Neuropsychiatry of Suicidal Diathesis

by

Maxwell R Bennett

Submission to the Senate Community Affairs Committee

Inquiry into Suicide in Australia

Maxwell R Bennett AO

Professor of Neuroscience

University Chair

Scientific Director, Brain and Mind Research Institute

University of Sydney

100 Mallett Street, Camperdown

NSW 2050

Email: max.bennett@sydney.edu.au

Suicidal diathesis – a synapse disease

The Joint Submission to the Senate Community Affairs Committee Inquiry into Suicide in Australia by Lifeline Australia and others poses the questions as to why people commit suicide and self-harm and what can we do about it (see Chapters 3 and 4 of the Submission). In this paper I examine the neuropsychiatric basis of suicide, and show that it is likely to be primarily associated with a loss of synaptic connections in certain parts of the frontal lobes of the brain in the largest cohort of suicide victims. This cohort consists of those that have been subjected to sexual and physical abuse as children. Suggestions are made as to what may be done to prevent their appalling suffering.

Epidemiology shows that the major risk factors for suicide are sexual/physical abuse in childhood and a family history of suicide, together with mental health problems such as borderline personality disorder and post-traumatic stress syndrome, factors that are predominant in males and in the indigenous members of the population (see Figures 5 and 6 on pages 50 and 53 of the Lifeline Australia and others submission). These risk factors are not independent as adolescent male suicide attempters are 5.6 times more likely to suffer from post-traumatic stress syndrome and 3.1 times more likely to suffer from borderline personality disorder if they have been sexually abused as children [1]. Indeed those that have been sexually and/or physically abused when children amount to about 65% of all those who attempt suicide in a study of adolescents in a State comparable to that of an Australian State (namely, Seattle, State of Washington, [2]; for a review see [3]). In this Seattle study suicide rates in which the victim injures themselves are five times higher if they have been sexually abused as children than if they have not been abused [2].

Besides sexual/physical abuse the other major risk factor is a family history of suicide. Family, twin and adoption studies indicate that suicidal behavior has an underlying genetic predisposition which, although distinct from a genetic predisposition to mental illness, is nevertheless perhaps contingent on it [4-9], so that these genetic predispositions are not independent when considering suicide. For example a large cohort amongst those that commit suicide or attempt to do so consists of patients with borderline personality disorder and impulsive-aggressive behavior [10-13]. Levels of impulsive-aggressive behavior are correlated with the history of suicidal behavior in patients [14] such that suicide behavior is at least partly explained by familial transmission of impulsive-aggressive behavior [15-17].

In the last few years the changes that occur in the brain of those suffering from psychiatric diseases such as major depression and stress have been ascertained with the introduction of non-invasive magnetic resonance imaging techniques. These, together with animal experiments, have pin-pointed the loss of synaptic function and connections between nerve cells in certain parts of the brain as the main concomitants of childhood abuse leading to stress, depression and suicidal diathesis as outlined below. It is argued that only through an understanding of suicidal diathesis as essentially a disease of the synaptic connections in certain parts of the brain will the stigma of suicide victims be removed and rational procedures put in place to both protect children and rehabilitate those that have suffered this debilitating loss of synaptic function.

Synaptic connections in the brain

Our psychological capacities as in thinking, remembering, perceiving and feeling are dependent on the normal working of our brains (Fig.1). A brief description is given here of synaptic connections in the brain, before turning to consideration of what goes awry with these connections in suicidal diathesis.

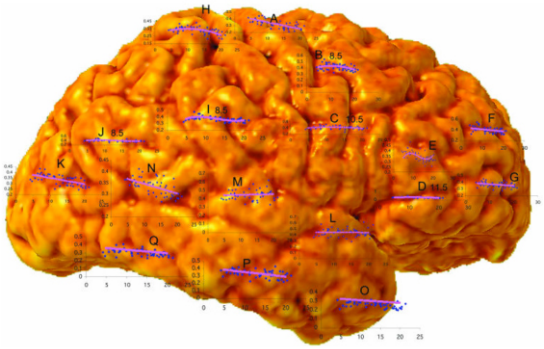

Figure 1. Illustration of the human brain

A principal cell of the brain is the neuron, consisting of a round cell body about 20 μm (1/50 of a millimeter) in diameter, possessing about nine processes. Eight of these processes are relatively short and called dendrites whereas the ninth is called the axon and proceeds from the cell body for distances that range from a few one thousandths of a millimeter up to metres (Fig.2).

The brain contains about 100,000 million neurons, each with an axon forming connections onto many other neurons such that on average each neuron possesses about 10,000 connections (Fig.2). This provides for an immense amount of connectivity (namely 100,000 million multiplied by 10,000 connections) served by well over 100,000 kilometres (62,000 miles) of axons. There is, in general, parcellation of neurons, their connections and long axonal projections in the cortex of the brain. The grey matter of the brain consists of cell bodies together with the connections between them collectively called the

neuropil. The white matter of the brain consists of myelinated axons.

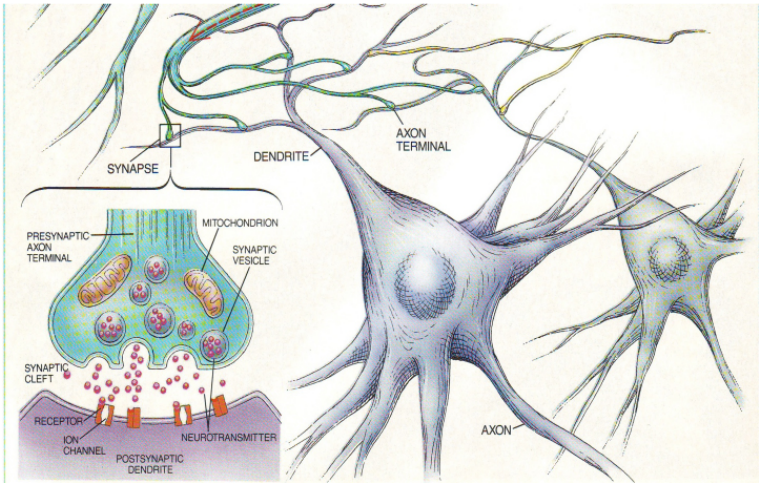

Figure 2. Diagram of neurons and synaptic transmission

The neuropil is of great interest in the context of psychiatric diseases. Fig. 2 shows a diagram indicating two neurons each with their dendritic (labeled) processes together with their single axon (labeled) which is ensheathed by the processes of an oligodendrocyte (not shown). Boxed is the ending of an axon that forms a bulb on the surface of the dendrite of another neuron to form a connection called a synapse. This synapse is shown enlarged in the insert and possesses small circular synaptic vesicles that contain chemical substances released at the ‘presynaptic axon terminal’ into a ‘synaptic cleft’ where they diffuse to attach to a receptor molecule on the ‘postsynaptic dendrite’ of the neuron membrane. Following activation of the receptor molecule the neuron may generate an electrical propagating signal down its axon. The dimensions of the synapse are about 1 μm or 1/1000 of a millimeter.

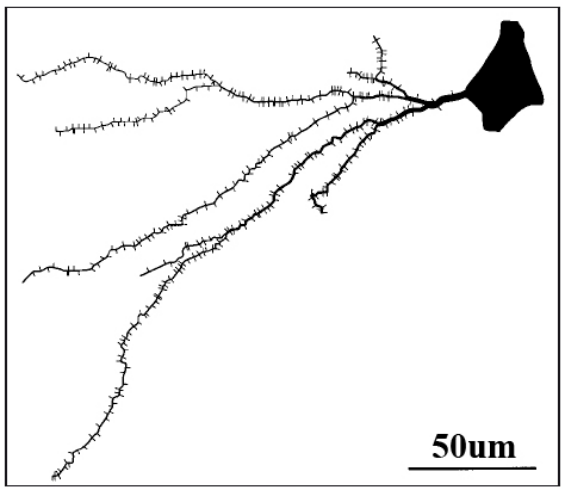

Figure 3. Sites of synaptic connections along the length of the dendrite and its branches

A real neuron in the cortex together with one of its dendritic processes is shown in Fig. 3. This figure shows the sites of synaptic connections along the length of the dendrite and its branches, with each site delineated by a small spineous process emanating from the dendrite [18]. Given that the horizontal calibration bar in this image is 50 μm there is at least one synaptic spine each 2 μm along a dendrite. Although each of these synapses is only about 1 um in extent, the large number of them (10,000) on each neuron ensures that the total volume they occupy is more than that of the cell body of the neuron. The neuropil then contains these dendrites and their connections at synapses.

Depression and the loss of synapses in the rostral anterior cingulate cortex

Functional magnetic resonance imaging or positron emission tomography can give a non-invasive estimate of the functional electrical activity of neurons in different parts of the brain, that is a measurement that does not involve any

invasive intrusion into the skull to gain access to the cortex. Using these techniques indicates that the cortex of the brain in patients suffering from major depression undergoes significant changes in activity, principally in two areas, the amygdala and the rostral anterior cingulate cortex (rACC) (Fig.4).

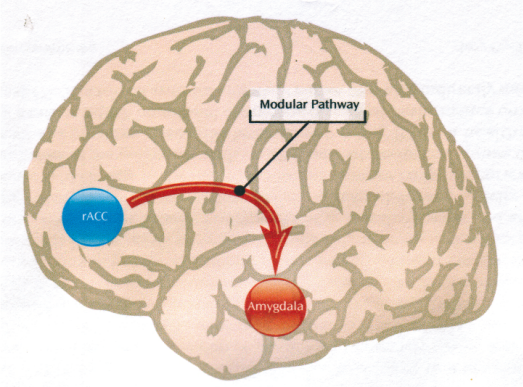

Figure 4. Illustration of the amygdala and the rostral anterior cingulate cortex (rACC).

Interestingly these two areas have connections between them in which the amygdala is normally under inhibitory regulation by the rACC (Fig.4; [19-21]). Similar observations have been carried out on the rACC of those suffering from generalized anxiety disorders in which it has been ascertained that the rACC is hypoactive rather than hyperactive as is the amygdala [22]. In this case the loss of normal activity in the rACC probably leads to the excessive activity that occurs in the amygdala as a consequence of a failure of the former to effectively inhibit the latter. What then are the physical changes in the rACC that lead to its failure to inhibit the amygdala? A search for the anatomical concomitants of the activity failure in rACC using magnetic resonance imaging shows a considerable decrease (about 12%; [23,24]) in the volume of the rACC of depressed patients. In Figure 5 are shown anatomical landmarks traced of the anterior and posterior sub-regions of the cingulate cortex [25]. It is the

volume included in the traced areas that declines in depression [26]. Indeed there is a good correlation between the extent of depression of a patient and the extent of decrease in volume of the rACC [27].

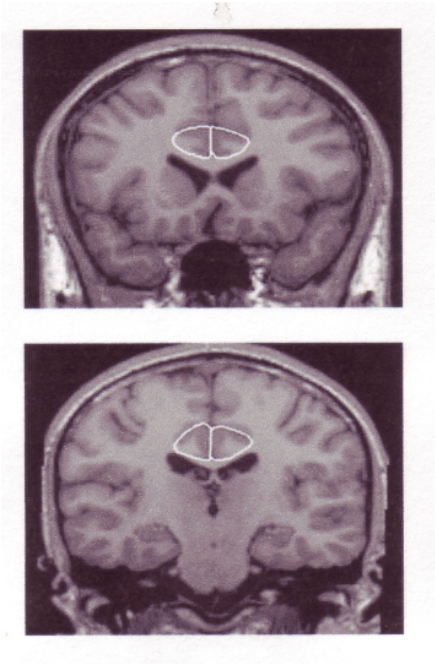

Figure 5. Anatomical landmarks of the anterior (top) and posterior (bottom) sub-regions of the cingulate cortex

Synaptic loss and dendritic atrophy in animals subjected to stressful conditions occur in brain regions that are homologous to the areas where grey matter loss is apparent in major depressive disorder patients, such as the medial prefrontal cortex [28-33]. Presumably this synapse loss and dendritic atrophy is responsible for the large decrease in grey matter volume consequent on the loss of neuropil in these patients. It is very likely then that homologous mechanisms to those that give rise to the loss of synapses and dendrites in stressed animals operate to induce the loss of synapses and dendrites in prefrontal cortex of those suffering from major depressive disorders and in bipolar disorder [30]. The fact that synapse loss and dendritic atrophy can be reversed by lithium administration [30], which also restores anterior cingulate

cortex grey matter volume to normal in bipolar depressed patients [34-36], greatly enhances the proposition that the volume changes in grey matter observed in major depressive disease and bipolar disorder are due to the loss of synapses and dendrites in medial prefrontal cortex regions such as the rostral anterior cingulate cortex. Such loss has now been directly observed in the cortex of patients in postmortem studies [37,38].

Stress, activation of hormones and synapse loss

A poor attachment and/or a stressful relationship between mother and child in the first 18 months results in relative inhibition of the child in approaching novel objects or participating in novel events [39]. The maternal relationship during childhood is critical in determining depression behavior in the adult [40,41]. Anxiety following stressful events is often followed by major depressive disorder in those so predisposed. Anxiety precedes the development of major depressive disorder in about 30% of first episode cases and in about 75% of recurrent episodes, with a 50% co-morbidity [42]. The number of stressful life events from age 21 years to 25 years is predictive of subsequent depression [43,44]. Like major depression**,** stress is accompanied by greatly enhanced activity in the amygdala and significantly reduced activity in the rostral anterior cingulate cortex (rACC; [45,46]).

These changes in amygdala activity associated with stress are similar to those observed in major depression and so might be due to changes in synapses. Animal studies show that stressful events lead to the loss of synapses and in some cases whole dendrites of neurons in prefrontal cortex, a process that leads to the malfunctioning of synaptic neural networks [47]. Mild stress of animals for 20 min during 7 consecutive days leads to decrease in the

number of synapses along dendrites of neurons in the prefrontal cortex [48]. Daily restraint stress of animals, for about 3 hr over 3 weeks, leads to a loss of about 30% of all synapses on neurons in medial prefrontal cortex and this is accompanied by a loss of distal dendritic branches ([32,49-50]; see also [31]). Figure 6 shows examples of randomly selected dendritic segments in control (A) and stressed (B) animals; numbers shown for each segment represent synapses per micrometer length of dendrite for each dendrite analyzed in prefrontal cortex [51,52]. Clearly there is a loss of synapses along the dendrites of the stressed animals.

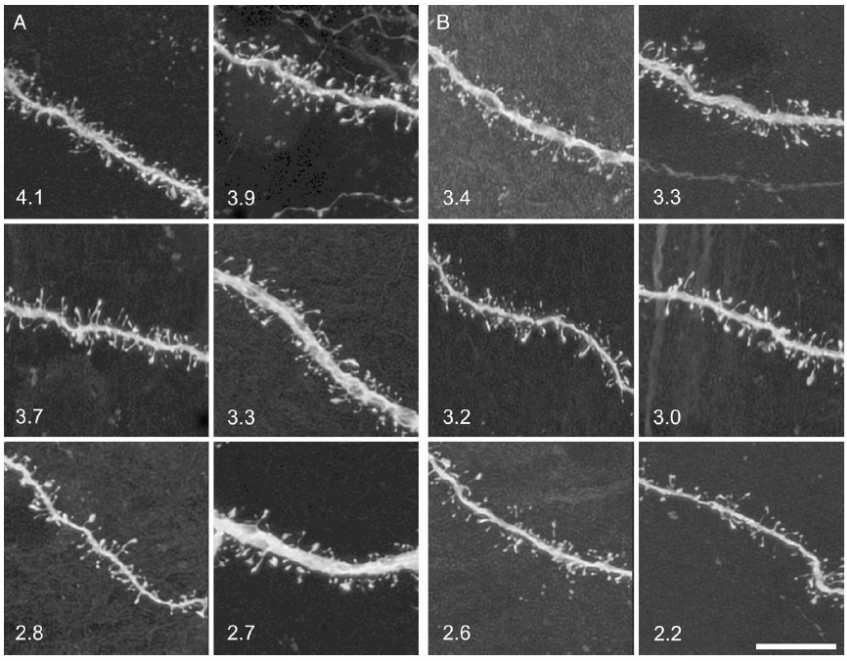

Figure 6. Loss of synapses along the dendrites of stressed animals.

The loss of synapses and dendrites is largely reversed if a period of rest from stress is allowed or if the agent lithium is administered. Thus a 3-week recovery period following a 3-week regime of daily stress results in the return of

most of the dendrites lost during the stress period [53]. A child or adolescent with fewer synapses than normal in the frontal regions following a stressful event might then be exceptionally vulnerable to depression as synapse loss occurs at a high rate in the prefrontal cortex of normal adolescents, so that more than 30% of synapses found at the beginning of this period have normally been lost by the end of it [54,55]. Figure 7 shows that synapses are added during normal childhood (at a rate of about half a million per second) until about 5 years and then there is a normal loss of synapses, mostly during adolescence, until a steady number of synapses is maintained (see the dark line in Fig.7).

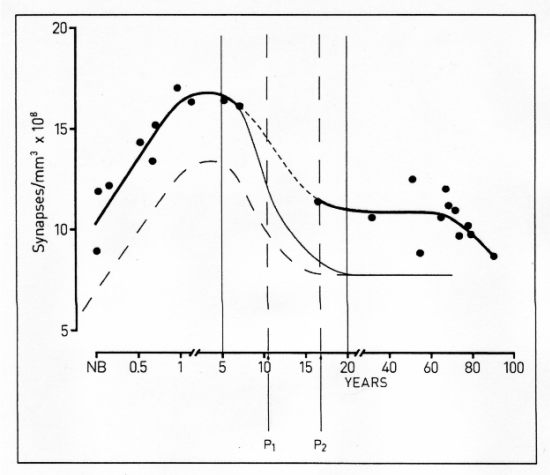

Figure 7. Average number of synapses across different ages.

If however a child at an early age possesses a low number of synapses (broken line in Fig.7) or looses excessive numbers of synapses during adolescence (thin line in Fig.7) then the number of synapses present when adulthood is reached is exceptionally low. This will lead to a failure of synaptic neural networks and therefore failure of normal brain function. As noted above, a more than 30% decrease in volume and activity of prefrontal cortex occurs in major depression disorder (for reviews see [56-58]) indicating a net loss of 60% of synapses there compared with childhood (see Fig.7 and [58-62]).

Stressful events, such as loss of employment or shifting one's house, are accompanied by activation of the amygdala as well as of the reticular formation, which engages the hypothalamus to secrete corticotropin-releasing hormone (CRH; see, for example, [63] and references therein; Fig.8). This brings the adrenohypophysis of the pituitary into play so that it releases adrenocorticotropic hormone (ACTH) that acts on the adrenal cortex to in turn release the glucocorticoid cortisol (Fig.8).

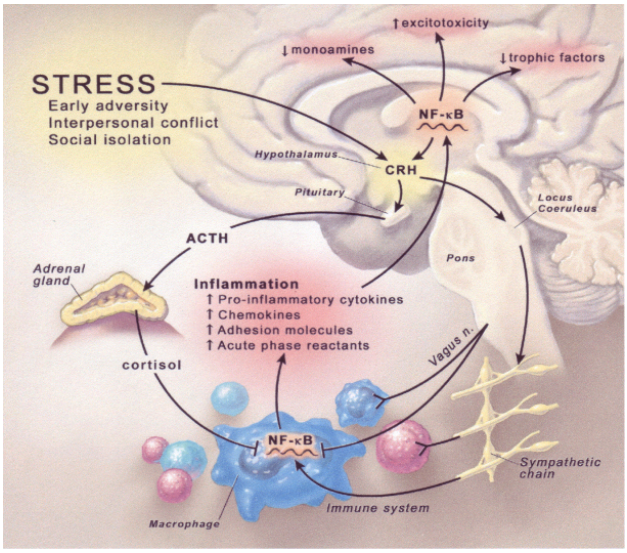

Figure 8. The effects of stress on the hypothalamic-pituitary-adrenal network.

This glucocorticoid (GC) functions as a negative regulator of both the pituitary ACTH and the hypothalamic CRH, completing the hypothalamic-pituitary-adrenal network (Fig. 9). This figure 9 shows the negative feedback of the glucocorticoid on the release of CRH and ACTH (indicated by a bar at the end of the pathways) as well as on the activity of the hippocampus, required for retaining memories. In contrast to this, the glucocorticoid acts back to excite the

amygdala (indicated by an arrow at the end of the pathway), the brain structure implicated in depression as noted above.

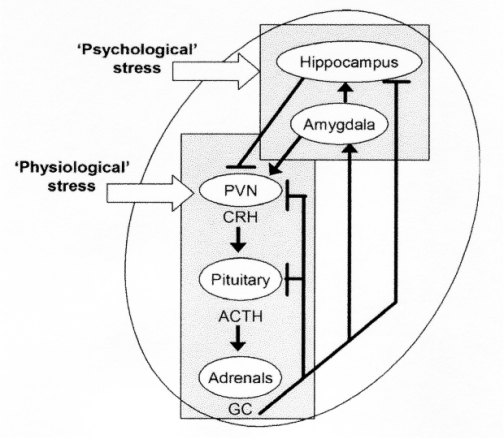

Figure 9. Glucocorticoid as a negative regulator of the hypothalamic-pituitary-adrenal network.

Are the high circulating glucocorticoid levels that accompany stress responsible for synapse loss? Chronic administration of glucocorticoids alone produces loss of synapses. Daily injections into animals of the glucocorticoids that binds to glucocorticoid receptors (GR) in medial prefrontal cortex, leads to loss of synapses and dendrites [48,64-66]. Young children in an insecure relationship with a carer show elevated glucocorticoid cortisol levels when experiencing depressing events whereas those in secure relationships with a carer do not (for a review see [67]). Older children with such insecure relationships not only show enhanced levels of the glucocorticoid cortisol in stressful situations but also a higher risk of behavioral and emotional problems in maturity [68,69]. Indeed adults suffering from clinical depression that have been abused as children show increased responsiveness of the hypothalamic-

pituitary-adrenal system as compared with depressed adults who have not had such experiences when children [40,70].

In summary, CRH is modulated by stress during early development, when maternal care determines the level of central CRH expression and can alter the 'set point' of CRH gene sensitivity into adulthood, through activation of the central-stress response [71]. Decreased maternal care gives rise to offspring that are more fearful when adults and possess higher brain levels of CRH [72-74]. Increased maternal care in animals during the first 10 days of life ensures that when they are adults, exposure to acute stress leads amongst other things to decreased levels of CRH messenger RNA and reduced plasma ACTH, compared with those that do not receive such increased maternal care, with a consequent reduction in activation of the hypothalamic-pituitary-adrenal system responses to stress [75,76]. These effects are probably mediated by changes in the GR gene, a mechanism that I will now comment on because of its implications in suicide diathesis [77].

Childhood abuse and the epigenetic origin of synapse loss

Childhood abuse is a significant factor in suicidal diathesis [11]. Early life abuse increases significantly the risk of life-time major depressive disorder [78,79]. Even children who experience mild adversities are likely to be more reactive to later major difficulties in life [80]. Major depressive disorder is accompanied by changes in the 'set-point' of the hypothalamic-pituitary-adrenal system, with increased CRH, ACTH and cortisol secretory activity occurring which is contingent on impairment in the expression of the glutocorticoid receptor (GR_{II}; Fig.8; [81]), so that cortisol no longer inhibits the release of CRH

and ACTH (Fig.9). Abused girls have a greater incidence of suicidal ideation and suicide attempts than those not abused, and this is accompanied by dysregulation of the hypothalamic-pituitary-adrenal system (Fig.9; [82]). Indeed the failure of the synthetic glucocorticoid dexamethasone to suppress cortisol release in patients is a strong predictor of subsequent suicide ([83]; for a review, see [84]). The inability of dexamethasone to suppress serum levels of cortisol in these suicidal patients points to failure in the normal function of the GR_{II} [85]. Maternal care has effects that militate against this impairment of the GR_{II} [86]. This involves changes in the expression of the GR gene in new-borns, determined in part by both prenatal mood and postnatal care [87].

Partial down-regulation of GR_{II} throughout the brain and the hypothalamic-pituitary-adrenal system in animals gives results very similar to those observed in suicidal youths: these are normal basal levels of glucocorticoids, failure to suppress the release of these with dexamethasone and increased depressive behaviour when stressed, as well as substantial increases in cortisol release when stressed. There is now good evidence that what are called epigenetic effects lead to a decrease in GR_{II} and that this might occur following childhood neglect and abuse leading to suicidal diathesis. Epigenetics is the ensemble of alterations in gene functions that are heritable, but cannot be explained by changes in the DNA sequence itself, the normal basis for changes in gene function [88,89]. It is now known that suicide victims with a history of childhood abuse possess epigenetic changes that lead to down-regulation of GR_{II} [88,90,91]. Methylation of the promoter region of the GR_{II} gene could give rise to such down-regulation of GR_{II}.

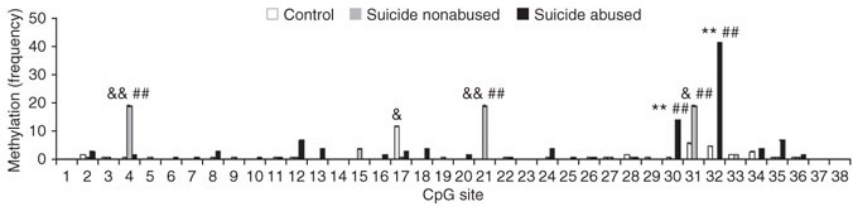

Figure 10. Methylation of various sites of the GRII gene promoter region.

Figure 10 shows changes in the methylation of a promoter region of the GR_{II} gene with the frequency indicated for the extent of methylation observed at various locations along the gene promoter region for suicide victims with a history of childhood abuse (black histogram bar), suicide victims with no history of childhood abuse (grey histogram bar), and control subjects (clear histogram bar) [91]. Clearly there is a much higher degree of methylation for suicide victims that have experienced childhood abuse than for those without a history of such abuse.

In major depressive disorder the medial prefrontal cortex has a reduced volume [92] due to a decrease in grey matter [93]. This is particularly the case following sexual abuse as a child [94]. A reduced volume also occurs in the anterior cingulate cortex [95], but not the amygdala that increases in size in major depressive disorders [96] as noted above. In suicidal patients with depression, there is a very large decrease in the volume of grey matter in the medial prefrontal cortex with a concomitant increase in grey matter in the amygdala [97]. In animal studies, in which direct staining and counting of synapses can be made, there is about a 30% decrease of synapses in 3-month-old rodents that have been subjected to a lack of paternal/maternal care in the first 3 weeks [98], suggesting that the loss of grey matter volume following abuse in infants is due to a loss of synapses.

Suicidal diathesis and synapse diseases

In suicidal patients with depression, there is a large decrease in the volume of grey matter in the anterior cingulate cortex due to a loss of neuropil, mostly reflecting the loss of synapses. Such changes in synapses are probably in part due to the action of the glucocorticoid cortisol acting on GR_{II} located at the synapses, although various dysfunctions in transporters and receptors at synapses which use the transmitters serotonin, dopamine or glutamate may also contribute to loss of function of synapses and their degeneration (for reviews, see [99,100]). There is now a plausible model linking epigenetic changes in GR_{II} brought about by childhood abuse, subsequent failure of the intrinsic regulation of the hypothalamic-pituitary-adrenal system, increased cortisol release under stress, loss of synapses in the rACC resulting in increased amygdala activity, followed by suicidal diathesis [50,70]. Such a model is likely to apply to the 65% of all adolescent suicide attempters that have a history of childhood sexual/physical abuse [2].

Suicidal diathesis is largely a synapse disease, in which loss of synapse function and of entire synapses occurs as a result of childhood abuse in the large majority of suicide victims that suffer such abuse. This reveals such victims as having been exposed to conditions that lead to the decline of normal brain function as a consequence of the loss of normal synapses so that they cannot avoid lapsing into conditions, such as post-traumatic stress syndrome, traditionally referred to as mental health problems. No more stigma should be applied to such victims than applies to a child that has a limb broken by a brutish parent: we have for more than a century been able to see that the limb is broken with X-rays, now we can see the ‘broken’ synaptic neural networks giving rise to

grey matter loss with magnetic resonance imaging. Three priorities should now be emphasized in suicide prevention. First, to keep a careful watch on families that show any record of childhood abuse so as to optimize the chances of preventing the onset of synapse diseases in the child. Second, to identify and apply appropriate pharmacological and cognitive behavioral interventions to reverse synapse diseases that support the path to suicide. Finally, to maintain careful follow-up and tracking of individuals with these diseases in order to ensure that their synapse disease state remains in remission.

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Figure References