

## Review



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# The serotonergic system in mood disorders and suicidal behaviour

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A stress-diathesis explanatory model of suicidal behaviour has proved to be of heuristic value, and both clinical and neurobiological components can be integrated into such a model. A trait deficiency in serotonin input to the anterior cingulate and ventromedial prefrontal cortex is found in association with suicide, and more recently non-fatal suicidal behaviour, and is linked to decision-making and suicide intent by imaging and related studies *in vivo*. The same neural circuitry and serotonin deficiency may contribute to impulsive aggressive traits that are part of the diathesis for suicidal behaviour and are associated with early onset mood disorders and greater risk for suicidal behaviour. Other brain areas manifest deficient serotonin input, that is, a trait related to recurrent major depressive disorder and bipolar disorder. Thus the serotonin system is involved in both the diathesis for suicidal behaviour in terms of decision-making, and to a major stressor, namely episodes of major depression.

## 1. A hypothetical explanatory model of suicidal behaviour

Major depressive episodes and suicidal behaviour often appear to be triggered by stressful life events, but are not normal responses to stress. They occur in patients in whom there is a diathesis or predisposition to either recurrent mood disorders or to suicidal behaviour, often to both. Suicidal behaviour is a complication of psychiatric illness, most commonly major depression. Most patients with a major depression never attempt suicide and the ones that make a suicide attempt have a diathesis for suicidal behaviour. This has been formulated as the stress-diathesis model for suicidal behaviour [1]. Work on the components of the diathesis for suicidal behaviour and on the diathesis for recurrent mood disorders is a relatively new field of research, but some findings are emerging. The diathesis for suicidal behaviour is partly heritable and certainly transmitted in families [2]. Components that have been identified include aggressive/impulsive traits, pessimism or a tendency towards hopelessness, more severe suicidal ideation and subjective depression in the context of an episode of major depression, and cognitive rigidity or impaired problem solving.

The cause of this diathesis is both genetic [3–6] and non-genetic, with the latter at least partly the result of childhood adversity. Although the diathesis for suicidal behaviour is partly heritable, with estimates of over 50 per cent [7], the specific genes involved remain mostly unknown. Genome-wide array studies have proved to be disappointing in terms of confident identification of candidate genes for both major depression [8] and for suicidal behaviour [9–12]

In an effort to identify the relevant genes underlying the diathesis for suicidal behaviour, another research strategy has been to examine the known neurobiological abnormalities associated with suicidal behaviour. Because genetic abnormalities involve trait biological phenotypes, and trait clinical, emotional and cognitive phenotypes, important research has focused on such biological and clinical phenomena. Traits have the advantage that the abnormality is present all the time and can predict future risk of suicidal behaviour, in addition to being a marker of a possible past suicide attempt. A set of potential endophenotypes can be identified in relation to suicidal behaviour and the genes associated with these endophenotypes may be easier to identify than the genes associated with suicidal behaviour [13].

## 2. A stress-diathesis model of suicidal behaviour

A psychiatric disorder, of which the commonest is an episode of major depression, is present in association with over 90 per cent of all suicides according to psychological studies conducted in the United States and western Europe [14–18]. Part of the neurobiology observed in recurrent major depression, that is present between episodes as well as during episodes, is a series of abnormalities in the serotonergic system [19]. Cerebrospinal fluid (CSF) levels of the main serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are low in more lethal suicide attempters, and predict the risk for future suicide with an odds ratio of 4.6 [20]. Convergent evidence comes from some reports of low CSF 5-HIAA in suicide attempters with other diagnoses such as schizophrenia [21,22], bipolar disorder [23] and personality disorders, although there are fewer studies and less consensus in these other disorders [24,25]. Nevertheless, if correct, such findings suggest that less serotonin transmission, as implied by less 5-HIAA, appears to be associated with suicidal behaviour across psychiatric diagnostic boundaries, as would be expected if it were associated with the diathesis for suicidal behaviour instead a specific psychiatric disorder. A review of post-mortem brain studies of suicides has found much the same thing: most studies find suicides have lower levels of serotonin and/or 5-HIAA in the brainstem serotonin neurons compared with psychiatric-matched groups [26–28]. These findings are puzzling because some studies find more serotonin neurons and more tryptophan hydroxylase 2 in the raphe nuclei of depressed suicides [29,30], and others find no differences [31]. Thus, a serotonin deficit appears to be present in both fatal and non-fatal suicide attempts [32]. This may be a trait because low CSF 5-HIAA predicts the risk for future suicide, and other studies have shown that CSF 5-HIAA levels are fairly stable, partly heritable and lower in adult non-human primates who experience maternal deprivation. The latter effect appears to be mostly in those non-human primates who carry the lower expressing 5' upstream promoter variants in the non-human primate homologue of the human serotonin transporter gene known as 5-HTTLPR [33,34]. As mentioned above, aggressive traits are part of the diathesis for suicidal behaviour, perhaps because they reflect a predisposition to act on emotions such as anger or depression. In that context, low CSF 5-HIAA correlates with severity of lifetime aggressive behaviour and can predict impulsive aggression such as arson and homicide [35,36]. Thus, aggression and suicidal behaviour may share common regulatory aspects that include a role for serotonin inputs to control or suppress the probability and seriousness of these behaviours. Other indices of serotonergic function in the brain, such as the prolactin response to serotonin release by fenfluramine, correlate with severity of past suicide attempts [37] and aggressive behaviours [38], and predict future suicide attempts [39]. Such findings are consistent with trait low serotonergic activity related to the diathesis for both suicidal behaviour and externally directed aggressive behaviour.

## 3. The neural circuitry of the diathesis for suicidal behaviour

Post-mortem autoradiography studies of the serotonin transporter, which is located on serotonin nerve terminals, and the 5-HT<sub>1A</sub> receptor, which is expressed by target neurons

in the terminal fields of the serotonin system, have found that a decrease in transporter binding and an increase in 5-HT<sub>1A</sub> binding is confined to the anterior cingulate and ventral prefrontal cortex (PFC) in suicides post-mortem [40]. There are many studies of post-mortem brain serotonin indices in suicide and depression, and there is some disagreement about specific findings [26,41]. Nevertheless, the numerous positive studies indicate that where there is smoke there is fire. We may not be sure of all the specifics of a serotonin system abnormality, but there seems to be one in depression, impulsive aggression and suicidal behaviour. The affected brain regions include the orbital prefrontal cortex and anterior cingulate identified by autoradiography of serotonin indices in suicide. These regions are involved in behavioural inhibition [42] and decision-making [43], including delayed discounting [44], and are regulated by higher structures such as the dorsal lateral prefrontal cortex that is engaged in willed action [45]. A hypothesis is that deficient serotonin input into these brain regions contributes to risk of suicide.

*In vivo* brain imaging studies of non-fatal suicidal behaviour using positron emission tomography (PET) scanning with <sup>18</sup>F-fluorodeoxyglucose (FDG) or 11-C-methyl-tryptophan show similar things to the post-mortem findings, namely less uptake in ventral or medial PFC in association with seriousness of suicidal behaviour [46]. 11-C-methyl-tryptophan is an analogue of tryptophan and is taken up by serotonin neurons and trapped. The more active the serotonin neurons, the more they need tryptophan, because it is the essential precursor for serotonin, and therefore presumably the greater the uptake in serotonin terminals. Trapping of this tracer in orbital PFC is associated with some polymorphisms in the TPH2 gene [47]. A FDG PET study of suicidal behaviour in major depression [48] found lethality of suicide attempts correlated with two brain regions including the anterior cingulate and medial prefrontal cortex as well as an area in the lateral PFC. This study linked the findings to serotonin because the same FDG scan was done first after placebo and then after fenfluramine: the area correlated with lethality of suicidal behaviour and doubled in size in the fenfluramine scan. Other studies find lower prefrontal cortical 5-HT<sub>2A</sub> binding in suicide attempters [49] that may be related to hopelessness and other suicide-related personality traits [50]. The serotonin transporter binding appears to be lower in some brain regions in suicide attempters with major depression compared with non-attempters with major depression. Several studies relate similar serotonin indices to impulsive aggressive traits in many types of patient populations [51–57] and to response inhibition [58]. Monoamine oxidase A (MAO) binding is also found to be low in aggressive individuals [59] consistent with other reports that a human genetic variant that fails to express the full transcript is linked with impulsive aggression in males and with an aggressive phenotype in male knockout mice. MAO catabolizes serotonin.

Thus, we have convergent evidence for a serotonin abnormality in parts of the PFC and anterior cingulate being related to suicidal behaviour. In terms of determining why such brain regions may be abnormal in the first place, we know very little. Genetic and developmental factors must be considered. Another option is based on the observation that omega 3 polyunsaturated fatty acids (PUFAs) are thought to be deficient relative to omega 6 PUFAs in suicide attempters and suicides [60], and that relative deficiency may predict the risk for suicidal behaviour [61]. Not all studies find these relationships [62], but the findings raise the question of what mechanisms relate PUFAs to suicidal behaviour? PUFAs correlate with PET

$^{18}\text{F}$ -FDG uptake in brain regions [63] that partially overlap with brain regions that correlate with lethality of recent suicidal behaviour. Perhaps these brain regions are related to the neural circuitry regulated by PUFAs that in turn regulates the risk for suicidal behaviour. Although the effectiveness of PUFAs for the treatment of depression has been debated, more recent meta-analyses have found that supplements rich in eicosapentaenoic acid (EPA) and lower in docosahexaenoic acid (DHA) show robust benefit, whereas supplements with more DHA do not show antidepressant benefit [64]. The anti-suicidal effect of EPA remains to be determined. Several lines of research have linked neuroinflammation to suicidal behaviour [65,66]. Although there is debate over the mechanisms involved, one model links neuroinflammation to the serotonin system [67]. In support of this model, interleukin-6 (IL-6) and tumour necrosis factor alpha correlate with CSF 5-HIAA and homovanillic acid (HVA), and IL-6 is elevated in suicide attempters, especially more serious violent attempters, and is correlated with depression severity [68].

Other studies have involved manipulating brain activity *in vivo* by methods such as repetitive transcranial magnetic stimulation (rTMS) or rapid transcranial stimulation to inhibit the function of some key brain region and study the effects on cognition and emotion. TMS inhibition of the dorsolateral PFC in healthy men produces an increase in risky decision-making [69]. The authors proposed that inhibition of the dorsolateral PFC reduces its enhancement of orbital PFC, and compromises the effect of orbital PFC in inhibiting risky decision choices. Such a formulation highlights the potential role of the orbital PFC in reducing the risk of aggressive and suicidal behaviours.

#### 4. The role of childhood stress and genes in determining responses to stress in adulthood

A reported history of childhood stress is associated with increased risk of major depression [70] in addition to the recognized role of genes [71] and of suicidal behaviour [72] in adulthood. Some studies have shown that adult stressors such as the destruction of the World Trade Center on 9 September 2001 or effects of deployment in the US military to Iraq can trigger as many cases of major depression as of post-traumatic stress disorder (PTSD). Not all those exposed to childhood adversity have an increase in adult stress-related psychopathology. Non-human primate studies of maternal deprivation [73] and human studies of childhood adversity [74,75] suggest that some genes increase the risk of long-term psychopathological consequences. For example, carrying a low-expressing 5-HTTLPR allele in the serotonin transporter gene or a low-expressing promoter variant for the monoamine oxidase A gene (MAOAP) can result in a history of childhood adversity predicting greater risk in adulthood of stress triggering a major depressive episode or a suicide attempt in the case of HTTLPR carriers [74] and more anti-social behaviour in the case of MAOP carriers [76]. Subsequent studies have not all replicated these findings but the principle is of importance and future studies need to look more broadly for candidate genes of small effect. It seems probable that direct gene effects, gene–gene interactions, gene–environment interactions and direct environmental effects can all play a role in determining psychopathology. The possibility of a critical period in childhood or development when certain genes can be modified in enduring ways by epigenetic mechanisms such as DNA

methylation or histone marks, to alter adult responses to stress, must be the subject of future research [77]. Although the relative role of genes and epigenetic mechanisms remain to be determined, in both non-human primates and in patients [78], a history of maternal deprivation or physical violence in childhood can result in lower CSF 5-HIAA that persists into adulthood and may contribute to early onset mood disorder, impulsive aggressive traits and greater risk of suicidal behaviour in patients.

#### 5. Biological phenotypes of stress-sensitive psychopathology

We have previously reported that 5-HT<sub>1A</sub> binding is increased in major depression, at least partly because of a higher expressing promoter variant (C-1019G promoter polymorphism 5-HT<sub>1A</sub>PR GG genotype) that is associated with both major depressive disorder [79–81] and with bipolar depression [82]. In post-mortem studies of suicide, higher binding has been reported in orbital PFC in suicides [83]. Higher binding has been reported in association with aggressive traits by PET studies [84]. Although recent studies of 5-HT<sub>1A</sub> binding in PTSD are negative [85], a recent study suggests that there may be elevated binding (G. M. Sullivan *et al.* 2013, unpublished data). If that finding can be replicated, it suggests a common biological phenotype for major depressive disorder (MDD), PTSD, aggressive traits and suicide. The risk for developing these conditions is greater in those subject to childhood adversity and when confronted with stress in adulthood [86,87]. One model of the action of stress is that it impairs prefrontal cortical function and affects related psychopathology and decision-making [88]. Animal studies have identified a role for the 5-HT<sub>1A</sub> receptor in fear extinction, and suggests that lower signal transduction owing to less serotonin release can favour deficits in fear extinction [89]. We have proposed a model of reduced serotonin release due to greater 5-HT<sub>1A</sub> autoreceptor expression in major depression and in bipolar disorder, owing to the higher expressing G allele of the functional C-1019G promoter polymorphism resulting in lower neuronal firing [81,82].

Another phenotype of major depression is low serotonin transporter binding and we have reported this to be present during an episode of major depression [90]; if present between episodes, then it would represent a biologic trait perhaps related to the diathesis. The studies in suicide suggest that in some brain regions low serotonin transporter binding is related to the diathesis for suicide such as the orbital PFC and the anterior cingulate [40]. It remains to be determined by brain imaging whether this finding is also true for patients with a mood disorder who survive a suicide attempt. In suicides, the finding of an additional effect of lower serotonin binding related to suicide and not major depression suggests an additional serotonin system deficit in innervation of orbital PFC and anterior cingulate that may influence decision-making and favour suicide. Recently, it has been reported that MDD suicide attempters have lower serotonin transporter binding than both MDD non-attempters and healthy volunteers in midbrain raphe nuclei [91].

There are several potential causes of low serotonin transporter binding. One cause is the lower expressing promoter alleles that are not only identified in the upstream promoter region (5-HTTLPR), but also in other regions of the gene [92]. For reasons that are not clear, it is difficult to detect a

relationship between 5-HTTLPR genotype and serotonin transporter binding [93]. Perhaps other promoter variants play a major role and override this relationship. Another mechanism is epigenetic and it has been shown that DNA methylation can be related to gene expression and thereby transporter binding [94]. This may explain how childhood adversity can lead to less transporter binding in the brain in adulthood as has been shown in non-human primates [95] and in depressed patients reporting childhood abuse [96]. Finally, serotonin transporter internalization into the presynaptic nerve terminal from the membrane surface is regulated by intra-synaptic serotonin [97] and therefore less serotonin release (perhaps owing to less firing due in turn to more autoreceptors) may result in accelerated transporter internalization and less binding. Which of these mechanisms plays a role in determining lower serotonin transporter binding in suicide or major depression remains to be determined. What can probably be ruled out is the presence of fewer serotonin neurons and, therefore, fewer terminals. We have reported more serotonin neurons in depressed suicides in the dorsal raphe nucleus [98].

## 6. Downstream effects of impaired serotonergic function

The effect of impaired serotonin transmission can be manifested in terms of the neurotrophic actions of the serotonin system and in terms of the neurotransmitter function of the serotonin system on mood and decision-making. Hen & Dranovsky [99] describe how stress can reduce both neuron number in the dentate gyrus as well as neural process length, and both effects can be prevented or reversed by antidepressants including selective serotonin reuptake inhibitors (SSRIs). Adult human brain shows post-mortem evidence of greater neurogenesis in the dentate gyrus in major depression treated with an SSRI compared with untreated major depression [100]. This finding supports the hypothesis that human adult neurogenesis is also responsive to serotonin signalling. A number of studies report that there are fewer neurons in anterior cingulate, hippocampus and PFC in bipolar disorder or MDD, and this neuron deficiency may be partly due to impaired serotonin signalling, although there is no direct evidence.

The 5-HTTLPR serotonin transporter gene polymorphism lower-expressing alleles are associated with vulnerability to childhood stress and serotonin abnormalities such as fewer transporter sites and lower CSF 5-HIAA as discussed earlier. Administering an SSRI for a short period to infant rodents produces a depressed adult phenotype [101], suggesting that fewer serotonin transporters or a blockade of serotonin transporters during a critical period in infancy in rodents equivalent to the third trimester in man produces some long-term downstream

effect that is responsible for altered stress responsiveness and vulnerability to development of depression when stressed in adulthood. Evidence is emerging regarding such potentially important downstream effects. The 5-HTTLPR low-expressing alleles are decreased in functional coupling between amygdala and anterior cingulate [102], as has been also reported in mood disorders [103]. There is also altered white matter (diffusion tensor imaging) in the left uncinate fasciculus [104] that may be related to the functional uncoupling of amygdala and anterior cingulate. Finally, these connectivity deficits may contribute to the hyper-responsive amygdala in this genotype in a fearful faces matching task [105]. This hyper-reactivity of the amygdala may lead to over-encoding of adverse events, especially in childhood, predisposing such individuals to PTSD and excessive stress responses as adults. Finally, the lower-expressing S allele is reported to be associated with greater cortisol stress response in a meta-analysis of association studies [106]. The S allele is also associated with greater personal distress and physiological responses to films of others in distress and more anger, amusement and emotionally expressive behaviours to watching oneself in an embarrassing situation [107]. The association of all of these functional and structural connectivity abnormalities with the serotonin transporter promoter variant indicates how it may be translated into a neurobiologic phenotype that in turn may influence psychopathology and response to stress in adulthood. More research needs to be done to map the temporal course of these biologic, behavioural and cognitive changes.

A review of the role of the serotonergic system in the action of antidepressants is beyond the scope of this paper but it is of interest to note how the serotonin system is involved in the antidepressant action of treatments that appear quite different to SSRIs or medications that affect serotonin receptors such as atypical antipsychotics, or mirtazapine and nefazodone. Deep brain stimulation, most commonly studied when targeting the subcallosal anterior cingulate, shows promise for severe treatment-resistant major depression, and in rodent models of depression, like the forced swim test, appears to require an intact serotonin system to work [108].

## 7. Summary

The serotonin system is part of the stress response systems in the brain and is moulded by childhood experience of stress to determine stress response patterns in adulthood. Such responses determine the vulnerability to develop mood disorders and to respond to depression with suicidal behaviour. Some intermediate biologic phenotypes have been identified, but more work is needed to separate the relative roles of genes, environment and interaction effects.

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