Special Issue: Neuropsychiatric Disorders

The neurodevelopmental origins of suicidal behavior

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Suicide and related behaviors are complex phenomena associated with different risk factors. Although most individuals who display suicidal behavior do not have a history of early-life adversity, a significant minority does. Recent animal and human data have suggested that early-life adversity leads to epigenetic regulation of genes involved in stress-response systems. Here, we review this evidence and suggest that early-life adversity increases risk of suicide in susceptible individuals by influencing the development of stable emotional, behavioral and cognitive phenotypes that are likely to result from the epigenetic regulation of the hypothalamic–pituitary–adrenal axis and other systems involved in responses to stress.

Introduction

Worldwide, more people die by suicide every year than by homicides and all wars combined [1]. Such mortality statistics clearly indicate the magnitude of the impact imposed by suicide on all societies, a particularly alarming fact considering that suicide is frequently an avoidable outcome when effective treatments are delivered [2]. Suicide is the extreme of a continuum of behaviors commonly referred to as suicidal behaviors. In this article, we will discuss data from studies investigating both suicide completers and suicide attempters interchangeably. However, we acknowledge that these two phenotypes are likely to only partly share underlying etiological and neurobiological mechanisms.

Suicide is a complex phenomenon with several distal and proximal risk factors (Figure 1). Among the latter, a strong and robust relationship exists between the presence of psychopathology, most notably major depressive disorder (MDD), and suicide risk [3]. Comorbidity with substance disorders, such as alcohol and other drug dependences, is also frequently observed [3]. Recent life events conferring acute stress or experiences of demoralization, such as public humiliation or social rejection are frequent triggers of suicide, and a number of sociodemographic factors such as education, employment and income, among others, modify the impact of psychopathology on suicide risk [4].

Several factors are thought to contribute more distally to increase suicide risk. Among these are constitutional and demographic factors such as gender and a family history of suicide, which plays a discrete but significant role [5]. Genetic variation, according to consistent genetic epidemiological data [6], is thought to account for part of the familial aggregation of suicide, which is partially independent from the familial clustering of mental disorders [5]. Certain personality traits [7], coping and cognitive styles [8] have also been associated with distal suicide risk. In general, environmental variables explain a substantial amount of the total variance in suicidal behavior with stressful life events, low social support and quality of social environment among the most consistently-implicated risk factors [9].

Among distal risk factors for suicide, a history of early-life adversity is undoubtedly one of the factors with the strongest effects [10,11]. Although most individuals who display suicidal behavior do not have a history of early-life adversity, a significant minority ranging from 10 to 40% (depending on type of abuse, frequency and suicide phenotype) does [12,13]. Accordingly, several longitudinal studies conducted in epidemiologically representative samples consistently show that children who have histories of sexual and physical abuse during childhood are more likely

Glossary

Behavioral dysregulation: incapacity to manage and control behaviors resulting from high levels of personality traits such as impulsivity and aggression. Individuals with behavioral dysregulation manifest externalizing behaviors such as hostility and hyperactivity among others.
CpG sites: regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide in the same nucleic acid strand.
Distal and proximal risk factors: a distal risk factor is a factor that confers vulnerability for a given outcome, whereas proximal risk factors act as triggers or precipitants of the outcome.
DNA methylation: the addition of a methyl group to a DNA nucleotide, most commonly to a cytosine located next to a guanine (referred to as a CpG site).
Early-life adversity: or child maltreatment, refers to acts by a parent or caregiver that inflicts harm to a child. Early-life adversity includes sexual abuse, physical abuse, emotional abuse and neglect.
Emotional dysregulation: incapacity to manage and control emotions. Individuals with emotional dysregulation present high levels of personality traits such as anxiety.
Glucocorticoid receptor (GR): the receptor of glucocorticoids, which in humans are primarily represented by cortisol. The gene that codes for the human GR is known as NR3C1 and maps to chromosome 5. It spans over 80 kilobases and contains eight coding exons (exons 2 to 9) and 11 untranslated exon 1 variants.
HPA axis hyperactivity: or HPA axis overactivity, is a state in which the HPA axis is not normally responsive to the negative feedback exerted by glucocorticoids, therefore, remaining hyperactive.
Mediators and moderators: mediators are variables that fully or partially explain the relationship between a predictor and a dependent variable, whereas moderators are variables that modify the intensity and/or direction of a predictor and dependent variable. For example, in the variable relationships discussed in this review, high anxiety trajectories are mediators of the relationship between early-life adversity and suicide outcome, whereas gender is a moderator.
Suicide and suicidal behaviors: suicide is the act of taking one's own life voluntarily, and usually intentionally. Suicidal behavior is a general term used to refer to suicide and suicide attempts. Under the latter, we refer to the actions taken to end one's life, irrespective of the degree of intentionality that did not result in death. Although suicidal ideation is not a behavior, it is often considered under the category of suicidal behaviors. It refers to the wish to die, including thoughts of actively ending one's life.

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0166-2236/$ – see front matter doi:10.1016/j.tins.2011.11.008

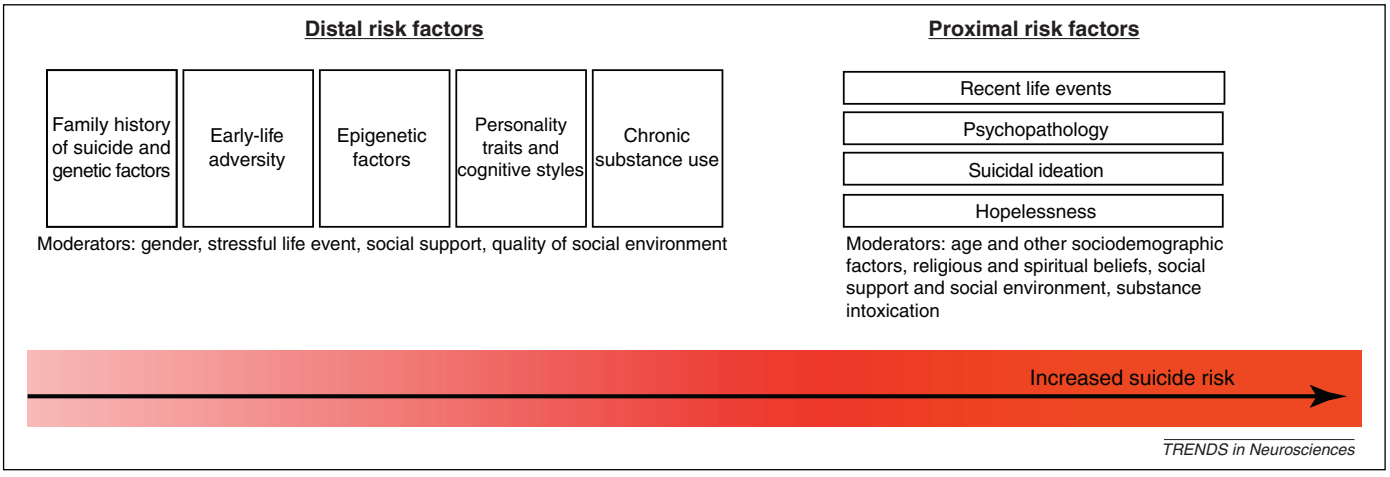

Figure 1. Schematic representation of distal and proximal risk factors for suicide. Distal risk factors comprise those increasing predisposition, whereas proximal risk factors are those that act as precipitants. Factors that may act as moderators of the relationship between distal and proximal risk factors are listed.

to manifest suicidal behavior in adulthood, even after other variables conferring major effects such as psychopathology are controlled for [10,11]. Long-standing effects of childhood abuse on suicidal behavior risk are also seen in diverse clinical populations and observed using different study designs (for example, [13,14]).

Frequency of the abuse and the identity of the abuser are important moderators of suicide risk. Abuse perpetrated by an immediate family member carries greater risk of suicidal behavior than abuse committed by an extended family member or an unrelated individual [13], suggesting that it is the psychological trauma associated with the maltreatment rather than the actual physical or sexual experience that confers the lifelong increased risk of suicidal behavior. Close family members are the main source of support during development and are essential to provide healthy attachment patterns, appropriate emotional regulation to environmental stimuli, and stress resilience [15]. Thus, the experience of repeated acts of abuse by parental figures, caregivers or other close relatives, signals a hostile and unreliable environment to which the organism may try to adapt by adjusting key response systems, such as those involved in reactivity to stress.

There is now increasing evidence suggesting that early-life environment regulates reactivity to stress partly by epigenetically adjusting the activity of genes involved in stress-response systems (Figure 2). The objective of this paper is to discuss this evidence and to review recent data

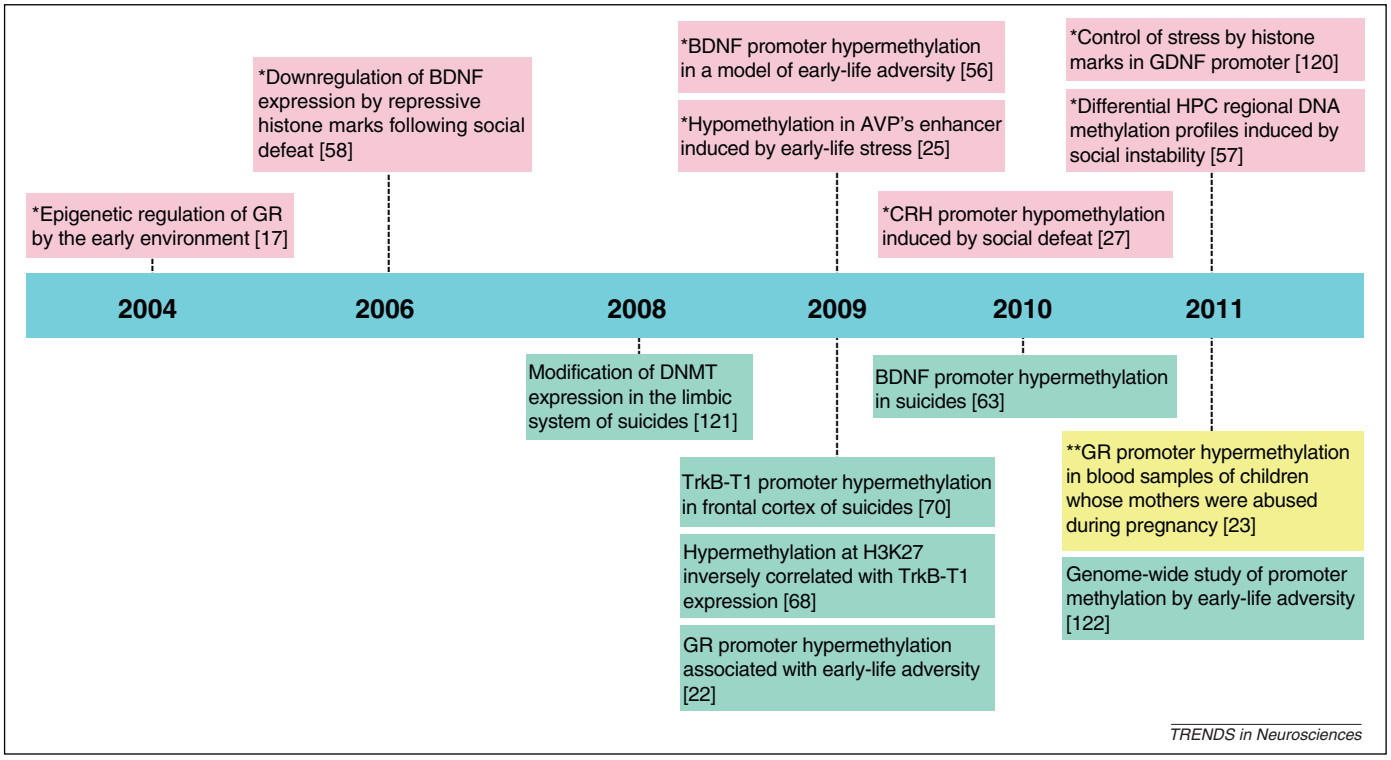

Figure 2. Schematic timeline of representative studies investigating epigenetic effects of environmental variation on the brain and their impact on behavioral phenotypes. Studies in animals are indicated by an asterisk (highlighted in pink [17,25,27,56–58,120]); studies in blood samples are indicated by a double asterisk (highlighted in yellow [23]); all other studies (highlighted in green [22,63,68,70,121,122]) were performed in postmortem human brain tissue. Abbreviations: BDNF, brain-derived neurotrophic factor; CRH, corticotropin releasing hormone; DNMT, DNA methyltransferase; GDNF, glial-derived neurotrophic factor; GR, glucocorticoid receptor; H3K27, histone repressive mark; HPC, hippocampus; TrkB-T1, splice variant (T1) of the tyrosine receptor kinase type B (TrkB) that lacks tyrosine kinase catalytic activity.

Table 1. Genes epigenetically modified in animal models as a result of variation in early-life environment or early-life stress[a]

Gene	Animal model	Brain region	Refs
GR	Low/high licking and grooming	HPC	[17,123]
BDNF	Intruder test	HPC	[58]
	Stressed mothers	PFC	[56]
	PTSD model	HPC	[57]
AVP	Maternal deprivation	PVN	[25]
CRH	Intruder test	PVN	[27]
GDNF	CUMS	STR	[120]
GAD1	Low/high licking and grooming	HPC	[124]

[a]Abbreviations: AVP, arginine vasopressin; BDNF, brain-derived neurotrophic factor; CRH, corticotropin releasing hormone; CUMS, chronic unpredictable mild stress; GAD1, glutamate decarboxylase 1; GDNF, glial-derived neurotrophic factor; GR, glucocorticoid receptor; HPC, hippocampus; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus; STR, striatum.

suggesting that a series of lasting neurobiological changes resulting from early-life adversity may help explain developmentally stable emotional, cognitive and behavioral phenotypes (collectively referred to as personality traits), which in turn increase suicide risk.

Molecular consequences of early-life adversity: epigenetic and transcriptional changes

What molecular changes are triggered by adversity in early life? Significant insight into this critical issue comes from animal studies that suggest a mediating role of epigenetic mechanisms on the effects of variation in the early-life environment (Table 1).

Hypothalamic-pituitary-adrenal (HPA) axis

Groundbreaking research investigating variation in maternal care in the rat found that the frequency of maternal pup licking and grooming (LG) over the first week of life programs the expression of genes that regulate behavioral and endocrine responses to stress [16]. One of the most robust effects involves the expression of the glucocorticoid receptor (*GR*) gene in the hippocampus. The offspring of high LG mothers were observed to have increased hippocampal GR expression and more modest responses to stress compared to the offspring of low LG mothers [16]. This maternal behavior was found to be associated with an epigenetic modification of a neuron-specific exon 1_7 promoter of the *GR* gene in the offspring [17]. More specifically, increased maternal LG led to decreased exon 1_7 promoter methylation and higher expression of GRs in the hippocampus [17]. Critical to hippocampal GR expression levels is a particular CpG site (see Glossary) where the transcription factor nerve growth factor inducible A (NGFIA) binds, and furthermore, this site is highly differentially methylated between offspring of high and low LG mothers [17]. This suggests that variations in the quality of maternal care directly regulate epigenetic states, and thus, exert sustained effects on gene transcription [18].

There are important parallels between behavioral and molecular changes observed in the rodent models of parent–offspring interactions and behavioral and biological alterations that associate with a history of early-life adversity in humans. Pups reared by low LG mothers show increased behavioral and HPA responses to mild stress [16]. In humans, such effects are observed in individuals who have been exposed to childhood abuse [19], in particular HPA dysfunction, and associate with increased vulnerability for suicide [20]. In addition, adversive and stressful familial environments lead to altered parent–child interactions and increase risk for suicidal behavior in children [21].

A number of recent studies have translated these findings from animal studies to humans (Table 2). Evidence of an effect of childhood adversity on the epigenetic state of the human genome was first observed by investigating the methylation state of the *GR* gene in the hippocampus of individuals who died by suicide and had histories of early-life adversity [22]. These individuals, when compared to normal controls and suicides with no histories of early-life adversity, presented decreased mRNA expression levels of total GR and GR exon 1_F (an untranslated exon 1 variant that is homologous to the rat exon 1_7) in the hippocampus. Similar to the maternal effects on the GR exon 1_7 promoter methylation observed in the rat, the human study indicated that abused suicides had increased methylation in the exon 1_F promoter. Moreover, the methylation effects observed occurred at a comparable genomic site to that seen in the rats [22], where the transcription factor NGFIA binds.

Recent independent studies using alternative designs have also yielded consistent results [23,24]. For example, a study investigating intrauterine exposure to maternal stress found increased GR exon 1_F methylation in peripheral DNA samples of exposed children [23]. Another study investigating GR expression in the hippocampus of depressed subjects with no histories of childhood abuse who died by causes other than suicide found decreased exon 1_F expression, but did not observe differences in 1_F promoter methylation [24]; a finding that is consistent with the original study[22], which indicated no effect of psychopathology on 1_F promoter methylation.

More recent animal studies indicate that in addition to variation in maternal behavior, early-life stressors can also regulate CpG methylation states and the expression of genes involved in the stress response. Accordingly, prolonged periods of maternal separation in the mouse regulate

Table 2. Genes epigenetically modified in suicide and/or related phenotypes[a]

Gene	Psychopathology	Brain region/tissue	Refs
TrkB	Suicide	Frontal cortex	[68,70]
BDNF	Suicide	Wernicke's area	[63]
GR	Suicide with childhood abuse	HPC	[22]
	Depression	Limbic system	[24]
	Intrauterine maternal stress	Lymphocytes	[23]
Polyamines	Suicide	PFC	[125,126]
5HTT	Childhood abuse PTSD	TLCL	[127,128]

[a]Abbreviations: 5HTT, serotonin transporter; BDNF, brain-derived neurotrophic factor; GR, glucocorticoid receptor; HPC, hippocampus; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; TLCL, transformed lymphoblastoid cell line; TrkB, tyrosine receptor kinase type B.

the methylation of a regulatory intergenic sequence between the neighboring vasopressin (*avp*) and oxytocin genes in the hypothalamic paraventricular nucleus (PVN). This sequence functions as an enhancer of avp, leading to altered *avp* expression and HPA responses to stress [25]. In addition, exposure to prenatal stress early in gestation in the mouse determines increased stress responsivity in male offspring. Such a response is associated with long-term alterations in central (hypothalamus and amygdala) corticotropin-releasing hormone (CRH) and GR expression, and with altered *CRH* and *GR* gene methylation, which are correlated with gene expression [26]. A subsequent study found that socially defeated mice have increased CRH expression in the PVN that correlates with hypomethylation of this gene's promoter [27]. Interestingly, this study was conducted in adult animals, suggesting that at least some of the epigenetic regulation of genes that occurs as a function of the negative emotional environment is not limited to early development. This conclusion is in line with recent data indicating that in adult mice a small proportion of neuronal CpG sites undergo dynamic methylation changes [28].

Early-life adversity and suicidal behavior associate with HPA dysfunction

There is substantial evidence, both from animal and human studies, that exposure to an unfavorable environment during development elicits persistent changes in the regulation of stress-response systems, most notably the HPA axis (reviewed in [19]). Similarly, individuals who manifest suicidal behavior also have alterations suggesting HPA axis hyperactivity (Figure 3), although the evidence is not always consistent. For instance, suicide completers present hyperactivation of CRH neurons in the PVN as suggested by increased CRH mRNA levels [29,30] and increased numbers of CRH-positive neurons [31]. Suicide completers also have decreased GR mRNA in the hippocampus [22] and increased pro-opiomelanocortin (POMC) pituitary mRNA levels [32]. They also show evidence of elevated cerebrospinal fluid (CSF) CRH levels [33], decreased CRH binding sites [34], altered CRH receptor type ratios [35], as well as elevated CRH immunoreactivity and mRNA levels in several brain regions [36,37]. Moreover, suicides have increased adrenal weight [38], which seems to be accounted for by cortical hypertrophy [39], also suggesting chronic HPA axis hyperactivity. These results from postmortem studies should be considered in light of their limitations, which among other things include retrospective and proxy-based collection of phenotypic data and several postmortem confounders. Nevertheless, many of these limitations can be properly controlled for, providing a unique opportunity to gain insight into brain molecular changes underlying suicide and psychopathology.

Studies investigating markers of HPA axis function in suicide attempters also suggest hyperactivity, although

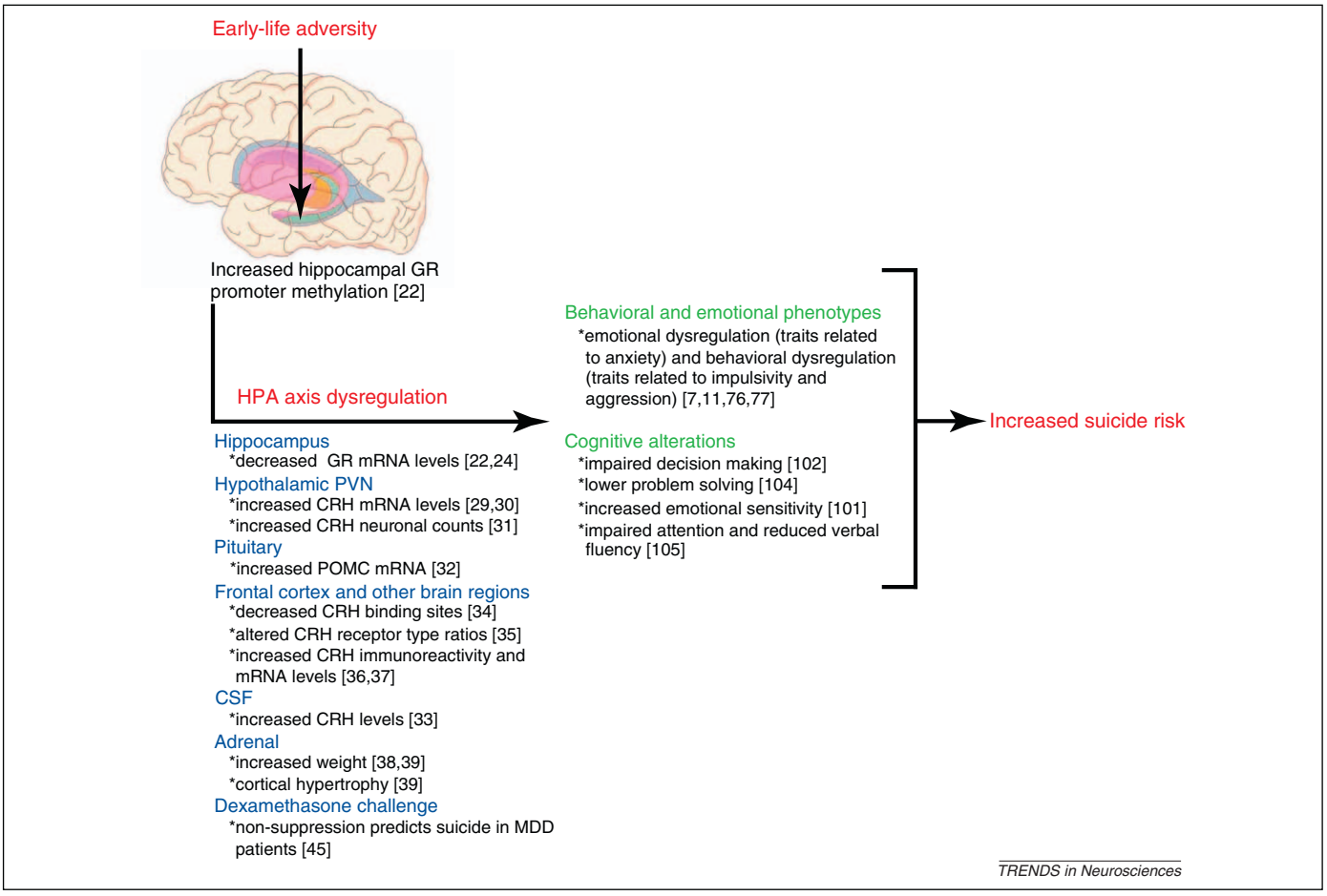

Figure 3. Model explaining increased risk for suicide in individuals exposed to early-life adversity. Exposure to early-life adversity increases promoter methylation of glucocorticoid receptor (GR) in the hippocampus, leading to hypothalamic–pituitary–adrenal (HPA) dysregulation and development of emotional, behavioral and cognitive phenotypes, which in turn increase risk for suicide. Under each panel, studies supporting these associations are listed.

these results are more discordant than those found for suicide completers [20,40–43]. Indices of HPA axis dysfunction correlate with both the severity of the associated psychopathology [43] and with the violence of the suicide attempt [42]. Although there is similar evidence indicating HPA hyperactivity in MDD (reviewed in [44]), most studies investigating HPA markers in suicide are confounded by psychopathology. Yet non-suppression to the dexamethasone suppression test predicts death by suicide [45] or suicidal behavior among patients with MDD [46], suggesting that HPA axis dysfunction may increase risk of suicidal behavior independently of its association with psychopathology. In addition, this notion is also supported by data from euthymic first degree relatives of suicide completers, who show evidence of blunted HPA responses when exposed to an experimental psychosocial stress paradigm in a laboratory setting [47].

Neurotrophic factors

In addition to the findings involving stress-response systems, interesting results have been reported for neurotrophins, and particularly with the brain-derived neurotrophic factor (*BDNF*) gene and its high-affinity receptor, tyrosine receptor kinase type B (TRKB). Since the initial identification of BDNF in the late 1970s [48], it has been extensively investigated in the context of psychiatric disorders [49] and other neurological phenomena (see [50] in this Issue). The first indication that BDNF may have a role in psychiatric disorders came in the mid 1990s when studies in rodents showed that stress and glucocorticoids altered the expression of BDNF in brain [51] and that BDNF interacted with the dopaminergic and serotonergic systems [52]. Chronic stress had long been suspected of causing damaging structural changes in the brain [53], and hence, BDNF was considered a potential mediator of the interaction between stress and physiological structural changes. Although the hypothesis that stress-induced decreases of BDNF lead to structural brain changes has not been supported by all brain studies [54,55], it seems clear that BDNF does have a role in mediating stress responses in the brain, although this effect is probably dynamic, complex and non-linear.

Recently, a number of studies have examined the interactions between BDNF expression levels, epigenetic modification of BDNF, and stress response in rodents. Maternal maltreatment, induced by exposure of dams to unfamiliar environments with limited bedding material, decreases prefrontal cortex (PFC) BDNF mRNA expression, which is associated with site-specific hypermethylation in the promoters of exons IV and IX of the *BDNF* gene [56]. Interestingly, site-specific hypermethylation seems to follow a developmental pattern, with exon IX promoter hypermethylation occurring immediately after the maltreatment regimen, whereas promoter IV methylation increases gradually to reach significantly altered levels only at adulthood [56]. Recently, this same group of investigators identified epigenetic regulation of the BDNF exon IV promoter in the dorsal hippocampus of adult rats using a model of post-traumatic stress disorder (PTSD) [57], suggesting that the epigenetic programming of BDNF by DNA methylation may not be limited only to developmental periods. Relatedly, defeat stress in adult mice was found to induce lasting downregulation of BDNF transcripts III and IV by H3K27, a repressive histone mark [58].

Studies of BDNF in humans, including those examining anxiety-related traits, have focused primarily on polymorphisms in the *BDNF* gene (such as the common Val66Met polymorphism) and their association with disease rather than on their functional impact, although there are notable exceptions. For example, recent evidence suggests that carriers of the *BDNF* Met allele exposed to childhood abuse have decreased serum BDNF levels [58]. This same study found that exposure to negative life events resulted in decreased serum BDNF levels independent of genotype [59]. Decreased BDNF expression levels in the lymphocytes or platelets of depressed subjects or suicide attempters, compared to control subjects, have also been found [60,61]. Furthermore, evidence from some human studies suggests that decreased BDNF expression, at least in blood, is associated with suicide attempts and anxiety-related traits [62].

To examine a possible association between BDNF changes in the brain and suicidal behavior, the methylation state of BDNF has been assessed in postmortem brains from suicide completers [63]. The human *BDNF* gene is composed of 11 exons preceded by nine non-coding first exons regulating BDNF expression in different tissue [64]. In this study [63], three different methods were used to quantify methylation levels in a region encompassing part of non-coding exon IV and its promoter in the Wernicke's area of the cortex. These results showed that methylation in four CpGs, located downstream from the promoter IV transcription initiation site, was significantly increased in suicide completers compared to controls. These differences were specific to the BDNF promoter because the investigation of genome-wide methylation in these subjects did not reveal any significant between-group differences. In addition, BDNF expression in subjects with high methylation levels was significantly lower than in subjects with low and medium methylation levels, supporting the repressive effects of methylation within this promoter on the transcription of BDNF. Although these results are consistent with some BDNF findings from rat models of early-life adversity, a history of childhood abuse was not examined in this study.

Experimental findings have also found changes in the expression of TrkB, the receptor for BDNF, in mood and related disorders. For instance, lower TrkB expression was observed in the PFC of depressed subjects [65] and antidepressant treatment has been shown to increase its expression in cultured astrocytes [66]. The *TrkB* gene is located on chromosome 9 at locus q22.1 and has five splice variants. Splice variant T1 or TrkB-T1 is an astrocytic truncated form of TrkB lacking catalytic activity [67]. Recently, analysis of the methylation pattern in the promoter of a subset of suicide completers with low levels of TrkB-T1 expression revealed two sites where methylation levels were higher compared to controls [68]. The methylation pattern at those two sites was negatively correlated with the expression of TrkB-T1 in suicide completers, and this effect was specific to the PFC because no significant difference was found in the cerebellum or in the Wernicke's area [69]. Such a pattern of expression and methylation are

thought to increase predispositions to suicidal behaviors. In addition, suicide completers with low TrkB-T1 expression showed enrichment of H3K27 methylation in the TrkB promoter [70], suggesting that the astrocytic variant of TrkB may be under the control of epigenetic mechanisms involving histone modifications and DNA methylation. Interestingly, recent data show that mice overexpressing the TrkB.T1 variant and presenting decreased BDNF signaling are more susceptible to chronic social stress than wild type mice, as demonstrated by consistent social avoidance [71]. Together, these data suggest that epigenetic changes in the TrkB.T1 promoter, resulting in expression changes of TrkB, could define the vulnerability to chronic social stress and possibly to early-life adverse experience.

Emotional, behavioral and cognitive phenotypes mediating the relationship between early-life adversity and suicide risk

How do molecular and cellular changes resulting from early-life adversity increase risk of suicidal behavior? A wealth of data from rodent and non-human primate studies investigating a variety of paradigms suggests that variation in early-life environment correlates with stable behavioral phenotypes [72,73]. For example, early maternal separation in rodents is associated with long-lasting reduction of exploratory behavior in novel environments and increased freezing behavior in an open field, among other changes [72]. Similar stable changes correlate with variation of naturally occurring behaviors in maternal pup LG in rats [74], and social deprivation in non-human primates is associated with the development of inappropriate and excessive aggressive behavior [73]. In agreement, and as discussed below, humans having experienced early-life adversity are more likely to develop certain stable emotional, cognitive and behavioral phenotypes, which in turn increase risk for suicidal behavior.

Emotional and behavioral phenotypes

Personality traits represent emotional, behavioral, motivational, interpersonal, experiential and cognitive styles that humans have in order to relate to and cope with the world [7,75]. Several individual personality traits, particularly emotional dysregulation (e.g. high levels of traits related to anxiety) and behavioral dysregulation (e.g. high levels of traits related to impulsivity and aggression) strongly associate with risk of suicidal behavior [5,7,11,76]. Evidence supporting a relationship between anxiety traits, impulsive-aggression and suicidal behavior is strong, coming from studies using different study designs and investigating representative and non-representative samples from clinical and epidemiological settings [7].

Of particular interest are the findings from longitudinal studies conducting trajectory analyses [76]. In contrast to cross-sectional observations relying on one-point snapshots or longitudinal analyses based on two-point associations, trajectory analyses allow the investigation of the development of a trait over multiple points of observation and, therefore, provide powerful data to test developmental hypotheses and study temporal relationships between variables. Investigating a prospective school-based cohort representative of the general population of Quebec and followed longitudinally for over 22 years, our group conducted a series of studies investigating the role of personality trajectories in suicidal behavior [13,76–78]. These studies suggest that developmental trajectories of anxiousness characterized by consistently high anxiety traits during childhood predict suicidal behavior in adulthood [76]. Similar effects are seen for trajectories characterized by high levels of disruptiveness (composite measure of impulsivity, aggressive behavior, hyperactivity and oppositional behavior). These observations are consistent with findings from other longitudinal and cross-sectional studies investigating youth and adult clinical and epidemiological samples [79–81] and suggest that developmentally stable emotional and behavioral phenotypes characterized by high levels of anxiety and impulsive-aggressive behaviors predict suicidal behavior in adulthood.

Likewise, emotional and behavioral dysregulation are frequently reported in individuals with histories of early-life adversity [82]. Mediation and moderation analyses suggest that these trait phenotypes explain, to variable degrees, the relationship between early-life adversity and suicidal behavior [11,83]. A critical question is whether the development of these trait phenotypes is explained by stable neurobiological changes, such as HPA axis overreactivity, which is observed to be associated with early-life adversity in animal studies (Box 1). Although recent studies suggest that this may be the case [84,85], additional data, particularly from longitudinal studies, are needed. Nevertheless, the evidence supporting associations between early-life adversity, emotional and behavioral dysregulation, and suicidal behavior, as well as between these individual factors and neurobiological dysregulation of stress-response systems (and to a lesser degree neurotrophic factors), is substantial. Taken together, such findings suggests that the developmental effects of early-life adversity on personality traits that increase risk for suicidal behavior may be associated with sustained neurobiological alterations.

Cognitive phenotypes

How can the emotional and behavioral dysregulation associated with early-life adversity result in increased risk for suicide? Recent research has indicated that perhaps, through its effects on stress-response systems, early-life adversity may have long-term consequences on cognitive functioning. For instance, in early-life stressed rats, persistently elevated hippocampal CRH activity contributes to cognitive impairments [86]. Humans maltreated during childhood present reduced performance in multiple cognitive domains including attention, concentration, motor speed, response inhibition, memory, working memory and verbal and reading abilities [87–90]. Some of these impairments may be related to chronic dysfunction in the HPA axis [53] and related hormones such as oxytocin and vasopressin [91]. At the structural level, early-life adversity correlates with significant alterations in the brain [92], including changes in grey matter volume in dorsomedial, dorsolateral and medial PFC [93], anterior cingulate [94], superior temporal gyrus [95], amygdala [96], hippocampus [97] and corpus callosum [98].

In turn, these cognitive deficits associated with early-life adversity may increase the risk of suicidal behavior

Box 1. Outstanding questions

- Is there a critical age period during which the organism is more likely to epigenetically regulate gene function as a result of negative life adversity? In other words, is significant life adversity occurring in adulthood also likely to associate with epigenetic changes in genes involved in stress-response regulation? If so, are these phenomena equivalent, or are they less dynamic, as the individual ages?
- Do epigenetic factors play a role in suicide that is not associated with early-life adversity?
- Considering the strong moderating role of gender in suicide risk, are there epigenetic differences between males and females exposed to early-life adversity?
- What other genetic pathways, beyond those involved in stress-response regulation and associated with anxiety, are epigenetically regulated in suicide? Are serotonergic genes, whose role has been extensively investigated in suicidal behavior, equally regulated by epigenetic factors?
- Are epigenetic changes associated with suicide in genes coding for non-HPA axis stress systems, such as the polyamine system (Table 2), related to early-life adversity?
- Extensive research efforts over the past two decades have been devoted to the identification of gene variants that increase vulnerability to psychiatric phenotypes, including suicidal behavior [6]. Although there is no consensus, a number of gene variants have been proposed as risk alleles increasing predisposition to suicidal behavior. An interesting question relates to the role of epigenetic changes in the modification of the potential risk conferred by alleles. If epigenetic changes are widespread, a related and methodologically important question to address would be to investigate if such modifications explain part of the inconsistencies found in genetic association studies of suicidal behavior?
- It is well established that after a developmental critical period, most brain regions and systems lose substantial capacity for plasticity. Is there such a critical period for stress systems?
- Is reduced hippocampal GR expression following early-life adversity related to a reduction in adult hippocampal neurogenesis?
- Can epigenetic processes associated with early-life adversity and suicide risk be reversed through therapeutic interventions, such as histone deacetylase (HDAC) inhibitors, which have shown promise in reversing cognitive deficits in a number of animal models [129]? If so, are there critical developmental time-windows for such an intervention?
- Are neurocognitive alterations associated with suicidal behavior similar in individuals with and without histories of early-life adversity?

[99,100]. Indeed, the vulnerability to suicidal behavior has been associated with several cognitive deficits, independently of comorbid disorders [8]. Individuals with a past history of suicidal acts show increased sensitivity to particular emotional signals [101] and disadvantageous decision-making [102] (associated with orbitofrontal cortical dysfunction [103]), lower problem-solving abilities [104], impaired attention and reduced verbal fluency [105] (associated with dorsomedial PFC [106]). Structural neuroimaging studies in suicide attempters have revealed alterations in diverse brain regions that overlap with those reported in maltreated individuals, including medial orbitofrontal cortex [107,108], anterior cingulate/ventral striatum [109], superior temporal gyrus [108], amygdala [107] and inferior-frontal gyrus [110].

These cognitive deficits are likely to mediate the relationship between early-life adversity and suicidal behavior [99,100]. Interestingly, the exposure to a stressful situation also has significant negative effects on decision-making and problem-solving, especially in predisposed individuals, i.e. those with stress-reactivity dysregulation. For instance, healthy individuals with higher cortisol reactivity following a social stress test show more decision-making impairment than those with lower cortisol reactivity [111]. More importantly, problem-solving following a negative emotional test is altered in individuals with, but not those without, a history of suicidal ideation [112]. Furthermore, adolescents with poor problem-solving have more suicidal thoughts following stress [113]. It has also been demonstrated that euthymic first-degree relatives of suicide completers display altered HPA reactivity and fail to improve in re-tests of executive function when exposed to a social stress test [47]. Collectively, these studies suggest a relationship between early-life adversity, stress-reactivity dysregulation, cognitive deficits (such as poor decision-making/problem-solving), and suicidal behavior.

Concluding remarks

Suicide is a complex phenomenon that is probably the common outcome of different etiological pathways. As such, no single neurobiological mechanism underlies the suicide process. However, a sizable subgroup of individuals manifesting suicidal behaviors were exposed to early-life adversity, and these cases share a number of common characteristics. We reviewed evidence suggesting that suicidal behavior in this subgroup of individuals may result from a cascade of developmental processes stemming from the abuse and/or neglect experienced early in life (Figure 3). First, the evidence suggests that early-life adversity may increase suicide risk by inducing stable epigenetic changes regulating genes coding for neurotrophic factors and other factors that regulate stress-response systems. These epigenetic changes may then lead to sustained neurobiological alterations such as HPA axis overreactivity, which in turn, is associated with the development of specific emotional and behavioral phenotypes characterized by high anxiety and impulsive-aggressive traits. Related to these developmental phenotypes are cognitive deficits, including poor decision-making and problem-solving. These traits would constitute the suicide diathesis, and act as distal risk factors, in individuals who have experienced early-life adversity.

When would such distal risk factors constitute a particular risk for onset of suicidal behavior? Most individuals who commit suicide die in the context of an episode of MDD. Those who do not, are often affected by other psychopathologies, such as schizophrenia. Notwithstanding the actual diagnosis associated with suicide, most individuals who commit suicide had depressive mood and felt hopeless when they acted on their suicidal thoughts. Major depressive episodes or depressive symptomatology in other psychopathological conditions are frequently triggered by negative life events, and moreover, either active or passive suicidal ideation frequently associates with depressed mood and is part of the natural history of MDD. Therefore, it is possible that individuals presenting the suicide diathesis summarized above would present a suicidal crisis when facing a difficult life event associated with depressive symptomatology. These would act as proximal risk factors.

As is the case with any etiological model of a psychiatric phenotype, the model of suicidal behavior discussed in this

paper has important limitations. Such limitations result, in part, from oversimplifications of a complex behavior and presentation, for clarity of argument, of variable relationships as if they were linear and casual. For instance, it is likely that the relationship between early-life adversity and suicide, as well as the effects of the neurobiological and trait-phenotype mediators discussed above, are moderated by several important factors such as gender, age, cultural context, spirituality and sets of beliefs about life and death. In other words, these and other variables are likely to significantly modify the intensity and/or direction of the associations outlined above. For example, a well-investigated moderator is gender, which significantly modifies the effect of personality traits on suicidal behavior [10,114], as well as the effect of stress on decision-making [111].

Another important point to consider is the specificity of the variable relationships discussed in this article. Although the variable associations considered are clearly significant and many are supported by different lines of evidence, they may have different effects on different phenotypes. A case in point is the association between HPA axis overreactivity and MDD, a relationship supported by a wealth of data produced over more than three decades [44]. It is possible, as it is becoming increasingly clear in mental health research, that many risk factors may not be specific in conferring risk to different phenotypes. A good example of such an effect is given by certain genetic variants, such as the serotonin transporter promoter ins/del variant [115] or some genome-wide association study findings, which replicate across different phenotypes [116–119]. If this is correct, one may speculate that some of the distal risk factors for suicidal behavior could confer unspecific risk, with specificity for suicide given by a certain combination of these risk factors. Alternatively, specificity may be associated with the onset of proximal risk factors, such as depression and suicidal ideation. It is hoped that a better understanding of early neurobiological correlates of suicide risk will help to reduce the mortality and societal burdens associated with this complex neuropsychiatric phenotype.

Acknowledgments

The authors thank Richard Violette for expert help in the preparation of this review. The authors' work is supported by grants from the Canadian Institute of Health Research, the Fonds de Recherche du Québec–Santé (FRQS), the Réseau Québécois de Recherche sur le Suicide, the American Foundation for Suicide Prevention and the Brain & Behavior Research Foundation. G.T., F.J. and N.M. are FRQS chercheurs-boursiers.

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