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The molecular bases of the suicidal brain

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Abstract

Suicide ranks among the leading causes of death around the world, and takes a heavy emotional and public health toll on most societies. Both distal and proximal factors contribute to suicidal behaviour. Distal factors — such as familial and genetic predisposition, as well as early-life adversity — increase the lifetime risk of suicide. They alter responses to stress and other processes through epigenetic modification of genes and associated changes in gene expression, and through the regulation of emotional and behavioural traits. Proximal factors associate with the precipitation of a suicidal event and include alterations in key neurotransmitter systems, inflammatory changes and glial dysfunction in the brain. This Review explores the key molecular changes associated with suicidality, and presents some promising avenues for future research.

Introduction

In most developed countries, suicide ranks among the leading causes of death for individuals of all ages and is the leading or the second most common cause of death for young people[1]. Due to the existence of effective treatments for suicidality and associated psychiatric disorders, death by suicide is often avoidable[2]. However, suicide remains, to a large degree, charged with prejudice and stigma, characteristics that do not encourage individuals who experience suicidal ideation or exhibit suicidal behaviour to reach out and seek help. Despite the extent of its public health impact, there is generally little societal awareness about suicide's toll, which has granted suicide the title of "the quiet epidemic"[3].

Suicide completion is commonly regarded as the extreme end of a continuum that also includes suicide attempts and suicidal ideation[4]. Forthe purpose of this Review, suicidality will be used to refer to both suicidal ideation and suicidal behaviours, and suicidal behaviours will be considered as a single entity. However, there is a debate about the relationship between these phenotypes, and disagreement about the inclusion of other presentations of self-harm, such as non-suicidal self-injurious behaviours, in this continuum[5]. Considerable variability exists between and within suicidality categories in terms of level of intent to self-harm, severity of self-harm outcome and associated psychopathology, among others; this variability probably reflects the underlying aetiological heterogeneity of suicidality and related psychopathology. Most individuals presenting with suicidal behaviour are affected by a psychiatric disorder[6,7], an association that is strongest among suicide completers (approximately 90% of individuals who die by suicide were

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affected by a psychiatric disorder before death, notably by major depressive disorder (MDD), schizophrenia, substance-related disorders, and/or personality disorders[7]). Of note, suicidal behaviour disorder (SBD) was recently proposed as a diagnosis for further consideration for the DSM[8]. Other variables partially explain the observed variability in each phenotypic suicidality group. Among suicide completers, differences in psychopathology, personality traits and suicide intent between individuals may be age related; for example, impulsive-aggressive traits are more strongly linked to suicide in younger subjects[9,10]. Sex also contributes to phenotypic variability in each category: male and female suicide attempters and suicide completers show clear differences in the methods used, their underlying psychopathology and comorbid diagnoses[11,12]. Thus, models of suicidal behaviours, including biological factors predisposing individuals to and mediating these phenotypes, will probably explain only a fraction of the total phenotypic variability that is observed. Nevertheless, they are helpful as they provide important conceptual frameworks that enhance our understanding of suicide-spectrum behaviours and can guide us toward new hypotheses.

Of the many existing models of suicide risk[13], most are conceptually related to the initial model proposed by Moscicki[14] and its refined version presented by Mann[15], and are based on the premise that suicide results from the interaction of risk factors acting distally to the suicidal event, which increase predisposition to such an event, with those acting proximally to the suicidal event, which precipitate the suicidal crisis. In this Review, I describe the relationships between such distal and proximal factors, focusing on molecular events that predispose individuals to suicidality, mediate suicidal ideation and behaviour and precipitate suicidal crises, rather than on the neural circuitry of suicidal behaviour.

Distal or predisposing factors

Distal factors confer risk of suicide but have a distant temporal relationship to the suicidal crisis. As such, these factors act by increasing predisposition to suicide rather than by precipitating suicide crises. Among distal risk factors for suicide, family history, genetic variation and early-life adversity(ELA) are the best investigated.

Familial and genetic predisposition

A large number of studies examining family history of suicidal behaviour, including a recent large-registry study that comprised the total population of Sweden[16], as well as studies directly interviewing relatives of probands with suicidal behaviour, have shown that suicidal behaviour runs in families, with relatives of suicide probands estimated to have a 3- to 10-fold greater risk of suicidal behaviour than relatives of controls[16–18]. As suicidal behaviour is strongly associated with psychopathology (see below), and psychiatric disorders also run in families, considerable effort has been made to understand to what extent the liability to suicidal behaviour is different from the liability to psychiatric disorders. In contrast to suicidal behaviour, suicidal ideation does not appear to be as clearly linked to family history of suicidal ideation[19–21], although a family history of suicide attempt or completion does predict a higher frequency of suicidal ideation (2.41–5.1 times greater risk)[21,22]. Studies have shown that familial transmission of suicide and psychopathology, although partially

overlapping, are distinct[20,23,24]. Thus, familial aggregation of suicide is not explained by transmission of psychopathology[24]. Evidence that the familial aggregation of suicidal behaviour is at least partly due to genetic factors has been provided by several twin studies, yielding variable estimates of heritability, but consistently pointing to increased concordance of such behaviour in monozygotic twins compared with dizygotic twins[16,17]; similarly, adoption studies have demonstrated concordant results, with biological relatives of suicide adoptees having a higher rate of suicide than relatives of control adoptees[16,25] or alternatively, with parental suicide having similar risk of recurrence in adopted away and non-adopted offspring[26].

Genetic variation

Guided by the genetic epidemiological data suggesting that genes increase predisposition to suicidal behaviour, many molecular genetic studies have been conducted over the past two decades to identify genetic variants that may explain liability to suicide. As for other psychiatric phenotypes, most studies used a candidate gene association approach, and particularly focused on genes coding for components of the serotonergic system, given the evidence suggesting that suicidal behaviour is associated with decreased serotonergic neurotransmission[27,28]. In particular, the genes coding for the serotonin transporter, tryptophan hydroxylase and monoamine oxidase A have been widely studied in molecular analyses owing to their well-defined roles in serotonin metabolism[27,29]. Unfortunately, given the lack of consistent findings between studies, the experience from candidate gene-based association studies told us little about the contributions of specific genes. More recently, genome-wide association studies (GWASs) of suicidal behaviour or of treatment-emergent suicidal events have been conducted to identify novel loci (Supplementary information S1 (table))[30–35]. Although these have produced mostly inconclusive or inconsistent results, it is notable that such approaches permit an unbiased analysis of molecular pathways implicated in disease and are an important avenue to explore. For instance, one GWAS identified 14 single-nucleotide polymorphisms (SNPs) that were associated with treatment-emergent suicidal ideation in patients treated with antidepressants[31], and another study examining suicide completers identified seven genes that were differentially expressed in suicide but not in mood disorders[36]. However, most of the GWASs used relatively small samples that lacked the power to detect effects other than major gene effects and their results require confirmation. In many of the large-scale GWASs conducted to date, SNPs that have been identified to be of interest in the discovery phase of studies have not been identified as such in replication cohorts[32–35,37].

Early-life adversity

Several lines of evidence support a strong relationship between ELA — such as experiences of sexual or physical abuse during childhood and parental neglect — and lifetime risk of suicidal behaviour. This evidence comes from prospective cohort studies that have investigated epidemiologically representative samples[6,38] and retrospective cross-sectional studies that have investigated epidemiological and clinical samples[39,40]. Maltreatment during early development is also among the strongest predictors of psychiatric pathology and of a severe clinical course for psychiatric disorders, including early onset of illness, poor treatment response and increased comorbidity[41–43]. However, the specific association

between ELA and lifetime risk of suicidal behaviour is robust and is not solely explained by the link between psychiatric disorders and childhood maltreatment[44,45].

Between 10 and 73% of individuals who manifest suicidal behaviour have a history of childhood abuse (the rate depends on the type and frequency of the abuse, and the form of suicidal behaviour)[38,46–48]. Thus, this association only explains a portion, albeit a notable to substantial one, of the total variance in risk of suicidality. A few important factors determine the strength of the relationship between childhood abuse and suicidal behaviour, including the sex of the abused, the identity of the abuser and the frequency of the abuse. For instance, the risk of suicidal behaviour is higher among individuals who have experienced abuse by close caregivers than individuals who have experienced abuse by extended family members or unrelated individuals[45], and frequent abuse increases the risk of suicidal behaviour[45]. During development, immediate caregivers are responsible for the establishment of adequate attachment styles and appropriate emotional responses to environmental and stress-related stimuli throughout the life of the individual[49,50]. Attachment styles define the ways in which individuals relate to others and can be broadly divided into secure and insecure attachments, with insecure attachments being characterized by anxiety or avoidance[51]. Thus, frequent exposure to maltreatment by those who are supposed to protect and provide care may signal that an environment is hostile. These signals in turn may prompt the developing brain to adjust stress-response circuits to adapt to this hostile environment by increasing levels of alertness. In support of this hypothesis, studies suggest a relationship between poor parent-child attachment, maladjustment in the parental role and childhood abuse, and suicidal behaviour[38,51].

Biological systems affected by early-life adversity

Biological embedding refers to the effects of early-life experiences on the differential regulation of biological systems and development[52]. Important insight into systems and pathways that undergo biological embedding and the underlying molecular mechanisms has come from animal studies that clearly suggest that variation in the early-life environment associates with stable expression changes in genes that are important for key behavioural and stress responses. Indeed, animal studies have shown that epigenetic processes, particularly DNA methylation of various genes in different brain structures, mediate biological embedding (Box 1).

Box 1

Biological embedding through DNA methylation

Biological embedding refers to the effects of early-life experience on the regulation of biological systems[52]. Animal studies have provided important insight into mechanisms explaining biological embedding. One of the best-investigated models is the maternal care model in rats, which is based on naturally occurring variations in quantifiable behaviours (licking and grooming (LG); arch back-nursing) in nursing rat mothers. Variations in maternal care have marked and stable effects on endocrine and behavioural responses in the offspring, for example increased tactile stimulation by mothers dampens the hormonal response to stress[203], and reduced behavioural fearfulness[104]. Other animal

models, such as the induced maternal abusive behaviours in rats[75] or early-life stress in mice[204] have shown similar effects. Subsequent studies in animals have shown that epigenetic processes, particularly DNA methylation involving different genes and brain structures, mediate biological embedding[205].

DNA methylation refers to the addition of a methyl group (CH3) to the 5′ carbon of a cytosine base. DNA methylation occurs commonly, but not exclusively, at sequences composed of cytosines followed by guanines (CpG dinucleotides). In general, cytosine methylation associates with transcriptional repression, which occurs by interference with the recruitment and binding of transcriptional machinery to gene regulatory regions[206]. However, in studies identifying DNA methylation within the gene body, it has been associated with transcriptional activation and alternative transcript selection[207]. DNA methylation is theoretically dynamic, but this is only the case for a minority of CpGs[208], and thus DNA methylation is generally a stable process involved in long-term gene silencing, including X-chromosome inactivation, suppression of alternative promoters and tissue-specific suppression of gene regulation.

The exciting findings from animal studies have led to a growing interest in the investigation of epigenetic factors — primarily DNA methylation — as possible mediators of biological embedding resulting from ELA in humans. Although theoretically appealing, studying methylation changes caused by ELA in humans and associating them with behavioural and emotional phenotypes poses a number of operational and logistical challenges. Epigenetic changes are tissue- and cell-type specific, but sampling brain tissue from living subjects is impossible. Thus, epigenetic studies on human brains are limited to post-mortem specimens. Although post-mortem studies are informative, it is difficult to establish temporal relationships between epigenetic marks and behavioural phenotypes from such studies. By contrast, peripheral samples are less challenging to obtain, but the extent to which they are informative about processes occurring in the CNS is currently under debate. In spite of these challenges, several epigenetic studies have been conducted investigating both CNS and peripheral samples of individuals exposed to ELA.

Of particular interest in the context of suicidal behaviour is the regulation of the hypothalamus-pituitary-adrenal (HPA) axis. The activation of the HPA axis leads to cortisol release, which is a steroid hormone secreted in response to stress that promotes arousal and attention, among other physiological changes[53]. Cortisol also binds to the glucocorticoid receptor in the hippocampus to inhibit further stimulation of the HPA axis in a negative feedback loop. The HPA is overactive in individuals with ELA, who are more likely than controls to display heightened stress responsiveness[54]. As such, *NR3C1*, which encodes the glucocorticoid receptor, has been widely studied. Several animal studies have suggested that the early environment regulates *Nr3c1* through DNA methylation changes (Box 2). The first evidence for an effect of ELA on the human epigenome indicated that childhood abuse or severe neglect in humans regulates both the patterns and levels of *NR3C1* methylation in the hippocampus, which can lead to increased HPA reactivity in humans exposed to childhood maltreatment[55]. Individuals who died by suicide and had histories of severe childhood abuse had a marked decrease in the level of both total *NR3C1* mRNA and untranslated exon 1_F

variant *NR3C1* mRNA, compared with individuals who died by suicide and did not have histories of childhood abuse and non-suicide controls. This decreased mRNA expression was associated with increased methylation in the exon 1_F promoter, particularly in a region where the transcription factor nerve growth factor-induced protein A (NGFI-A) binds, a finding in line with evidence from rats (Box 1). *In vitro* studies suggested that this increased methylation observed in suicide completers with histories of abuse could interfere with NGFI-A binding of the *NR3C1* promoter, resulting in decreased glucocorticoid receptor expression[55].

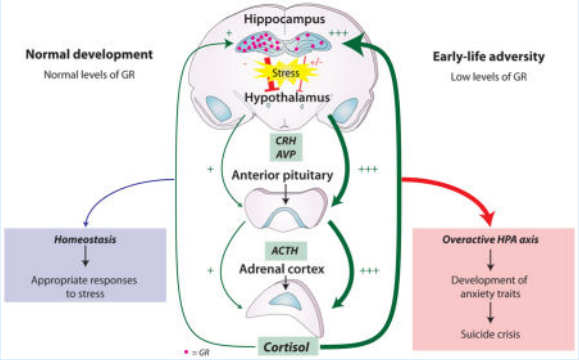
Box 2

Effect of early-life adversity on the hypothalamus-pituitary-adrenal axis

The hypothalamus-pituitary-adrenal (HPA) axis is activated by stress. Upon activation, the hypothalamus secretes corticotropin releasing hormone (CRH) and arginine vasopressin (AVP), which act on the anterior pituitary gland to trigger the release of adrenocorticotropic hormone (ACTH). This stimulates the adrenal cortex to produce cortisol, which heightens alertness. Cortisol-mediated activation of glucocorticoid receptors in the hippocampus exerts a negative feedback on HPA activity. The glucocorticoid receptor-encoding gene, *NR3C1*, is downregulated in the hippocampus of individuals exposed to ELA, leading to ineffective inhibition of CRH secretion and an overactive HPA. This overactive HPA may be associated with the development of anxiety traits, which in turn are mediators of suicidal behaviour risk. In humans, *NR3C1* mRNA may contain one of11 untranslated splice variants of exon 1, encoded by 7 different exon 1s, each with its own promoter, and each mRNA variant has a unique tissue-specific distribution[209]. There is remarkable homology between the human and rat exon 1 structure[209,210], and mRNAs containing exon 1_7 (in rats) and 1_F (in humans) are highly expressed in the hippocampus[209]. CpG methylation levels in the exon 1_7 promoter region are markedly increased at almost all CpGs in offspring raised by low LG rat mothers, whose increased physical attention to pups results in attenuated stress responses (Box 1), compared with offspring raised by high LG mothers. Importantly, one CpG located in the 5′ end of the binding site of the transcription factor, nerve growth factor-induced protein A (NGFI-A), is methylated in almost 100% of offspring raised by low LG mothers, whereas it is almost never methylated in offspring from high LG mothers[205].

Other animal studies on the effects of early life environments on behavioural phenotypes have shown comparable results in genes coding for components of the HPA axis or other key gene systems. For instance, in mice, maternal deprivation (placement in a cleaned cage, devoid of maternal odour, for three hours per day for the first ten days of life) produces sustained hyperactivity of the HPA axis that is characterized by increases in stress-induced corticosteroid secretion and in the expression of pro-opiomelanocortin (POMC) in the pituitary, and hypertrophy of the adrenals[204]. These changes in POMC expression associate with sustained POMC promoter hypomethylation[211]. These mice also present increased despair-like behaviour and memory deficits, phenotypes that are mediated through arginine vasopressin (AVP) signalling and epigenetic adaptations at an AVP enhancer locus. Accordingly, mice subject to early life stress present a persistent increase in AVP expression in the hypothalamic paraventricular nucleus (PVN), which

associates with decreased DNA methylation of an AVP enhancer element located in the intergenic region between AVP and oxytocin, where methyl CpG binding protein 2 (MeCP2) binds. As a result, MeCP2 occupancy of this AVP regulatory sequence is decreased, leading to sustained increased AVP expression[204]. Such overexpression of AVP can result in HPA hyperactivity and altered coping mechanisms resembling depression in humans. In adult animals, decreased AVP promoter methylation in the amygdala is associated with active coping mechanisms after exposure to stressful stimuli[212], and AVP expression is associated with aggressive behaviour[213–215]. Collectively, animal studies on early life environmental variation[75,205] indicate that the early environment epigenetically regulates diverse genomic loci that are important in the regulation of emotional and behavioural traits of relevance to depression and suicide.



Since the initial study linking glucocorticoid receptor methylation in the brain with childhood abuse[55] was published, several independent studies have been conducted to investigate the relationship between *NR3C1* exon 1 methylation, ELA and suicidal behaviour or psychopathology, including phenotypes associated with altered parental care[56–61] (Supplementary information S2 (table 2)). Although these studies were conducted using different study designs, measures of adversity, and different tissue samples, there is a remarkable consistency in their findings, which largely indicate increased levels of methylation in *NR3C1* exon 1_F among individuals exposed to less favourable environmental experiences during early life.

Epigenetic processes are essential in the differentiation of cells and tissues, as well as in the developmental regulation of genes. Thus, there is a predictably higher variability when comparing epigenetic patterns between tissues from the same individual than when comparing the same tissue from different individuals[62]. However, there is also evidence of within-individual epigenetic variant correlation across tissues[62]. The consistency in the *NR3C1* methylation findings observed using different tissues suggests that social adversity may activate systemic signals such as steroids or other hormones that may have an impact on epigenetic patterns in multiple tissues.

A different line of evidence suggesting that ELA regulates the activity of the HPA axis through differential methylation comes from studies investigating FK506-binding protein 5 (FKBP5). This protein regulates the glucocorticoid receptor by decreasing its capacity to bind glucocorticoids, which hampers the ensuing translocation of the glucocorticoid receptor

complex to the nucleus. Certain sequence variants of *FKBP5* put individuals at increased risk of depression and posttraumatic stress disorder[63,64] and of exhibiting suicidal behaviour[65–67] or experiencing suicidal events in the course of antidepressant treatment[68,69], and the link with suicidality is particularly strong for subjects with a history of ELA[70,71]. Interestingly, one study reported that the interaction between *FKBP5* genotype and ELA occurs through decreased methylation affecting functional glucocorticoid response elements located in intron 7 of *FKBP5*, resulting in a downstream increase in FKBP5 expression and glucocorticoid receptor resistance[72].

ELA also differentially regulates genes and pathways involved in neuronal plasticity. For instance, genome-wide methylation studies in hippocampal tissue from individuals who died by suicide and had histories of ELA indicated that ELA was associated with differential methylation of genes involved in neuronal growth and neuroprotection[58,73]. Studies in peripheral samples from living subjects also suggested that a history of ELA was linked to differential methylation of neuronal plasticity genes[74]. These findings are concordant with animal studies that support early-life environmental regulation of plasticity genes, such as the gene coding for brain-derived neurotrophic factor (BDNF). Experiments conducted in rodents showed that when gestating females were put under conditions of stress (introduction to a new environment with inadequate bedding material), the expression of *Bdnf* was dysregulated. Specifically, *Bdnf* mRNA expression was decreased in the prefrontal cortex, and this decreased expression correlated with hypermethylation of the *Bdnf* promoters in exons IV and IX[75]. Similar effects have been reported for the *Bdnf* exon IV promoter in the dorsal hippocampus in an adult rat model of post-traumatic stress disorder[76].

Another neurotrophic factor, glial-cell derived neurotrophic factor (GDNF), is also epigenetically regulated by environmental experience in rodents through chromatin modification and DNA methylation of its gene promoter, and these changes associate with behavioural responses to chronic stress[77]. However, these methylation changes in *Gdnf* were observed in adult mice, thus suggesting that the epigenetic programming of neurotrophic factors such as GDNF may not be limited to developmental periods. It remains unclear whether the epigenetic changes occurring as a result of ELA are of a similar quality, intensity and stability if they occur during childhood or later in life(Box 3).

Box 3

Stability of DNA methylation changes over time

In well-characterized brain circuits, brain plasticity is considerably more pronounced during childhood than in later years[216], and clinical studies suggest that abusive experiences during early-life are more likely to result in pervasive behavioural phenotypes than similar events experienced in adulthood[217–219]. However, the relationship between timing of the stressor, epigenetic impact and behavioural consequences remains one of the most critical questions in epigenetics studies of mental health phenotypes.

Recent publications have begun exploring longitudinal analyses of methylation in relation to the subject's environment. Although the stability of epigenetic changes over time has

not yet been clearly demonstrated, a study evaluating methylation at a wide range of loci indicates that DNA methylation is likely to be stable over long periods (11–20 years)[220]. Although this finding requires confirmation, it is interesting to note that the authors specifically examined genes involved in the stress response (*NR3C1* and *CRH*) and found their methylation status to be stable over time. Additionally, emotional adversity during childhood effects long-term changes in methylation. In a study evaluating monozygotic twins at 5 and 10 years of age, Ouellet-Morin and colleagues showed that children who had experienced bullying exhibited increased methylation at the serotonin transporter gene (*SERT*) compared with their non-bullied monozygotic twin[221]. Interestingly, this study also showed that individuals with increased *SERT* methylation exhibited decreased cortisol response to stressful situations, pointing to a link between the serotonergic response and the hypothalamus-pituitary-adrenal axis. Lasting changes in DNA methylation also appear to occur into adulthood, as shown by recent studies on post-stroke depression. In patients having suffered a stroke, those experiencing post-stroke depression or worsening depression during the year following their stroke had increased methylation of *BDNF* and *SLC6A4*[222,223]. Such examples of long-lasting epigenetic changes help to understand how distal events, such as early-life adversity, can contribute to increased suicide risk, and how proximal events, such as stressful life events, can precipitate suicidal acts by altering gene expression profiles in the brain that have a profound impact on behaviour.

BDNF and the gene encoding its high-affinity receptor, tropomyosin-receptor-kinase B (TrkB), have received significant attention in human studies of suicidal behaviour, although most of these studies have not examined whether the participants had a history of ELA. Some of these studies have revealed that suicide completers have decreased mRNA and/or protein levels of BDNF, TrkB or both in the prefrontal cortex[78–81], temporal cortex[82] and hippocampus[78,83]. Moreover, others have reported differential methylation patterns in regulatory regions of *BDNF* and *TRKB*[80,83]. Specifically, in the Wernicke area of suicide completers, four CpG sites located downstream of the *BDNF* promoter IV transcription initiation site were more highly methylated in suicide completers than in controls, and this increased methylation was associated with significantly lowered BDNF expression, which is consistent with the expected repressive effects of methylation in promoter sequences on transcription[84]. In line with these findings, recent studies have reported that living depressed patients display differential methylation of the *BDNF* promoter in peripheral samples[85–87]. In addition, studies have revealed that suicide completers exhibit differential methylation in the promoter[80] and in a transcript-specific 3′UTR[81] of *TRKB* in the prefrontal cortex.

In addition to hypothesis-driven studies, a growing number of genome-wide studies have investigated changes in the methylome associated with ELA and/or suicide. In spite of the inherent sources of variation when measuring methylation levels[88], and the relatively small sample size of these studies, particularly in comparison to those of GWASs, it is noteworthy that epigenome-wide association studies have identified methylation differences at several genomic loci. Studies using peripheral samples[74,89] and brain samples[58,73] have been conducted and have pointed to differential methylation in gene pathways involved in stress, neural plasticity and cognitive processes. Studies that investigated brain tissue and

conducted cell sorting[58,73] found that these differences were mostly accounted for by methylation changes in neuronal DNA. These strong associations between ELA and DNA methylation point to long-lasting changes in the regulation of gene expression that are triggered by early environment experiences, and these changes are strongly linked to suicidal behaviour [90,91].

Mediators of suicide risk

Distal factors affect biological systems and, in turn, the resulting changes in these systems can increase the risk of suicide. Thus, distal factors do not directly cause suicidal behaviour. Indeed, if they did, these factors would have been subject to selective pressures and progressively eliminated. Moreover, if distal factors had a direct link with suicide risk, ELA would have a more specific relationship with suicidal behaviour, instead of being linked to an increased risk of several negative mental health outcomes. Distal factors are therefore thought to act indirectly, through developmental traits, which may act as intermediate phenotypes, or endophenotypes, for suicidality[92,93].

Although it is unclear what specific genes contribute to the total genetic variance increasing predisposition to suicidal behaviour, family studies have consistently indicated that familial aggregation for suicidal behaviour is partially explained by transmission of impulsive-aggressive traits. Familial clustering of suicidal behaviour is increased in families in which probands have higher levels of impulsive-aggressive traits than in those in which probands have lower levels of such traits[20]. Moreover, compared with controls, relatives of suicide completers have elevated levels of impulsive-aggressive traits and are more likely themselves to have histories of suicidal behaviour[23,24]. In addition, impulsive-aggressive traits show evidence of familial loading in families of suicide completers and mediate the relationship between family history and suicidal behaviour[24]. Thus, the transmission of behavioural traits (or endophenotypes[92]) such as impulsive-aggressive behaviours is probably explained by familial, and possibly genetic, susceptibility for suicidal behaviour.

In studies examining the link between endophenotypes and suicidality, anxiety, impulsivity and aggressive traits correlate with suicidal behaviour[24,38,94]. These findings have been supported by clinical and epidemiological studies on samples that are representative and non-representative of the general population[95,96]. Although they are more difficult to conduct than cross-sectional studies, longitudinal studies using multiple observation points offer stronger evidence of causal relationships and allow temporal relationships between different variables to be examined. A series of longitudinal and trajectory studies have investigated predictors of suicidal behaviour[38,45,46,97–99]. Collectively, this work shows that high levels of childhood anxiety and disruptive behaviour (characterized by impulsivity, aggression, hyperactivity and oppositional behaviour) are linked to suicidal behaviour in adulthood[94]. Supporting these findings, cross-sectional studies and two-point longitudinal studies have shown that stable anxiety and impulsive-aggressive behaviour are associated with suicidality in adulthood[100–102].

ELA is likely to act through developmental dysregulation of behavioural and emotional traits. In animal studies, changes in the early-life environment correlate with stable

behavioural phenotypes[103,104]. For instance, in non-human primates, social deprivation leads to sustained aggressive behaviour[103]. In humans, individuals with histories of ELA frequently display dysregulation of emotional and behavioural traits such as internalizing and externalizing disorders[105], and the personality trait phenotypes of individuals with histories of ELA share characteristics with those seen among individuals with suicidal behaviour[38,106]. However, this association is mitigated by other variables, such as sex and underlying disorders. High-anxiety trajectories fully mediate the relationship between ELA and suicide attempts among individuals with externalizing disorders, such as attention deficit and hyperactivity, oppositional-defiant and conduct disorders, whereas among individuals without externalizing disorders, this mediation, although still marked, is partial[91]. The relationships between these mechanisms may explain the link between ELA and development of high-anxiety trajectories (Fig. 1). Similarly to high-anxiety trajectories, highly disruptive trajectories, which are characterized by high levels of impulsive-aggressive traits, hyperactivity and oppositional behaviour, partially mediate the relationship between ELA and suicide attempts among females, but not among males[91].

Approximately 40% of individuals who die by suicide have lifetime histories of alcohol dependence or abuse and around 25% have histories of illicit substance dependence or abuse[9]. Exact rates vary globally and between studies[7], but there is a robust association between chronic substance use disorders and suicide. Impulsive traits strongly associate with substance use disorders, and although it is difficult to establish in human studies whether impulsivity is a cause or an effect of the chronic use of substances, animal experiments suggest that chronic substance use leads to increased impulsivity[34]. Interestingly, suicide cases that were associated with a high number of distal (predisposing) risk factors had particularly high levels of comorbidity with substance use disorders[107,108]. Thus, chronic use of substances may further increase the levels of impulsive-aggressive traits among individuals at risk of suicide. Consistent with this hypothesis, suicide completers with comorbid substance use disorders had higher levels of impulsive-aggressive behavioural traits than those without such disorders [109].

To date, the molecular factors underlying or correlating with mediators have not been well characterized, but there are a few promising leads. Impulsive-aggressive behaviours are associated with low levels of serotonin[110], as discussed below, and suicidal behaviour is associated with low levels of cholesterol[25,111–113]. Overall, studies exploring the link between cholesterol levels and suicidal behaviour have indicated that subjects with low serum cholesterol levels are at higher risk of suicidal behaviour, increased impulsive-aggressive behaviour, violence, and violent methods of suicide attempt (reviewed in REF[25]). The mechanisms underlying these relationships are currently unclear, but brain cholesterol is essential for continued neural plasticity, and it is tempting to speculate that predatory behaviours such as impulsive aggression should be modulated to some degree by dietary needs, which correlate with serum lipid levels.

Proximal or precipitating factors

Suicidal crises are typically triggered by recent life events[114] and strongly associate with the onset of episodes of psychopathology. Thus, approximately 90% of individuals who die by

suicide meet criteria for a psychiatric disorder in the last six months of life, according to a large number of retrospective, proxy-based studies (known as psychological autopsies)[7], epidemiological and registry-based studies[115], and studies in clinical at-risk populations[116]. Although only an average of 50% of individuals who die by suicide meet the criteria for MDD (a proportion that increases with age) at the time of death[7], virtually all individuals who are suicidal, regardless of their main psychiatric diagnosis, present some degree of suicidal ideation, hopelessness, or other similar cognitive distortions that are characteristic of depressive states. When these cross-nosological depressive symptoms drastically alter the individual's problem-solving capacity and judgment, they may be interpreted as precipitants of suicidal crises. These depressive states associate with molecular changes that are likely to underlie proximal risk factors for suicide and the most important are reviewed below.

Serotonergic alterations

Decreased serotonergic neurotransmission mediates depressive states. Almost four decades ago, Asberg and colleagues suggested that, among patients with depression, those with lower cerebrospinal fluid (CSF) levels of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are more likely to exhibit suicidal behaviour[117]. Subsequently, important postmortem studies pointed to altered serotonergic binding in the frontal cortex of suicide completers[118,119], and since then, researchers have extensively investigated serotonergic changes in suicide and related behaviours (reviewed in REF[15]). A detailed discussion of this extensive body of work is beyond the scope of this paper. One of the most consistent findings suggests that responses to challenges with fenfluramine, a potent serotonergic agonist, is blunted among living subjects who attempted suicide[110]. Additionally, post-mortem work using the brain cortex of suicide completers revealed decreased availability of the serotonin transporter[118], and both post-mortem binding studies and *in vivo* studies using PET have reported altered 5HT1A and 5HT2A receptor availability in suicidal brains, suggesting that insufficient serotonin in certain areas of the brain may be linked to suicidality[27,28].

Two important questions remain in relation to the association between serotonin and suicide. First, to what extent are serotonergic changes in suicide explained by depressive psychopathology? Although there is some evidence suggesting that serotonin alterations may be specific to suicidal behaviour[120,121], these alterations partially overlap with those observed in the depressed brain. For example, the more pronounced serotonergic changes observed in suicide might be a function of more intense hopelessness and suicidal ideation. This key point has not been adequately addressed, particularly in post-mortem brain studies, in large part due to the methodological challenges of assessing subjective and non-behavioural symptoms of depression by means of proxy-based interviews, which is the process whereby post-mortem brain studies obtain clinical information on the subjects they investigate. Another challenge is obtaining brain tissue from individuals who were affected by depression of equivalent severity to that presented by suicides, but who died from other causes. The second question is to what extent are serotonergic changes associated with suicide state markers of suicidality or depression, or trait markers of predisposition? There is evidence that lower serotonergic neurotransmission also associates with behaviours that increase suicide risk, such as impulsive-aggressive traits[122], and that serotonergic genes have

both shared and unique contributions to the risk for depression and suicidal behaviour[123]. However, it is also clear that changes in serotonin levels associate with onset of depressive and suicidal states in euthymic individuals who had previous depressive episodes[124], and in individuals at risk for depression[125]. Thus, serotonergic changes underlie proximal depressive and suicide risk factors.

The polyamine stress response

Our group and others have studied changes in the polyamine stress response (PSR) system in the context of suicide. The PSR, like the HPA axis, is implicated in physiological responses to physical, emotional and hormonal stressors, including glucocorticoids (Box 4). The mRNA and protein levels of several components of the polyamine system are altered in cortical and subcortical brain regions of suicide completers[126–129], as well as in peripheral samples from suicide attempters[130,131] and psychiatric patients[132]. In addition, non-human primate models of depression suggest that stress induces changes in gene expression that lead to altered brain polyamine levels[133]. Spermidine/spermine N^1-acetyl-transferase (SAT1), which is the rate-limiting enzyme in the catabolism of polyamines, is decreased in the cortex of suicide completers[126], and may even act as a peripheral biomarker of suicidality. Epigenetic regulation of some key polyaminergic genes, involving different epigenetic processes in both biosynthetic and catabolic polyamine genes, has been reported in suicide cases[134–137]. Although the evidence suggests differential epigenetic regulation of several polyaminergic genes in suicide, further studies are necessary to understand the external validity of these findings, their functional impact on the PSR, and their relationship to peripheral markers.

Box 4

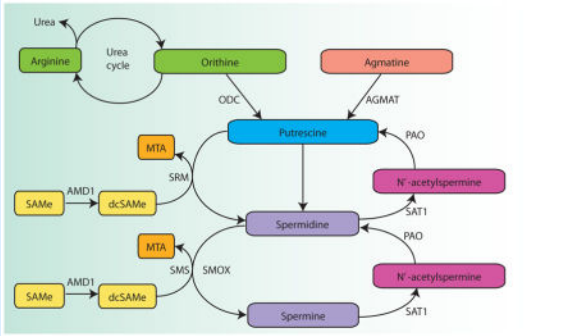
The polyamine stress response system

Polyamines are ubiquitous aliphatic molecules containing two or more amine (NH2) groups. This group of molecules primarily comprises putrescine, spermidine, spermine and agmatine, whose presence in mammalian brains was discovered fairly recently[224]. Polyamine synthesis is highly regulated, with several rate-limiting enzymes, like ornithine decarboxylase (ODC), S-adenosylmethionine (SAM) decarboxylase (AMD1) and spermidine/spermine N^1-acetyl-transferase (SAT1). Their activities are tightly controlled with polyamine-mediated feedback loops. Other enzymes, such as spermidine synthase (SRM) and spermine synthase (SMS) may be induced in some conditions but otherwise exhibit constant activity levels, whereas polyamine oxidase (PAO) activity is controlled by substrate availability (see the Figure; reviewed in [223]). Ornithine is produced through the metabolism of arginine in the urea cycle, which is itself controlled by substrate-limited enzymes.

Polyamines have a multitude of functions, including regulation of gene transcription and posttranscriptional modifications, in addition to modulating the activities of several proteins[225]. Polyamines regulate the expression or release of several neurotransmitters, including catecholamines[226], glutamate[227], GABA[228] and nitric oxide[229], and agmatine itself is thought to act as a neurotransmitter[230]. They also interact with several transmembrane channels and can thus influence the properties of excitable cells[227,231].

In the mammalian brain, stressful stimuli such as physical, emotional and hormonal stressors, including glucocorticoids, elicit the polyamine stress response (PSR)[232]. Activation of the PSR results in elevated levels of putrescine and agmatine in both the brain and peripheral tissues. The magnitude of the PSR is related to the intensity of the stressor, and correlates with levels of behavioural and physiological responsiveness under stressful conditions[232]. The PSR can be pharmacologically manipulated[233,234], and there is strong evidence showing that elevated agmatine and putrescine levels in the brain are beneficial: numerous animal studies have shown that these compounds display both anxiolytic and antidepressant effects[235], and polyamine depletion can produce altered emotional reactivity and anxiety-like behaviours[236]. Similarly, there are some encouraging pilot data in humans suggesting that agmatine has antidepressant properties[237], and in agreement with these results, studies investigating the effects of antidepressants indicate a role for the polyamine system in the antidepressant response, particularly through agmatine or putrescine allosteric binding to NMDA receptors [235].

SAM: S-adenosylmethionine; **AMD1:** S-adenosylmethionine decarboxylase; **dcSAM:** decarboxylated SAM; **MTA:** 5′methylthioadenosine; **SMS:** spermine synthase; **SMOX:** spermine oxidase; **SRM:** spermidine synthase; **SAT1:** spermidine/spermine N^1-acetyltransferase; **PAO:** polyamine oxidase; **ODC:** ornithine decarboxylase; **AGMAT:** agmatinase



Glutamatergic and GABAergic alterations

Several studies have been conducted over the past decade investigating genome-wide transcriptomic changes associated with depression and suicide[138,139]. These studies typically used mRNA microarrays to compare post-mortem brain tissue from individuals who were diagnosed with MDD and died by suicide and individuals with good mental health who did not die by suicide. They reported dysregulation of genes involved in glutamatergic and GABAergic signalling in diverse cortical and subcortical regions. In particular, for GABAergic signalling, genes encoding GABA type A receptor subunits and their associated binding proteins were consistently found to be upregulated, notably in the prefrontal cortex, hippocampus and anterior cingulate[138,139]. Among genes related to glutamatergic signalling, those encoding AMPA and NMDA glutamatergic receptor subunits were upregulated in the anterior cingulate and dorsolateral prefrontal cortex, whereas the glutamine synthase gene (*GLUL*), which is implicated in glutamate recycling, and the genes encoding the solute

carriers SLC1A2 and SLIC1A3 were downregulated in these cortical areas and the amygdala[138,139]. GLUL and the solute carriers are of particular interest, as these are primarily expressed in glial cells, which are altered in depression and suicide (see below). Although glutamatergic receptors have multiple functions and these expression differences may signal global expression changes that may not be specific to the underlying psychopathological processes taking place in the suicidal brain, they are consistent with growing evidence of the efficacy of glutamatergic agents as rapid-acting antidepressants that are both useful in the treatment of depressed mood[140] and acute suicidal ideation[141,142].

Inflammatory factors

Large amounts of data produced over the past few decades support a relationship between inflammation and depressive states[143]. Notably, such states have been linked to increased levels of proinflammatory cytokines, particularly tumour necrosis factor (TNF)-α and interleukin (IL)-6[144–147]. Furthermore, high levels of comorbidity have been observed between inflammatory autoimmune illnesses and depression, and a substantial proportion of patients undergoing therapy with cytokines, such as interferon (IFN)-α, have been found to develop depression[148–151]. In contrast to the clear evidence indicating an association between changes in inflammatory markers and depressive states, there is only sparse evidence linking these markers and suicidal behaviour, but the existing data seem to support an association. There are several reports of an association between suicidal behaviour, irrespective of depression status, and inflammatory cytokines (reviewed in REF[152]), with the most consistent results suggesting that patients with suicidal behaviour have an increase in IL-6 and a decrease in IL-2. Other inflammatory factors have been described to be altered in such individuals, including reports of decreased vascular endothelial growth factor (VEGF)[153], increased quinolinic acid[154] and increased kynurenic acid in patients with major depressive disorder with a history of attempted suicide[155,156]. Although most studies investigating inflammatory markers in suicidal behaviour have investigated blood samples, some studies were conducted in CSF[154,157] or in post-mortem brain tissue[158–161], and the results of these studies have led to the suggestion that suicide is associated with low-grade inflammation in the brain. Glucocorticoids can blunt immune and inflammatory responses, but recent studies have shown that they can also stimulate immune responses in certain circumstances, such as during acute cellular damage or the death of brain tissue (reviewed in REF[162]). Glucocorticoid-mediated regulation of the immune system could lead to lasting effects of ELA on immunomodulation, as has been suggested by others[163], and this is supported by the observation that victims of childhood maltreatment exhibit heightened immune activation as adults[164].

Glial and astrocytic dysfunction

Traditionally, psychiatric phenotypes have been understood to result from dysfunction in brain neurons, and glia have been considered primarily for their role in supporting neuronal function. As neuroscience has gained increased insight into the diversity of functions that glial cells perform in the brain, more interest has been paid to glial cells, and particularly to astrocytes, in psychopathology. Studies investigating animal models of depression have reported glial cell alterations, such as impaired glial function[165,166], and post-mortem brain studies have suggested that glial cell counts are decreased in cortical grey matter from

patients with depression[167], and that astrocytes are hypertrophied in cortical white matter from depressed individuals who died by suicide[168]. These results are in agreement with the findings from several mRNA expression studies using genome-wide microarrays in post-mortem brain tissue from depressed individuals who committed suicide, which consistently showed alterations in the expression of a number of astrocytic genes[138,169,170]. Among the most pronounced findings, these studies have pointed to a marked downregulation of the expression of connexin 30 (*Cx30*) and *Cx43* — two genes coding for gap-junction proteins that in the brain are almost exclusively expressed in astrocytes. Interestingly, *Cx30* and *Cx43* single knock-out mice exhibit altered reactivity to novel environments and important changes in brain neurotransmitters, including serotonin[171,172]. Other astrocyte-specific genes have been reported as differentially expressed in suicide completers. For example, expression of the gene encoding the truncated splice variant of TrkB, TrkB.T1, which lacks the catalytic activity of the full-length protein[173], is reduced in the frontal cortex of suicide completers compared to controls[80]. This is also consistent with results from work in mice indicating that mice overexpressing TrkB.T1 have an increased sensitivity to chronic social stress, resulting in consistent social avoidance[174].

Neuroendocrine dysfunction in suicide

As discussed above, the HPA axis is dysregulated in individuals having experienced ELA. In suicide attempters and completers, there is also evidence of HPA dysregulation, regardless of ELA history. Studies investigating suicide attempters have shown that HPA axis dysregulation correlates with the violence of the suicide attempt[175]. There is also evidence that HPA axis alterations may be more closely linked to suicidal behaviour than to individual psychopathologies, since the ability to suppress dexamethasone (a synthetic glucocorticoid used to measure HPA response) predicts suicide completion[176] and suicidal behaviour in patients with MDD[177]. Post-mortem studies of suicide completers have revealed that such individuals have increased corticotrophin-releasing hormone (CRH) activity in the paraventricular nucleus (PVN)[178–180], increased CRH expression in the CSF[181], fewer CRH binding sites in the frontal cortex[182], decreased glucocorticoid receptor expression in the hippocampus[55] and increased POMC in the pituitary[183], indicating altered HPA function in the brains of suicide completers. Concordant with these findings is the observation that suicide completers have increased adrenal weight and cortical hypertrophy[184,185], and relatives of suicide completers also exhibit altered HPA responses in experimental evaluations of stress response[186].

Considerations for future directions

Suicide is a complex behaviour that results from the interaction of different factors. This Review examined evidence focusing on molecular changes associated with distal factors that increase the lifetime predisposition to suicide; the molecular and behavioural changes that are associated with factors mediating suicide risk; and, finally, those changes that are associated with depressive states that function as precipitants of a suicidal crisis (Fig. 1). Although this Review discusses these factors as if ‘suicidal behaviour’ were a single phenotype, this is not the case. There is only partial overlap between suicide attempts and suicide completion, and there is clear clinical, phenomenological and likely aetiological

heterogeneity in and between each of these phenotypes. Thus, aetiological models, such as the one discussed in this paper, are helpful as they provide theoretical relationships that can be tested, but they should not be taken at face value. In addition, many of the studies discussed here focused on depression as a precursor to suicide, yet other psychiatric conditions, such as schizophrenia, bipolar disorder and personality disorders, are important contributors to suicidality, both in terms of suicidal ideation and suicidal behaviour[7,102]. In this regard, the recently proposed diagnosis of suicidal behaviour disorder should be considered in future research, as proposed in the DSM-5. This practice will help us better separate neurobiological factors associated with suicidal behaviour from those related to psychopathology.

One avenue of investigation that may shed some light into the molecular basis of suicidality is the study of the molecular basis of treatment-emergent suicidal events and mechanisms of action of pharmacological agents that act on suicidality. For instance, recent advances in clarifying the mechanism of action of lithium suggest that it functions by modulating dopaminergic, glutamatergic and GABAergic pathways, as well as by upregulating neuroprotective factors, such as BDNF and BCL-2, and downregulating apoptotic factors[187]. Lithium is effective at reducing the risk of suicide in patients with mood disorders, an effect that seems to be independent of its mood-stabilizing effect[188], and it may also decrease aggression and impulsivity[189]. As such, further exploring lithium activity in suicidal patients may identify new genes involved in suicidality. Similarly, studies investigating dynamic molecular changes associated with treatment-emergent suicidal events or with fast cessation of suicidal ideation, such as seen with rapid-acting glutamatergic agents[141], may point to new molecular pathways of interest to understand suicide.

The studies discussed above have led to increased interest in the investigation of epigenetic factors associated with both ELA and molecular processes mediating suicidality. However, before embarking on large sequencing-based studies, the field should consider a number of adjustments to the current approaches that could enhance the quality of the results generated. First, consortium-based initiatives, such as those seen in genetic variation studies of schizophrenia, should be promoted as they have recently produced encouraging results[190,191,192]. Second, alternative designs focusing on related phenotypes should be considered. For instance, investigating simple Mendelian conditions like Lesch-Nyhan disease[193], in which the genetic architecture is reasonably well understood and phenotypes of interest, such as self-injurious behaviours, are manifested, should help us identify gene pathways of interest. Third, a major focus of upcoming research initiatives should be to improve comparability of the data. Standardizing the way methodologies are reported (for example, by including exact sequences of DNA regions investigated, detailed descriptions of probes or specific stimuli and parameters controlled for) will improve comparability and help to avoid some of the drawbacks linked to genetic variability.

Other methodological aspects to consider for studies of suicide are the use of peripheral tissues to study epigenetic changes linked to suicidality and the use of tissue homogenates. Although epigenetic studies conducted on peripheral tissues are feasible and cost-effective, their scientific value has not been well characterized, and we do not know to what extent epigenetic modifications in peripheral tissues are representative of those in the CNS.

Epigenetic regulation is, to a large degree, cell- and tissue- specific[194–196], with greater epigenetic variability existing between different tissues of a single individual than between similar tissues of different individuals[62,197–199]. There is therefore a need to clearly establish the relationship between peripheral epigenetic marks and CNS counterparts, a task that should become easier once reference epigenomic maps are generated from different brain regions and cellular fractions and compared to similar reference maps from peripheral tissues. In addition, studying single cell types can be facilitated through the use of laser capture microdissection[200] or fluorescence-activated cell sorting[201]. Alternatively, computational methods allowing for estimation of cell populations within tissue homogenates[202] could be used to refine results from studies using whole-tissue homogenates. Finally, epigenetic studies to date in suicide research have mainly focused on DNA methylation. However, other mechanisms of epigenetic regulation have been uncovered and should be further explored in the coming years (Box 5).

Box 5

Rethinking epigenetic mechanisms in suicidal behaviour

Most epigenetic research investigating suicidal behaviours to date has focused on DNA methylation. As we gain insight into which different epigenetic marks are enriched in the brain, we should investigate the role of other epigenetic mechanisms that may be associated with suicidal behaviours, namely the activity of intermediaries of cytosine methylation, histone modifications and the effects of noncoding RNAs.

Epigenetic modifications of cytosine residues leads to the formation of intermediate products of methylcytosine oxidation, such as hydroxymethylcytosine, formylcytosine and carbocytosine, all of which are enriched in brain tissue. These intermediaries are likely functional, and their potential contribution to the regulation of gene expression should be explored further. Cytosine methylation outside of CpG dinucleotides is also more prevalent in brain tissue than in other tissues. Most studies to date have focused on CpG methylation, and investigating the contribution of non-CpG methylation to the regulation of gene expression in brain tissue may be a promising avenue of research in suicide studies.

Histones are essential protein complexes that regulate the accessibility of DNA to transcriptional machinery by modulating the level of chromatin compaction. Post-translational modifications of the N-terminal tails of histones change their impact on chromatin structure and activity. Specific genomic loci are linked to distinct histone modification profiles, for example active promoters are associated with histone 3 lysine 4 (H3K4) dimethylation and trimethylation and histone 3 lysine 27 (H3K27) acetylation and H3K4 monomethylation in enhancer regions, whereas repressed promoters are associated with H3K9 and H3K27 dimethylation and trimethylation. Specific contributions of histone modification to the emergence of suicide-related phenotypes have yet to be fully explored, but histone modification represents a ubiquitous mechanism for regulating gene transcription.

Another new aspect of epigenetic regulation of gene expression is the role of non-coding RNA. A large portion of the transcriptome is composed of regulatory RNAs that do not

encode protein and instead regulate mRNA transcription, function and availability, and interact directly with DNA, regulatory proteins and enzymes. Among non-coding RNA species, long ncRNAs are of particular interest as they are highly expressed in the brain and are less evolutionarily conserved than other RNA species, and thus may associate with human brain processes that could be relevant to suicide research.

Such methodological improvements would allow us to confidently draw conclusions from studies on epigenetic modifications linked to suicide and might accelerate the identification of useful biomarkers for increased risk of suicide. In the long-term, this would translate into better management of high-risk patients and improved health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Suicidality
This broad term encompasses all forms of suicidal behaviour and suicidal ideation.

Suicidal ideation
This term describes the wish to die, including thoughts of actively ending one's life.

Suicidal behaviour
This term describes behaviours that result in self-injury, and is generally used to refer to suicide attempts and suicide completion.

Self-harm
This broad term includes suicidal behaviour and non-suicidal self-injurious behaviours.

Non-suicidal self-injurious behaviour
Deliberate self-injury, often in the form of superficial skin cuts that are made with the intent to decrease emotional pain, rather than to die.

Suicidal behaviour disorder
This disorder has recently been proposed as a condition for further study in the DSM-5, and is defined by the occurrence of at least one suicide attempt with some intent to die within the last 24 months. Conditions for further study in the DSM are disorders that should be investigated and considered for its future versions.

Suicidal crisis

Period when suicidal ideation becomes acute, which is often associated with emotional instability.

Distal risk factors
Predisposing factors that occur or are expressed temporally distant from the onset of the phenotype.

Early-life adversity
Acts by a parent or caregiver that result in physical, sexual and/or psychological abuse of a child or that lead to neglect of essential physical or psychological needs of childhood.

Treatment-emergent suicidal events
This term describes suicidal ideation or suicidal behaviour that occurs in association with treatment, and is typically used for clinical trials with antidepressants.

Childhood sexual abuse
Any completed or attempted sexual act, or exposure to sexual interactions, with or without physical contact, with a child by a caregiver.

Childhood physical abuse
The intentional use of physical force against a child that results in, or has the potential to result in, physical injury.

Parental neglect
Failure to meet a child's basic physical, emotional, medical or dental, or educational needs; or a failure to ensure a child's safety.

Attachment styles
Stereotypical interpersonal styles that are rooted in early-life interactions with caregivers.

Mediators
Mediators are variables that fully or partially explain the relationship between a predictor and a dependent variable.

Biological embedding
The effects of early-life experiences on the differential regulation of biological systems and development.

Endophenotypes
These are traits that associate with an illness in the population, are heritable, state-independent, co-segregate with the condition investigated, and are present in non-affected family members of affected individuals at a higher rate than in the general population.

Impulsive-aggressive behaviours
The tendency to react with animosity or overt hostility without consideration of the possible consequences, when piqued or under stress.

State marker

Biological, psychological, behavioural or clinical markers associated with a given phenotype.

Trait marker

Biological, psychological, behavioural or clinical markers that indicate a predisposition to or risk of a given phenotype.

Proximal risk factors

Precipitating factors that occur or are expressed temporally close to the onset of the phenotype.

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Biography

Gustavo Turecki is Professor of Psychiatry at McGill University, Montreal, Canada, where he directs the McGill Group for Suicide Studies and the Depressive Disorders Program. He received his MD from UNIFESP, Brazil, where he also completed his psychiatry residency, and obtained his PhD from McGill University. His research focuses on molecular mechanisms of depression and suicide.

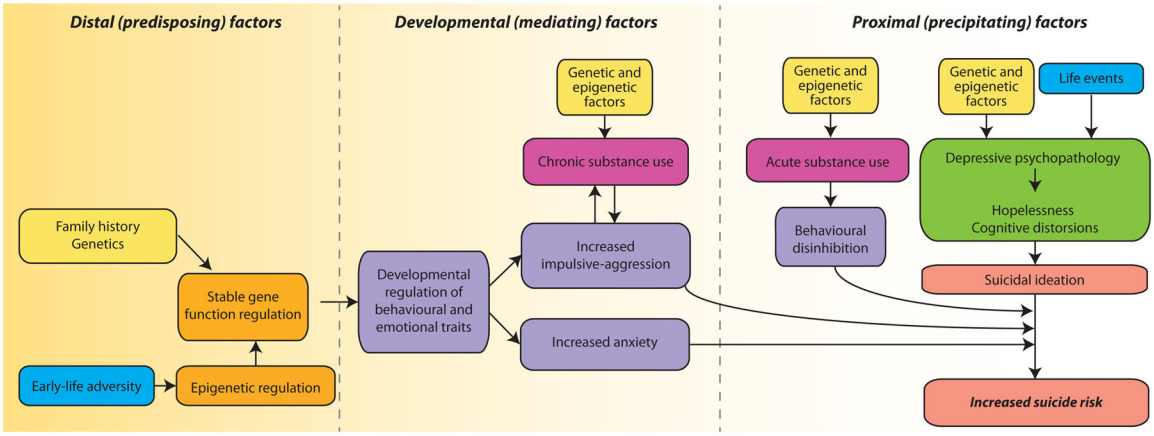

Figure 1. Overview of the contributors to suicidal behaviour

Suicidal behaviour is regulated by a number of different factors that can be broadly categorized as distal (predisposing), developmental (mediating) or proximal (precipitating) factors. The model proposed here takes into account the classic psychosocial and genetic risk factors for suicide, and integrates newer findings on epigenetic changes associated with suicidality. Predisposing factors include family history of suicide, and associated genetic predisposition; and early-life adversity and associated epigenetic changes. In both cases, predisposing factors lead to long-term effects on gene expression and regulation. Predisposing factors do not directly trigger suicidal events, but are linked to increased suicide risk through the effects of mediating factors. Mediating factors, which may directly result from the gene changes that occur as a consequence of predisposing factors, or may be associated with other factors such as chronic substance abuse, increase the risk of suicide by accentuating traits linked with suicidality. Specifically, family disposition and early-life events can shape behavioural and emotional traits such as impulsive-aggressive behaviour and anxiety traits, which increase the risk of acting on suicidal ideation, a common feature of depressive psychopathology and hopelessness. Proximal risk factors, such as depressive psychopathology and acute substance abuse, can also be associated with genetic and epigenetic factors and are often triggered by life events.