide. Arango and colleagues (26) studied binding to 5-HTT sites, messenger ribonucleic acid (mRNA) expression, and

5-HT<sub>1A</sub> autoreceptor binding in the brain-stem dorsal raphe nucleus (DRN) and found indications for comparatively lower numbers of 5-HT<sub>1A</sub> receptors and DRN neurons expressing SERT mRNA among individuals with depression who committed suicide. Recent studies have provided evidence that, in addition to quantitative receptor alterations, the signalling cascade through which these receptors mediate their physiological responses is also involved in the pathophysiology of suicide. More particularly, post-mortem studies have shown alterations in both the phosphoinositide and adenylyl cyclase-cAMP signalling systems associated with suicide (27,28). Post-mortem studies of the noradrenergic system have revealed fewer noradrenergic neurons in the locus coeruleus of suicide victims, increased brain stem levels of tyrosine hydroxylase, and lower levels of postsynaptic adrenergic receptors in the cortex. A possible explanation for these findings is that they are associated with an increased stress response before suicide, resulting in the excessive release of norepinephrine, a secondary upregulation in tyrosine hydroxylase biosynthetic activity, and a downregulation of postsynaptic adrenergic receptors in the cortex (24).

Functional neuroimaging is a relatively new and useful tool for the *in vivo* study of neurobiological characteristics of the central nervous system. Using single photon emission computerized tomography (SPECT) and a highly selective radioligand, our group has recently demonstrated reduced binding potential of the 5-HT<sub>2A</sub> receptor in the (particularly dorsolateral) prefrontal cortex of patients who have attempted suicide, the reduction being more outspoken in violent than in nonviolent attempters (29).

While there is little doubt about the familial clustering of suicide (for example, see reference 30), findings from studies on the heritability of different aspects of suicidality have been contradictory (for an overview of familial aggregation and molecular genetic studies, see reference 31). In a recent sibling-pair study, Farmer and coworkers could not show a genetic effect on the occurrence of suicidal ideation (32); however, differences in the allelic distribution of the gene coding for the 5-HT<sub>2A</sub> receptor were described when healthy control subjects and patients suffering from major depression, particularly those reporting suicidal ideation, were compared (33). With regard to suicide, McGuffin and coworkers have estimated that 43% of the variance in the liability to suicide is attributable to additive genetic effects (34). Indeed, first-degree relatives of individuals who have committed suicide (including dizygotic twins) have more than twice the risk of the general population, while for identical cotwins of suicide victims, the relative risk increases to about 11. Twin and adoption studies suggest that most or perhaps all the familiarity of suicide results from genetic factors. It is not

known at present whether the genes predisposing to suicide are identical to those predisposing to affective disorder, but it seems probable that the overlap is incomplete. A recent large, population-based, case-control study showed that completed suicide and psychiatric illness in relatives are risk factors for suicide and that the effect of family suicide history is independent of the familial cluster of mental disorders (35). It also seems probable that the mode of inheritance of suicide is complex, involving many genes. However, in view of the well-documented association between 5-HTergic disturbances and suicidal behaviour, as reviewed above, it is not surprising that molecular genetic studies have focused on genes involved in metabolic 5-HTergic pathways. More particularly, such studies have suggested a role for the genes coding for tryptophan hydroxylase, the 5-HT<sub>2A</sub> receptor, and the 5-HTT (for an overview, see reference 33). In addition, an association between monoamine oxidase-A (MAO-A) gene polymorphism and suicide in depression patients has recently been described (36). However, the results of most of these studies are currently to be regarded as inconclusive (for a metaanalysis of tryptophan hydroxylase studies, see reference 37). Among other factors, this is owing to differences in phenotypic characterization of subjects with regard to the suicidal behaviour and the accompanying psychiatric disorder. Moreover, it has recently been suggested that completed suicide and attempted suicide differ with regard to genetic variability (38).

In summary, it appears that at least 3 neurobiological systems are involved in the pathogenesis of suicidal behaviour. First, urinary cortisol production, CSF studies, DST nonsuppression, and post-mortem brain studies suggest a hyperactivity of the HPA axis associated with suicidal behaviour. Second, indications for an excessive release of norepinephrine and associated changes in the noradrenergic neurotransmission system have been found. Third, a large number of studies using blood platelets, CSF, post-mortem brains, functional neuroimaging, and genetics have convincingly shown a deficient 5-HTergic system associated with suicidal behaviour. In addition, CSF and post-mortem studies indicate the involvement of the dopaminergic system, but more research is required to confirm this.

### Clinical Correlates of Neurobiological Findings

Two studies have investigated trait-related correlates of the increased 24-hour urinary cortisol production in attempted suicide patients and have found increased cortisol production to be correlated with increased emotional distance from others (6,39).

As described above, there is ample evidence of an association between suicidal behaviour and the 5-HT neurotransmission

system. Divergent research approaches have provided similar results, suggesting a causal interpretation of this association. How an impaired 5-HTergic function is actually involved in the pathogenesis of suicidal behaviour is, however, much less clear. Several hypotheses have been put forward, and several studies have shown associations between reduced activity of the 5-HT system on the one hand and disinhibition, impulsivity, disturbed regulation of anxiety and aggression, and behavioural inhibition on the other hand.

For instance, Mann and colleagues described an association between tryptophan hydroxylase (TPH) polymorphism and anger-related traits (40) and between cortical 5-HTT binding and aggression (41). Lower CSF 5-HIAA levels were found to be independently associated with severity of lifetime aggressivity and a history of suicide attempts with higher lethality (16). Noteworthy is the recent finding of decreased dysfunctional attitudes—that is, negatively biased views of oneself, the world, and the future—in healthy volunteers following the administration of the 5-HT agonist d-fenfluramine. In the same study, it was found that dysfunctional attitudes in depression patients are positively associated with cortical 5-HT<sub>2</sub> binding potential, especially in Brodmann's area 9 (25). Our group recently demonstrated that the binding potential of the 5-HT<sub>2A</sub> receptor in the prefrontal cortex correlates significantly with levels of hopelessness and with scores on the temperament dimension "harm avoidance," which is a trait marker of behavioural inhibition (42).

### Toward a Psychobiological Model of Suicidal Behaviour

As stated in the introduction to this paper, major advances in our knowledge of the pathogenesis of suicidal behaviour have recently been made in the biological and cognitive psychological domains. The previous paragraph has described how we are now gaining insight, not only in the clinical correlates of biological findings but also in the association between biological findings and cognitive psychological characteristics that may be typical for suicidal patients. It is becoming clear that such biological and psychological characteristics may show a considerable overlap, thus allowing for the description of a psychobiological model of suicidal behaviour (4).

The 3 cognitive psychological characteristics associated with suicidality, as described in this paper's introduction, form a starting point for the elaboration of this hypothetical model.

From a cognitive psychological point of view, involuntary hypersensitivity to stimuli signalling "loser" status, attributable to an attention bias, constitutes the first component of the model. Research has shown that social, and particularly interpersonal, stressors commonly precipitate suicidal behaviour. From a personality-based point of view, temperamental dimensions such as "reward dependence" (43) or "stability"

**Table 2 Three components of the trait-dependent predisposition for suicidal behaviour: a hypothetical psychobiological model (4)**

Cognitive psychology	Clinical phenomenology	Neuropsychology (assessment)	Neuroanatomy	Personality	Neurobiology
Loser status	Sensitivity to social stress	Attention (modified STROOP)	FTC + HC	RD	NE 5-HT <sub>1A</sub> HPA AVP
No escape	Impaired problem solving	Memory (working memory; AMT)	PFC	—	—
No rescue	Hopelessness impulsivity aggression	Fluency (modified fluency task)	(DL)PFC + A	HA	5-HT <sub>2A</sub> dopamine

A = amygdala; AVP = arginine vasopressin; AMT = autobiographical memory test; (DL)PFC = (dorsolateral) prefrontal cortex; FTC = frontotemporal cortex; HA = harm avoidance; HC = hippocampus; HPA = hypothalamo-pituitary-adrenal axis; NE = norepinephrine; RD = reward dependence; 5-HT<sub>1A</sub> = serotonin-<sub>1A</sub> system; 5-HT<sub>2A</sub> = serotonin-<sub>2A</sub> system

(39) mediate sensitivity to interpersonal events. We have demonstrated that attempted-suicide patients show lower scores on reward dependence than do psychiatric control subjects without a history of suicidal behaviour. Further, the score on this dimension (as with the stability dimension, 39) correlates significantly with 24-hour urinary cortisol production, reflecting activation of the HPA axis, as described above (6). It thus appears that the first component of the psychobiological model comprises an interrelated trait-dependent interpersonal sensitivity and activation of the HPA axis, possibly mediated by attentional biases. It has been suggested that the frontotemporal 5-HT<sub>1A</sub> system (in conjunction with the hippocampus) is involved in resilience toward psychosocial stressors (44). Further research is needed to elucidate the role of noradrenaline and AVP in this component: as described above, both appear to be associated with the activation of the stress system. In this context, it is important to point to the suggestion that both noradrenaline (43) and neuropeptides such as oxytocin and vasopressin (45) are involved in the neurobiological modulation of reward dependence. Moreover, there is evidence that noradrenaline has a role in the modulation of attentional processes (for example, see reference 46). As Table 2 indicates, the first component may thus comprise several potentially interrelated psychological and biological characteristics.

The second cognitive psychological characteristic associated with suicidal behaviour is a perception that there is “no escape” from psychosocial or interpersonal adversity. Based on their extensive study of this phenomenon, Williams and coworkers have linked this perception to deficient problem solving, which is in turn associated with overgeneralized autobiographical memory and leads to the sense of entrapment (5). Current knowledge does not allow for any speculation about a neuroanatomical and neurobiological basis for

this component of a psychobiological model of suicidal behaviour.

A perception that there is “no rescue” from the psychosocially adverse situation constitutes the third cognitive psychological characteristic of suicidal individuals. Fluency tasks have demonstrated that the tendency to this perception reflects a deficient capacity for generating positive events and not excessive anticipation of future negative events (5). In addition,

fluency in generating positive events was found to correlate negatively with levels of hopelessness; in other words, the less fluent patients were in generating positive future events (that is, rescue factors), the higher were their levels of hopelessness. A recent comparative functional neuroimaging study by our group used a fluency paradigm and showed blunted activation in the dorsolateral prefrontal cortex in patients who had attempted suicide (47). As described above, our group was also able to demonstrate a negative correlation between (mainly dorsolateral) prefrontal binding to 5-HT<sub>2A</sub> receptors and levels of hopelessness (42). This finding adds to the recent finding of a 5-HTergic modulation of dysfunctional attitudes about oneself, the world, and the future (25). In the same study, we found that both prefrontal 5-HT<sub>2A</sub> binding and levels of hopelessness correlate with scores on the temperamental dimension “harm avoidance,” which is a trait-dependent measure of behavioural inhibition or regulation of anxiety. Conversely, they do not correlate with novelty-seeking scores, including the impulsivity subdimension (43). As Table 2 (row 3) shows, a cluster of hopelessness, behavioural inhibition, and prefrontal 5-HT<sub>2A</sub> functioning may constitute the third component of the hypothetical psychobiological model of suicidal behaviour. How prefrontal 5-HT neurotransmission is involved in the neurobiological modulation of fluency remains to be demonstrated. Moreover, how the above-noted findings with regard to impulsivity and aggression fit into this model is also currently unclear. Thus, there is evidence that 5-HTergically modulated behavioural inhibition has a primary role of in the pathophysiology of suicidal behaviour. However, it may well be that, for suicidal behaviour to occur, aggressive impulses (perhaps dopamine-driven) are needed to break through behavioural inhibition and that the association between 5-HTergic measures and trait-dependent aggression or impulsivity is secondary in nature.

Epidemiological research has shown that attempted suicide is associated with a high risk of repetition and with a strongly increased risk of completed suicide. In a way similar to that described by Post for affective disorders (48)—that scarring and

residua add to the trait-like vulnerability and thus increase the probability of recurrence—it may well be that having had one episode of self-harming behaviour increases the risk of a subsequent episode. The state–trait interaction may thus be responsible for the suicidal process phenomenon, as defined above, which displays a progression of suicidality (with repeated attempts commonly characterized by increasing levels of suicidal intent, medical severity, and lethality of the method used) and which may reflect an increase in the trait-dependent vulnerability for suicidal behaviour. It remains to be demonstrated whether this increase is owing to the detrimental effects of hyperactivity of the HPA axis on the 5-HTergic system (for a thorough review of the neurobiology of the suicidal process, see reference 4).

### Implications for the Prevention and Future Research of Suicidal Behaviour

This paper has reviewed the rapidly increasing body of evidence for a neurobiological basis of suicidal behaviour. More particularly, hyperactivity of the HPA axis, the activation of the noradrenergic neurotransmission system, and deficiencies in the 5-HT system appear to be involved. There is increasing evidence for an overlap between findings from biological research and findings from cognitive psychological studies, allowing for the description of a hypothetical psychobiological model of suicidal behaviour. In this model, 2 issues are particularly important: first, a state–trait (or stress–diathesis) interaction; and second, a dissection of the trait-dependent predisposition into 3 components, each having underlying neuropsychological and neurobiological characteristics.

With regard to preventing suicidal behaviour, the consequences of this state–trait interaction model can be described in terms of risk assessment and treatment. Assessing the risk of suicidal behaviour should thus include not only particular characteristics of the depressive episode, such as severity of depressive symptoms and level of hopelessness, but also trait-dependent issues. The latter should include, first, a familial and personal history of suicidal behaviour and, second, the clinical assessment of sensitivity to psychosocial stressors and problem-solving capacities.

The description of the (potentially interrelated) psychological and biological characteristics of a trait-dependent predisposition for suicidal behaviour indicates that treatment approaches can be defined in psychological and biological terms. As described by Williams and Pollock (5), the psychotherapeutic treatment of the predisposition for suicidal behaviour should address the 3 core cognitive psychological characteristics by teaching patients, first, to identify when their hypersensitivity to particular stimuli may occur, so that they can distance themselves from its effects. Second, patients should practise detailed recollection of past events to learn to encode events in a more specific and less schematic way. For instance, they can participate in dialectical behaviour therapy (which includes the detailed rehearsal of precipitants of suicidal urges or acts) or mindfulness-based cognitive therapy (which aims to help patients focus on the moment-by-moment experience in a nonjudgemental way, thus reducing overgeneralized autobiographical memory). Third, patients

should be encouraged to practise generating positive (that is, rescue) events.

From a psychopharmacological point of view, it may be clear from this review that 5-HT agonists can be expected to play a role in the treatment and prevention of suicidal behaviour, not only by effectively treating depressive episodes but also through their effect on the trait-dependent predisposition. There are few studies of the effects of 5-HTergic drugs on suicidal ideation and behaviour (suicidal patients are often excluded from participation in clinical trials); however, a recent study assessed the effects of paroxetine in a group of patients with a history of multiple suicide attempts but not major depression (49). While no overall effect on the repetition of suicide attempts could be demonstrated, post hoc analysis showed a beneficial effect in so-called “minor repeaters”—patients with a history of fewer than 5 suicide attempts.

As described above, the role of trait-dependent 5-HTergic dysfunction in the pathophysiology of suicidal behaviour is not confined to depressive disorders. This dysfunction also appears to be involved in the development of suicidal behaviour in the context of other disorders, such as schizophrenia, substance abuse, and bipolar disorder; some (50), but not all (51,52), studies indicate that the use of 5-HTergic drugs in the treatment of these disorders—that is, the use of atypical antipsychotics and lithium, respectively—is associated with a decreased risk of suicidal behaviour.

Despite increasing insight into the pathogenesis of suicidal behaviour, it is currently not clear to what extent interventions, such as those described above, are actually associated with a reduced occurrence of suicidal behaviour. For instance, based on our current knowledge, it is unclear whether psychotherapeutic or pharmacologic treatments effectively decrease repetition of suicide attempts (53). The neurobiological modulation of neuropsychological functions involved in the cognitive psychological characteristics of suicidal individuals, described above in the context of the psychobiological model of suicidal behaviour, suggests that a combination of psychopharmacological and psychotherapeutic interventions is needed. Drug treatment can thus be expected to enhance the substrate for learning from psychotherapy. Further research is clearly needed to study the effects of such a multimodal approach to treating and preventing suicidal behaviour.

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**Résumé : La neurobiologie du suicide et de la suicidabilité**

**Objectif :** Évaluer l'état actuel des connaissances sur la neurobiologie du suicide et de la suicidabilité.

**Méthode :** La documentation sur la neurobiologie du suicide et de la suicidabilité a été examinée.

**Résultats :** Il y a des preuves concluantes que l'activité de 3 systèmes neurobiologiques joue un rôle dans la pathophysiologie du comportement suicidaire. Ce sont l'hyperactivité de l'axe hypothalamus-pituitaire-surrénal, la dysfonction du système sérotoninergique (5-HTergic), et l'activité excessive du système noradrénergique. Alors que le premier et le troisième système semblent participer à la réaction aux événements stressants, la dysfonction du système sérotoninergique est estimée dépendre des traits et être associée aux perturbations du réglage de l'anxiété, de l'impulsivité et de l'agressivité. On peut formuler l'hypothèse que les dysfonctions neurobiologiques favorisent l'apparition du comportement suicidaire par la modulation perturbée des fonctions neuropsychologiques de base.

**Conclusion :** Les connaissances croissantes sur le fondement neurobiologique du comportement suicidaire indiquent que les agonistes de la sérotonine (5-HT) jouent un rôle important dans le traitement et la prévention du comportement suicidaire. Les études sur l'efficacité de ces médicaments ont toutefois été décevantes. Étant donné que le comportement suicidaire est toujours un grand problème de santé publique, il est évident qu'il faut plus de recherche, y compris des études sur l'effet des approches pharmacologique et psychothérapeutique combinées.