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Neurobiological underpinnings of suicidal behavior: Integrating data from clinical and biological studies

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ABSTRACT – *Background and Objectives*: Every year, suicide accounts for approximately one million preventable deaths worldwide. Suicidal behavior is complex and multi-determined with risk factors identified in multiple domains including clinical, genetic, environmental, behavioral, neurophysiological, and neurocognitive. Modeling causal pathways that integrate these factors may assist in better identification of high-risk individuals would allow for effective preventive intervention.

Methods: Published literature in the English language was reviewed to identify evidence supporting a multi-dimensional model of putative causal pathways for suicidal behavior.

Results: There is evidence that clinical, neurochemical, neuroendocrine, neurocognitive, and neurophysiological contributory factors may be useful as intermediate phenotypes in describing putative causal pathways from genetics and early-life adversity to suicidal acts.

Conclusions: Determining the causes of suicidal behavior involves integrating risk factors from multiple domains.

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Introduction

Suicide accounts for approximately one million deaths a year worldwide[1], and has devastating personal, family, and socioeconomic consequences. In the USA, it is the eleventh leading cause of death for all ages, and in 2005 suicide accounted for approximately 32,000 deaths, 1.3% of all deaths in the U.S[2]. The US suicide rate in 2005 was 11/100,000, with a rate of 17.7/100,000 in males and 4.5/100,000 in females[2]. Although lower than the USA, suicide rates in Spain for the same period, were also high: 12.0/100,000 in males and 3.9/100,000 in females[1]. In the US, suicide is the fifth leading cause of years of potential life lost before the age of 65[2]. The impact of suicidal behavior is even greater than the death rates suggests, because it not only involves the older population, but also markedly affects adolescents and young adults. In 2007, 14.5% of U.S. high school students reported they had seriously considered suicide during the preceding year, and more than 6.9% reported they had actually attempted suicide one or more times during the same period[3]. For every suicide death in the 15 to 24 year-old age group, it is estimated that 100 to 200 attempts are made[4].

Over 90% of those who die by suicide have a psychiatric illness, with 60% of all suicides occurring in the context of a mood disorder[5]. Suicide attempt rates are also elevated among individuals with psychiatric disorders, with reported rates of suicide attempt of 29% in Bipolar disorder, 16% in Major Depressive Disorder[6], 16-29% in alcohol use disorders[7-10], and 23-30% in psychotic disorders[11, 12], compared to 4.6% reported in general population surveys[13]. However, the majority of psychiatric patients do not attempt suicide, so a more specific explanation for suicidal behaviour must be sought.

Many factors have been associated with suicide attempt and suicide in studies of clinical populations, including abnormal serotonergic, noradrenergic system and HPA axis function, deficits in executive function, smoking, and higher aggression, impulsivity, hopelessness, and pessimism[14-16].

There is no single causal factor for suicidal behavior. Rather, it has been proposed that suicidal behavior occurs in the context of an interaction between a diathesis for suicidal behavior and the occurrence of acute stressors[17]. The diathesis refers to an individual's predisposition to manifest suicidal behavior in response to a stressor, is considered trait based, and is independent of psychiatric condition[17]. The diathesis for suicidal behavior is hypothesized to comprise factors or traits from multiple domains including biological, genetic, cognitive, personality, behavioral, and clinical (see[18] for an overview). Stressors act as triggers or precipitants and relate to both the timing and probability of suicidal acts and are considered state-related[17]. Stressors may include a major depressive episode, acute substance intoxication, or personal stressors (familial, social, or financial). Thus, suicidal behavior is not simply a reaction to extreme stress, nor does it necessarily correlate with the severity of a stressor, but results instead from the interaction of the individual's diathesis or predisposition to engage in suicidal acts and the occurrence of a trigger[17]. Given the multiple contributory causal factors, both in the diathesis and stressor domains, an explanatory model for suicidal behavior must be able to integrate risk factors into a multidimensional model that includes clinical, biological, genetic, behavioral, personality, and psychosocial traits as well as stressors and delineate causal pathways leading to suicidal outcomes.

An Integrated Model of Suicidal Behavior

The endophenotype approach is particularly relevant to the study of complex multidetermined behaviors such as suicide and suicide attempt. An endophenotype is an intermediary phenotype in the etiologic pathway from genes to disease[19], and represent more basic constructs, symptoms, or characteristics that are more amenable to quantification[19]. Beyond focusing on the casual pathways between genes and suicidal behavior, the concept of an intermediary phenotype can also be useful as an approach to tracing the etiological pathways from observed neurochemical, neuroendocrine, and neurophysiological dysfunction to suicidal outcomes via behavioral, clinical, and cognitive alterations. In figure 1 we outline a putative model of suicidal behavior which originates with genetic and environmental factors and then delineates clinical, biological, and other risk factors identified in the literature, that may function as endophenotypes. Developing such explanatory models is a crucial step not only for identifying areas which require further investigation, but also for improving assessment of risk for suicidal behavior and identifying targets for preventive intervention. We will first outline some putative clinical, biological, and neurocognitive endophenotypes and describe the relationship between them, and then examine genetic and environmental considerations.

Clinical Endophenotypes

Clinical traits repeatedly associated with suicide attempt and suicide death across psychiatric diagnostic groups include impulsivity, aggression, pessimism, and hopelessness (for a review see[20]). However, they are not sufficient to explain suicidal behavior, and these constructs or traits themselves are often complex or may be too loosely defined. For example, there are many types of impulsivity, which may potentially result from different underlying neurobiological anomalies[21]. Moreover, clinical traits may be causally interrelated, for example both pessimism and aggression/impulsivity predict suicidal acts, but they also have an additive

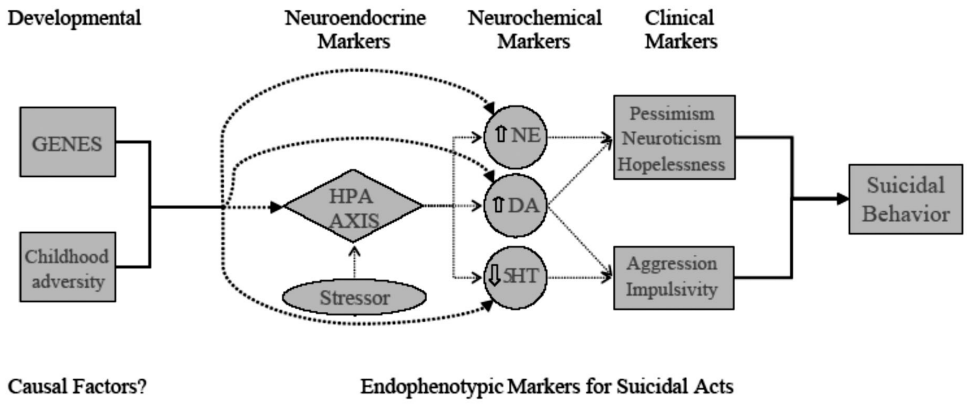

Figure 1

effect on suicide attempt risk[22]. Addressing this complexity may require defining more precise constructs, and contextualizing traits in terms of related biological, genetic, and other domains of risk, so that a more fine-grained assessment of the relevance of such traits to suicidal behaviors is possible.

Neurochemical Endophenotypes

Biological studies have examined the role of the serotonergic, noradrenergic, and dopaminergic systems in suicidal behavior, as well at the HPA axis stress response system.

Serotonergic system

The most consistent finding in suicidal individuals is dysfunction in the serotonergic system[16]. In suicide, altered serotonergic function has been evidenced in studies of the serotonin metabolite 5-hydroxyindoleacetic acid in cerebrospinal fluid (CSF 5HIAA), and of serotonin receptors and transporters in postmortem brain[23-26]. In a metaanalysis of prospective studies, individuals with below median levels of CSF 5-HIAA were 4.5 times more likely to die by suicide than those in the above median group[27]. Lower concentration of CSF 5-HIAA has also been reported particularly in individuals who use violent methods to suicide or make higher lethality non-fatal attempts[28-31]. Postmortem studies of the brain in individuals who have died by suicide indicate a localized reduction in serotonin transporter (SERT) binding in the ventral prefrontal cortex, which could reflect reduced serotonin input in this area[32, 33]. SERT mRNA is found in the serotonergic neurons of the dorsal raphe nucleus and median raphe nucleus[34]. Some hypothesize that findings in suicide victims of increased tryptophan hydroxylase, reduced SERT mRNA, and reduced number of 5-HT_{1A} inhibitory autoreceptors, are homeostatic mechanisms that arise secondary to serotonergic deficit[34].

In support of a role for altered serotonergic function in suicidal behavior *in vivo* imaging studies report lower C-α -methyl-L-tryptophan trapping in the orbital and ventromedial prefrontal cortex in high-lethality suicide attempters, with a negative correlation with suicide intent[35], and a negative correlation of 5-HT_{2A} binding with levels of hopelessness, a correlate of suicide and suicide attempt[36]. Oquendo et al., in a PET study, reported found that in response to the administration of the serotonin agonist fenfluramine, depressed high-lethality suicide attempters had lower fluorodeoxyglucose (^{18}F) regional cerebral metabolism of glucose rCMRGlu) in anterior cingulate and superior frontal gyri, compared with depressed low-lethality attempters[26]. In that study, lethality of the most serious lifetime suicide attempt correlated negatively with rCMRGlu in the anterior cingulate, right superior frontal, and right medial frontal gyri suggesting prefrontal cortex hypofunction in high-lethality depressed suicide attempters[26].

Altered serotonergic function has been associated with certain clinical traits mentioned above. There is substantial literature supporting the role of serotonergic function in aggressive[37] and, to a lesser extent, impulsive[21] behavior. This is consistent with observations that alterations in SERT binding associated with higher risk for suicide appear to be concentrated in the ventral PFC, known to mediate inhibition and restraint[32, 33]. Additionally prefrontal hypofunction and impaired serotonergic responsivity are related to the lethality of a suicide

attempt suggesting that aggression may be an intermediate clinical phenotype for serotonergic dysfunction and suicidal behavior[26]. Other brain imaging studies offer support for this, reporting lower serotonin transporter binding in the frontal and midbrain regions in impulsive violent subjects[38] and inverse correlation between 5-HT_{1A} binding in the orbital frontal cortex and aggression scale scores[39]. Altered serotonin function has also been associated with other clinical traits related to suicidal behavior, including pessimism and dysfunctional attitudes[40, 41] and hopelessness[36, 42].

Noradrenergic function

Suicidal and depressed patients have a decreased number of norepinephrine (NE) neurons in the locus ceruleus[43]. Secondary to lower NE levels, greater β-adrenergic cortical receptor binding (downregulation)[44], and lower α-adrenergic binding (upregulation)[45] have been reported. These changes are suggestive of cortical noradrenergic overactivity that may be attributable to NE depletion from the smaller population of NE neurons found in suicide victims[46]. Moreover, the exaggerated sympathetic responses to stress exhibited by individuals with a history of childhood trauma[44] might further deplete NE function[47]. In cross-sectional studies lower cerebrospinal fluid 3-methoxy-4-hydroxphenylglycol (CSF MHPG), a metabolite of noradrenalin, has been reported in suicide attempters compared to non-attempters in major depression[48] and a sample of criminal offenders[49], however the majority of cross-sectional studies observe no differences (reviewed in[50]). Prospective studies, potentially better suited to tracking state-dependent noradrenergic stress response, have also produced inconsistent results, with one study reporting that individuals who engaged in repeat suicidal behavior in the year following hospitalization for a suicide attempt were more likely to have above median CSF MHPG levels[51], and others finding no association with future suicide[23, 52, 53] or suicide attempt[29, 31]. However, a recent prospective study using survival analysis techniques found lower baseline CSF MHPG was associated with increased risk of making a fatal or non-fatal suicide attempt in the 12 months following a major depressive episode[54].

In studies of the relationship of noradrenergic function and clinical endophenotypes for suicidal behavior, higher NE concentrations are shown to be associated with higher levels of aggression[16] and increased CSF MHPG with greater hostility[55]. Catecholamine depletion resulted in an increase in hopelessness in remitted depressed individuals treated with NRIs[56], consistent with preclinical studies suggesting NE intervenes in the development of pessimism and hopelessness[57].

Dopaminergic function

Altered function in the dopaminergic system has been found in depressive disorders and alcohol use disorders[58], however the role of the dopaminergic system in suicidal behavior is uncertain as the abnormalities observed in some studies may be attributable to depression[16, 59]. Reduced dopamine turnover, indicated by low dihydroxyphenylacetic acid levels, was found in the caudate, putamen, and nucleus accumbens reported in depressed suicides[60]. In another study, the same group found no difference in number or affinity of the dopamine transporters[61], suggesting it is unlikely that the reduced dopamine turnover initially observed is a result of decreased dopaminergic innervation of those regions. Prospective studies disagree as to whether the dopamine metabo-

lite homovanillic acid (HVA) levels in CSF predict suicidal behavior[51, 62-64]. In terms of clinical endophenotypes for suicidal behavior and dopaminergic function, higher CSF HVA levels correlate with increased aggression (for a review see Ryding[37]) and striatal dopamine D2 receptor binding was correlated with neuroticism scores in a healthy community sample[65].

Neuroendocrine Endophenotypes

Hypothalamic-Pituitary-Adrenal Axis

Postmortem studies of suicides have reported fewer corticotrophin releasing hormone (CRH) receptor binding sites in the frontal cortex[66] and increased CRH concentrations in CSF[67]. Hyperactivity of the HPA axis has been associated with suicidal behavior evidenced by a failure to suppress cortisol secretion following the administration of Dexamethasone (DST). Coryell et al. estimate that DST non-suppressors have a 14-fold higher risk of suicide compared to suppressors[68]. However, DST non-suppression is also associated with posttraumatic stress disorder and depression, and these conditions may mediate the relationship of dexamethasone nonsuppression to suicidal behavior[69]. In non-fatal suicide attempt, DST response is an uncertain indicator of risk, with the majority of prospective studies finding no association between DST nonsuppression and future suicide attempt, although a small number find an association with serious or violent attempts (see[70] for a review). In other indices of HPA axis function there are reports of lower CSF CRH but no difference in plasma CRH or plasma cortisol[71], higher urinary cortisol in violent attempters[72], and higher serum cortisol after 5-hydroxytryptophan administration[73]. DST findings provide strong support for a role of abnormal HPA axis mediated physiological stress response in suicide, however the role in non-fatal suicidal behavior requires further elucidation.

HPA axis and neurotransmitters

The HPA axis has complex relationships with the serotonergic, noradrenergic, and dopaminergic systems, further complicating the biological picture. The HPA axis has a bidirectional relationship with the serotonergic system[74]. CRH neurons of the central amygdala are connected to the raphe nuclei[75], the principal serotonin source to the forebrain. Projections from the raphe nuclei extend to various brain regions that contain CRH and participate in the stress response[75]. HPA hyperactivity observed in suicidal patients may mediate or moderate some of the serotonin abnormalities found in these patients[76], and corticosteroid modulation of serotonin receptors as a response to stress may have important implications for the pathophysiology of suicide[59,76]. The HPA axis also has a bidirectional relationship with the NE system. Stress activates not only the HPA axis but also the *locus ceruleus* (LC) the major source of NE neurons in the brain[77]. This activation leads to increased NE release during stress. LC neurons influence the neuroendocrine stress response system through their broad innervation of the paraventricular nucleus (PVN) projection pathways. Reciprocal interactions connecting cerebral NE and CRH systems may generate a “feed-forward” loop[78]. Severe anxiety in response to stress may be associated with NE overactivity and hyperactivity of the HPA axis, thus contributing to suicide

risk[79]. Dopamine modulates the HPA axis response to stress[80, 81]. The DA system is particularly vulnerable to stress and even low intensity stressors, either acute or chronic, can activate DA neurons[82, 83]. However, there is a paucity of data on these effects with respect to suicidal behavior. These interactions suggest multiple pathways through which stress may contribute to the biological anomalies observed in suicidal behavior, both directly through dysfunction of the HPA axis and the noradrenergic system and interactions between these two systems, as well as indirectly through downstream effects on serotonergic and possibly dopaminergic system function.

Neuropsychological Endophenotypes

Deficits in a range of cognitive domains including executive function, attention, language fluency, memory, problem solving and decision-making skills, and impulsiveness have been observed in association with suicidal behavior (reviewed in[14]). Attentional deficits are frequent in depressed individuals, but significantly more frequent in individuals who have attempted suicide[14]. Although attention may be affected globally in suicide attempters, performance on interference-type tasks can provide more specific information. The Stroop Test and the Continuous Performance Test (CPT) are reliable predictors of attentional deficits[84, 85]. Although Stroop performance does not distinguish attempters and non-attempters[14], greater effects are observed in the Stroop interference sub-score in depressed suicide attempters compared to depressed non-attempters[86]. Moreover, among depressed attempters, Stroop performance distinguishes high- and low-lethality suicide attempters[86] suggesting that problems with executive control may be associated with more medically serious attempts[14, 86, 87]. Impairments on the Stroop interference task are indicative of difficulty shifting attention from "compelling but inappropriate" stimuli. In a suicidal individuals, such difficulty could predispose to attending to negative emotional states, such as pessimism and self-blame, and lead to action on such states[14]. Impaired attention may also underlie the cognitive rigidity that is a common clinical feature in suicide attempters[14, 88]. In other attention studies, higher rates of CPT omission and commission errors were reported in adolescent suicide attempters compared to non-attempters[89], however such differences were not observed among adults[14].

Genes and early-life environment

Figure 1 indicates two factors at the outset of a putative causal chain leading to suicidal behavior: genetics and early-life adversity. In this section we will review findings that suggest that these two factors impact on both biological and consequently clinical intermediate phenotypes and indicate potential causal pathways leading to suicidal acts.

Early-life environment

Adverse events in early-life, including sexual or physical abuse, neglect, parental loss, or severe family discord, have been associated with suicidal behavior[90, 91]. Sexual and physical abuse independently contribute to repeated suicide attempts after controlling for a range of other childhood adversities[92].

One pathway through which early-life adversity contributes to suicidal behavior later in life is through developmental effects on neurobiological systems that have functional consequences in adulthood. Evidence from both animal (see[44] for a review), and human studies demonstrates lasting alterations in HPA axis[93, 94], and serotonergic[95] and dopaminergic[95, 96] systems, associated with early-life adversity. These alterations may in turn increase vulnerability for the development of psychiatric disorders[97, 98], stress sensitivity[96], and behavioral and personality traits such as impulsivity and aggression[90] later in life, all of which are associated with increased risk for suicidal acts.

Genes and Suicidal Behavior

Twin, adoption, and family studies of suicidal behavior demonstrate a role of genetics in suicidal behavior independent from the presence of axis I or axis II disorders[99, 100]. Population based estimates of the contribution off additive genetic factors are between 30-50% for a broad phenotype of suicidal behavior that includes ideation, plans and attempts (see[101]), largely independent of the inheritance of psychiatric disorder. Twin studies report that the concordance rate for suicide in twins is higher in monozygotic (24.1%) compared with dizygotic twins (2.8%)[101]. Adoption studies reveal higher suicide rates in the biological parents of adoptees who died by suicide[102, 103], compared to biological parents of adoptees who did not. Offspring of depressed suicide attempters are more likely to become suicide attempters themselves compared to offspring of depressed non-attempters[100].

Genetic research in suicidal behavior has included linkage studies, and single nucleotide polymorphism (SNP) association studies. Given the likelihood of a polygenic mode of inheritance[104], more recent studies adopt novel methodologies involving functional genomics such as using microarray technologies to profile expression of thousands of genes simultaneously (for an overview see[105]), and genome wide arrays for hundreds of thousands of SNPs[106]. Candidate genes for SNP association studies have been selected largely based on the evidence from neurobiological studies in suicide. To date the serotonergic system has been the most extensively investigated, but other research targets have been the dopaminergic and noradrenergic systems, brain derived neurotrophic factor, and the HPA axis.

Serotonergic system genes

Specific polymorphisms of the 5-HT_{2A} receptor gene have been associated with suicide attempt in mood disorder patients, including the 102T-1438A and T102C polymorphisms (see Brezo et al.[107] for a review). It is unknown if there is some synergistic effect of the two on suicidal behaviour, or if the latter may just be a marker of the former[108]. However, not all studies show consistent results, and meta-analysis of 25 studies found no association between T102C polymorphism and suicide attempt or suicide[109].

There is a relatively common polymorphism of the serotonin transporter gene (5-HTTLPR) where the low expressing S allele has been linked to decreased serotonin function in vitro[110]. Meta-analysis that included 12 studies comprising 1599 subjects found a significant association of the 5-HTTLPR low expressing S allele and suicidal behavior[109]. However, studies of the 5-HTTLPR genotype and serotonergic function in suicide have been few. In studies examining 5-HTTLPR and serotonin transporter density in

postmortem brains individuals who died by suicide one reported an association[111] and four did not[33, 112-114]. A recent SPECT study in a small sample of male suicide attempters found that the S allele was associated with lower transporter availability in suicide attempters but not in controls[115]. Other imaging studies have examined brain function more generally, with respect to 5-HTTLPR genotype (see Brown & Hariri[116] for a review). In healthy adults, multiple studies report that individuals with the lower expressing SS genotype show increased amygdala activity when exposed to angry or fearful faces, negative words, or aversive pictures[117-122]. The amygdala has a central in role in encoding of emotional memories, emotional regulation and responses to stress[123], and is densely innervated by serotonergic neurons and 5-HT receptors are abundant[124-126].

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the synthesis of serotonin. Two variants have been described: TPH1 and TPH2[127]. Some, but not all, studies reported TPH1 SNP associations with suicidal behavior[128], and aggression[129] (see Baldessarini & Hennen[130] for a review). For TPH2, haplotype studies in psychiatric samples report associations with suicide[131] and suicide attempt[132,133], and single SNP studies report associations between TPH2 genotype and suicidal behavior in Chinese[134] and German Caucasian[135] psychiatric samples, but many others fail to observe any associations[107]. Potential endophenotypes for the expression of the TPH2 gene are suggested in studies that find genotype association with decreased executive function[136, 137] and attention[136], altered amygdala response[138] and, in an fMRI, study altered functioning in prefrontal and parietal brain regions associated with working memory[139].

Several studies have shown an association between alterations in the monoamine oxidase A (MAOA) gene and aggression[140, 141], an element in the diathesis for suicidal behavior. Additionally, the MAOA-uVNTR polymorphism has been associated higher impulsivity in males[142]. Because the gene for MAOA is sex linked, it is hypothesized that the higher rate of suicides among males could be due to greater impulsivity and aggression, secondary to specific MAOA polymorphisms[143]. An fMRI study found that the low expressing alleles of the u-VNTR were associated with increased risk of violent behavior and with alterations in the corticolimbic circuitry involved in affect regulation, emotional memory and impulsivity[144]. In two other fMRI studies MAOA genotype affected performance on response tasks indicative of impulsivity[145, 146].

Other genes

The catechol-O-methyltransferase (COMT) enzyme is a major enzyme in NE activation. COMT activity is affected by a single nucleotide polymorphism at codon 158 (COMT-Val/Met 158) where the allele encoding a valine residue (Val allele) is associated with higher catalytic activity compared with the allele encoding a methionine residue (Met allele)[147]. Some authors suggest that this polymorphism might modify not the susceptibility to, but the clinical course of suicidal behavior making it more violent and lethal[148]. Recent meta-analysis of 519 cases and 933 controls from 6 studies found suggestive evidence of an association between COMT-Val/Met 158 polymorphism and suicidal behavior, perhaps related to the lethality of suicide attempt[149]. Supporting this are reports of association between the low functioning Met allele and impulsive aggression in schizophrenia[150-152] and violent suicide attempts[153].

The noradrenergic and dopaminergic systems, HPA axis, and neurotrophic factor BDNF have also been examined for candidate genes, with no consistent associations yet identified (for an overview see Rujescu et al.[154]).

Genes and Early-Life environment

The disparate findings in genetic association studies may in part be attributable to differences in environmental characteristics of study samples. Pre-clinical studies demonstrate that early-life adversity interacts with genotype and the resultant biological and behavioral alterations endure into adulthood[155, 156]. In humans, there have been multiple studies of early-life environment/5-HTTLPR interaction and vulnerability for psychiatric disorder, with most, but not all, reporting an effect (see Uher[157] for a review). With respect to suicidal behavior, Caspi et al found that among individuals who had experienced childhood maltreatment, only those with the low expressing S 5-HTTLPR allele were at risk for suicidal ideation and suicide attempt[158]. Other studies of the 5-HTTLPR report childhood adversity-genotype interactions and suicidal behavior in mixed diagnosis inpatients[159] and among abstinent African American substance dependent patients[160]. Adverse child-rearing, in combination with a lower expressing variant of the MAO A gene was also found to contribute, in males only, to the development of antisocial behavior and more impulsivity, both of which may contribute to suicidal behavior[142, 161].

It is likely that such effects occur with genes related to the other neurobiological systems involved in suicidal behavior, for example, a recent study found an interaction effect between CRH Receptor 1 haplotype gene and early-life stress on the severity of depression[162]. That study did not examine suicide related outcomes, however it is suggestive of another potential pathway whereby genes and environment contribute to vulnerability for suicidal behavior. More recently, preclinical studies have begun to investigate epigenetic mechanisms such as methylation as a pathway through which environment interacts with genetics to influence biological development and behavioral outcomes[163].

Therapeutic Implications

Suicide prevention is possible as up to 83% of individuals who die by suicide have had contact with a primary care physician in the year prior to their death[164]. However, despite the development of theoretical models, it is not yet possible to reliably predict suicide and suicide attempt. However, the approach described here may allow better identification of high-risk populations. Studies of predictive utility of the two most extensively investigated biological alterations in suicidal behavior, CSF 5-HIAA and DST nonsuppression, have resulted in low positive predictive values for suicide, mainly due to lack of specificity but also because of the low base rates of suicide. Improvement in predicting suicide risk may involve combining several risk factors. Both biological and clinical prospective studies suggest that combining information obtained from two markers (i.e. CSF 5HIAA and DST results and aggression/impulsivity and pessimism) were better predictors than either marker alone[22, 27]. Further studies that utilize a combination of biological and clinical markers may prove even more successful.

Summary and Conclusions

An individual's risk of suicide and/or suicide attempt stems from the interaction between the diathesis, or predisposition, for suicidal behavior, and the occurrence of triggers[17]. The diathesis may comprise traits in the clinical, neurobiological, neurocognitive, genetic, behavioral, and personality domains. Via different pathways, these will affect the way in which an individual responds to stressful life events that may act as triggers for a suicidal act. Due to the complexity and multi-determined nature of suicidal behavior, a model that can integrate a number of risk factors identified as endophenotypes for suicidal behavior may better facilitate identification of high risk populations and thereby identify targets for intervention.

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