Suicidal behaviour: genes, environmental stress and temperamental traits

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Genetics and gene-environment interaction in suicide.

ABSTRACTS: Multiple risk factors have been involved in the risk for suicide and multiple trajectories have been hypothesized leading to suicidal behaviour. Consistent evidence suggests the involvement of heritable factors, as well as a critical role of life stress and early adversity. In the present article we will review the evidence for the involvement of genetic, environmental as well as personality traits in the risk for suicide, together with recent evidence supporting an interaction between these different factors.

Temperamental traits of impulsive aggression, neuroticism and introversion have also been implicated in suicidal risk. However, it is unlikely that these factors, themselves, can explain suicide. As regard genetic effects, suggestive evidence has been reported for serotonin transporter gene (SLC6A4), serotonin receptor 2A (5HTR2A), Tryptophan hydroxylase (TPH1, TPH2), Cathechol-o-methyl tranferase (COMT) and Brain derived neurotrophic factor (BDNF). Other interesting genes are dopamine receptor D2 (DRD2), Cortico-trophin-releasing hormone 1 (CRHR1). Studies addressed to investigate the combined effect of genetic predisposition and environmental influences reported positive findings for SLC6A, 5HTR2A, BDNF and Regulator of G-protein signaling 2 (RGS2). Finally, among genes influencing suicide-related traits, the Mono-amine oxidase A (MAOA) and the COMT showed interactive effects with early adverse events on impulsivity and anger in suicidal individuals. In conclusion, there is evidence of a genetic liability for suicidal behaviour, be modulated by environmental risk factors as well as individual psychological characteristics, such as temperamental traits. Future studies are required to address this complexity by an integrated approach.

Key words: suicide, life events, childhood trauma, temperamental traits, gene, gene-environment interaction.

Introduction

Suicide or suicide completion is the act of taking one’s own life voluntarily.

Suicide-related behaviour is a general term used to refer to self-injury, suicide attempt and suicide. According to Silverman et al. (2007), self-injury with no or undetermined intent to die refers to “self-harm” and “undetermined suicide-related behaviour” respectively. When clear or some degree of intent to die is present, we refer to “suicide attempt” when self-harm does not result in death and “suicide” when it has a fatal outcome. Suicide-related ideations and communications with some intent to die (suicidal threat and suicidal plans) may also be present independently from manifest self-destructive acts.

Suicide is a major public health problem, representing the 10th leading cause of death worldwide (Levi et al., 2003). The incidence rate for completed suicide varies considerably in different countries, from 1.1 per 100,000 inhabitants in Azerbaijan to 51.6 per 100,000 inhabitants in Lithuania (WHO, 2002). The highest suicide rates are found in Eastern European countries (Belarus, Estonia and Lithuania and Russian federation); low rates are found mainly in Latin America (Colombia, Paraguay) and some countries in Asia (Philippines and Thailand 3.6), while Countries in other parts of Europe, in North America, and parts of Asia and the Pacific tend to fall somewhere in between these extremes (as examples: Finland 28.4/100,000, France 20.0/100,000, USA 13.9/100,000). According to the World Health Organization (WHO) World Mental Health (WMH) Surveys (conducted 2001–2007); the 12-months prevalence estimate of suicide attempts is 0.3% (Borges et al., 2010). In most countries, men have a higher reported rate of completed suicide, whereas women have a higher rate of attempted suicide (Schmidtke et al., 1996). Suicide rates are highest in elderly people in most countries. However, over the past 50 years, rates have risen in young people, in particular in men (Wasserman et al., 2005; Wasserman & Wasserman, 2009), and decreased in elderly people (Pritchard & Hansen, 2005).

Over 90% of suicides had recognizable psychiatric illness at the time of their death (Tanney, 2000), mostly mood disorders, borderline personality disorder, post-traumatic stress disorder and schizophrenia (Bolton & Robinson, 2010). Nevertheless, the association between suicide and psychiatric disorders is not linear, therefore independent risk factors should account for the individual risk for suicide.

In the present article we aimed to review the current knowledge of genetic factors involved in suicidal behaviours, in particular completed suicide and suicide attempt, and their interaction with environmental risk factors. Moreover, we also took into account the few studies addressing the interplay between genetic predisposition, suicide-related temperamental traits and suicidal risk.

Methods

Literature search

Genetic studies in suicidal behaviour were located through several literature-search strategies. Up to March 2011, appropriate search terms (gene, genetics,
heritability, suicide, suicide attempt, completed suicide, suicidality, suicidal behaviour, suicidal ideation, suicide intent) were entered in the essential electronic literature databases (PubMed, PsycINFO and Web of Science). The same terms were entered in conjunction with other terms for gene-environment studies (stress, trauma, life events, adverse events, sexual abuse, physical abuse, emotional abuse, emotional neglect, physical neglect) and interaction studies on related suicidal traits (aggression, violence, impulsivity, impulsive behaviour, anger, hostility, neuroticism, negative emotionality).

The reference lists of all retrieved studies were pearled for possibly citing earlier studies of topical relevance.

Study inclusion criteria
The literature search was limited to English-language reports. Any study reporting data on genetic polymorphisms for a type of suicidal behaviour (i.e. completed suicide, suicide attempt or suicidal ideation), regardless of the study design, was eligible for inclusion in the review.

Study details
Regarding genes independently involved in suicidal behaviour, we reported only those investigated at least in two independent studies. Using the above extensive literature search strategies and applying the above wide criteria for study inclusion, 123 reports were detected on genetic variants involved in suicidal behaviours; 20 were detected for gene-environment interactions and 2 for interactive studies taking into account suicide-related traits.

Risk factors for suicidal behaviours
At the level of population, according to the data derived from the World Mental Health (WMH) Surveys (Borges et al., 2010), risk factors for suicidal behaviour include female sex, younger age, lower education and income, unmarried status, unemployment, presence of diverse 12-month DSM-IV mental disorders, parent psychopathology and childhood adversities.

Mental disorder is the most important risk factor for suicidal behaviour. Indeed, more than 90% of suicidal individuals suffer from mental disorders (Bertolote et al., 2004). Mood disorders are present in 30%, substance abuse in 18%, schizophrenia in 14%, and personality disorders in 13.0% of suicides. According to the National Comorbidity Survey study (Kessler et al., 1994), subjects at higher risk for suicide attempts were those affected by mood disorders (OR=12.9), Bipolar disorder (OR=29.7), substance abuse disorder (OR=5.8), anxiety disorders (OR=3.2), particularly generalized anxiety disorder, panic disorder and post-traumatic stress disorder (respective ORs: 5.6, 5.6 and 6.0), non-affective psychosis (OR=5.7) and antisocial personality disorder (OR=5.7). Moreover, comorbid conditions exponentially increased the risk of suicidal behaviour from 6.1 to 19.7 (OR) in subjects with 2 or more psychiatric disorders (Kessler et al., 1999).

Investigators have proposed many models to explain or predict suicide. One such explanatory and predictive model is the stress-diathesis model (Mann et al., 1999). According to this model, one stressor is almost invariably the onset or acute worsening of a psychiatric disorder, but other risk factors, such as familiar and genetic components and other psychosocial factors can also contribute. As will be reviewed below, the role of heritable factors in suicidal behaviour is well established, as demonstrated by family studies, post-mortem brain autopsies and modern molecular investigations in suicide attempters (Currier & Mann, 2008). Nevertheless, the neurobiology of suicide is complex, and differential genetic and environmental pathways to suicide have recently been proposed. According to Kendler et al. (2010), genes may influence the risk for suicide in a mediational model through their impact on response to stress, risk of psychiatric illness and/or personality traits related to suicide. Specifically, genes would mediate the effect of stress on the risk of developing or exacerbating psychopathological symptoms and suicidal ideation, as we will discuss below in more detail. Early severe trauma, such as sexual abuse or parental loss, may act directly on suicidality or through the risk for psychiatric disorders, also depending on genetic predisposition. Recent adversity would influence suicide risk mainly through interaction with genetic predisposition to stress reactivity and/or psychiatric disorders. Finally, it has also been hypothesized a gene x environment x development interaction, in which the effect of genetic predisposition would be modulated by environmental factors depending on the individual developmental stage (for details see Kendler, 2010).
In the following paragraphs, we will focus on environmental and genetic factors that have been implicated in suicidal behaviour. A separate paragraph will be dedicated to intermediate phenotypes related to suicide, i.e. personality traits associated with suicidal behaviours. Subsequently, we will summarize the findings of recent molecular studies addressing the interaction between genes and environmental stressors in suicide. Genetic studies on personality traits related to suicidal risk will also be briefly reviewed.

**Environmental risk factors**
The role of trauma, stress, and negative life events as risk factors for suicidal ideation and behaviour has been long recognized (Paykel et al., 1975). Several possible pathways between exposure to trauma have been suggested in the literature, including the mediating role of posttraumatic symptoms, depression, psychiatric comorbidity, and the impact on personality and cognitive development. Much attention has been paid to early trauma as risk factors for suicide in adolescence and adulthood, such as physical and sexual abuse, and parental neglect (Brodsky & Stanley, 2008; Bruffaerts et al., 2010; Perepletchikova & Kaufman, 2010; Roy, 2001; Sarchiapone et al., 2007). Other familial factors, such as parental suicide, parental psychiatric disorder, alcohol abuse and socioeconomic indicators have been associated with increased suicide risk in the offspring (von Borczyskowski et al., 2010).

Although some studies have found a relationship between physical abuse, neglect and suicidal behaviour, most studies showed a much greater effect of a history of sexual abuse on suicidal behaviour (Molnar et al., 2001), with an increased risk in those reporting more than one type of abuse (Anderson et al., 2002). The role of child sexual abuse in suicide has been confirmed by a recent meta-analysis of the literature (Maniglio, 2010). Childhood traumas have been hypothesized to induce neurobiological alterations correlated with suicide and aggression (Roy, 2002). A consistent finding from neurobiological studies is that low serotoninergic functioning is associated with increased impulsivity and self-destructive behaviour (Mann et al., 2001). Evidence from nonhuman primate studies supports the hypothesis that early trauma (maternal deprivation) contribute to the presence of biological correlates of suicidality in humans (Higley et al., 1992). For instance, in a previous study we found significant correlations between childhood traumas and traits of aggression in suicide attempters (Sarchiapone, Jaussent et al., 2009). Recent evidence suggests that early adversity may induce neurobiological alteration by affecting gene function via epigenetic programming, i.e. genes’ expression alteration (Labonte & Turecki, 2010). Stressful life events commonly reported shortly preceding suicidal behaviour are job problems, family discord, somatic illness, financial trouble, unemployment, separation, death and illness in family (Heikkinen et al., 1994). As mentioned above, acute stress may also elicit suicidal behaviours in interaction with an existing genetic predisposition. Moreover, recent stressors have been reported having a stronger impact in subjects that had also experienced childhood trauma, particularly sexual abuse in both childhood and adulthood (retraumatization) (Krysinska et al., 2009). This is consistent with the evidence that exposure to certain stressors early in life increases the sensitivity of the organism to later stress (Heim & Nemeroff, 2001), probably through persisting neurobiological alterations induced by early trauma in systems regulating response to stress, impulsivity and aggression. Finally, other severe traumas that have been associated with suicidality are military combat, criminal victimization, natural disasters, torture and even contact with traumatized individuals (secondary traumatization) (Krysinska et al., 2009).

**Genetic risk factors**
There is evidence that heritable factors play an important role in suicidality. Since the 1970’s, a number of family- and family history-studies have shown that suicide aggregates in families (Baldessarini & Hennen, 2004), even independently from the familial transmission of psychiatric disorders (Brent et al., 1996). From twin studies, the estimates of heritability for suicide range between 21–55% (Voracek & Loibl, 2007). However, although transmission of suicide risk is to a certain extent independent from psychiatric disorders, increased rates of suicidal ideation in the relatives of suicide probands are largely explained by increased familial rates of axis I and axis II disorders (Brent et al., 1996; Johnson et al., 1998) and comorbid mental disorders in probands strengthen the concordance for suicidal behaviours among relatives (Goodwin et al., 2004). According to large Scandinavian register data, the strongest risk factor for suicide attempt is mental illness necessitating hospital admission as well as family history of mental illness (Agerbo et al., 2002; Mortensen et al., 2000). Therefore, we may assume the existence of a genetic overlap between psychiatric diseases and suicidal behaviour, together with the existence of genes affecting independently the two disorders.

Studies of molecular genetics have poorly addressed the genetic specificity of suicide. This is not surprising, since more than 90% of suicidal subjects are concurrently affected by a mental illness (Tanney, 2000). Moreover, studies have often employed pure case-control designs (i.e. psychiatric suicidal subjects vs. healthy controls); such designs cannot establish whether the genetic differences detected depend on comorbid psychiatric illness or suicide itself, unlike designs based on non-suicidal psychiatric controls that are less biased from this point of view. To our knowledge, a first attempt to specifically disentangle similarities and differences of genetic effects in suicide and mood disorders has been only recently made by Brezo et al. (2010). Brezo et al. evaluated a large cohort, followed for 22 years, for both suicidal behaviour and mood disorders, focusing on genes involved in the regulation of the
serotonergic system. Further details will be provided and discussed below.

In the last two decades, the studies of molecular genetics in suicidal behaviour have mostly focused on genes encoding for neurotransmitters and their receptors, with strongest evidence for the serotonin (5-HT) system, but also for genes involved in stress systems (Hypothalamic-pituitary-adrenal axis), cell signaling and neuroprotective/growth factors. The 5-HT system has been widely investigated, because of the observed clinical benefit of antidepressant drugs on clinical syndromes with an increased risk of suicide and because of evidence coming from postmortem studies, which have reported fewer serotonin transporters in the prefrontal cortex, hypothalamus and brainstem of suicide victims (Purselle & Nemeroff, 2003). Thereafter, a large number of studies investigated the role of the 5-HT transporter gene (SLC6A4) in suicide. In particular, studies focused a promoterlength polymorphism in SLC6A4 (5-HTTLPR). The short variant (S-allele) of this polymorphism was found to have lower transcription efficiency and less transporter expression compared to the long variant (L-allele) (Heils et al., 1996). Many studies reported positive association with suicidal behaviour and two meta-analyses of the literature confirmed a positive association between the S-allele in 5-HTTLPR and suicidal behaviour, in particular violent suicide attempt (Anguelova et al., 2001; Bonnier et al., 2000; De Luca, Likhodii et al., 2004). However, many negative studies have also been published (Kia-Keating et al., 2003; Lin & Tsai, 2004). However, a previous meta-analysis on psychiatric disorders in general reported a positive association with suicidality (Rujescu et al., 2003). The neuronal tryptophan hydroxylase gene (TPH1) has also been associated with suicidal behaviour (Loeb et al., 2007; Perez-Rodriguez et al., 2010; Yoon & Kim, 2009; Zhou et al., 2005; Zill et al., 2004), though inconsistently (Brezo et al., 2010; Campos et al., 2010; De Luca, Hlousek et al., 2006; De Luca et al., 2004; De Luca et al., 2008; De Luca, Voinakesos et al., 2005; Mann et al., 2008; Mouri et al., 2009; Must et al., 2009; Perroud, Neidhart et al., 2010; Zill et al., 2007). Many other genes involved in serotonergic neuro-transmission have been investigated, but mostly negative findings have been obtained with few exceptions: Serotonin receptor 1A (5HTR1A) (Lemonde et al., 2003; Sawiniec et al., 2007), Serotonin receptor 1B (5HTR1B) (New et al., 2001), though a meta-analysis of the literature disconfirmed the finding (Kia-Keating et al., 2007), and Serotonin receptor 6 (5HTR6) (Azenha et al., 2009). However inconsistency was reported also for 5HTR1A (Brezo et al., 2010; Nishiguchi et al., 2002; Serretti et al., 2009; Serretti, Mandelli et al., 2007; Videtic et al., 2006; Wang et al., 2009; Yoon & Kim, 2009) and 5HTR6 (Brezo et al., 2010; Okamura et al., 2005).

Moreover, only few studies employing psychiatric controls reported positive findings, mostly in major depression, schizophrenia (Campi-Azevedo et al., 2003) and alcohol dependence (Preuss et al., 2001). A further variant in the SLC6A4 gene (VNTR in intron 2, STin2) was found to be associated with increased risk of suicidal behaving both schizophrenia and major depression (De Luca, Zai et al., 2006; Lopez de Lara et al., 2006). Overall, the SLC6A4 gene seems to be mostly associated with some features of suicidal behaviour, such as severity and lethality (Vince et al., 2008; Wasserman et al., 2007), violence and repetition (Bayle et al., 2003; Bellvier et al., 2000; Campi-Azevedo et al., 2003; Courtet et al., 2004; Gorwood et al., 2000; Neves et al., 2008; Shen et al., 2004).

Other genes involved in the regulation of the 5-HT systems have also been investigated. Interesting results have been obtained for the serotonin receptor 2A (5HTR2A) (Arias et al., 2001; Bonnier et al., 2002; Vaquer-Lorenzo et al., 2008), though the major findings have been obtained in violent-impulsive suicide attempt (Giegling et al., 2006; Saiz et al., 2008a). However, many negative studies have been reported as well (Arias et al., 2001; Bondy et al., 2000; Brezo et al., 2010; Correa et al., 2004; De Luca, Likhodii et al., 2007; De Luca et al., 2008; De Luca et al., 2009; Du et al., 1999; Ernegrul et al., 2004; Etain et al., 2004; Fanous et al., 2009; Geijer et al., 2000; Khait et al., 2005; Ono et al., 2001; Preuss et al., 2000; Tan et al., 2002; Turecki et al., 1999; Videtic et al., 2006; Yoon & Kim, 2008, 2009; Zalsman, Frisch et al., 2005; J. Zhang et al., 2008).

An enzyme involved in the synthesis of 5-HT, tryptophan hydroxylase 1 (TPH1) has recently been reported not to be associated with suicidal behaviour in schizophrenia according to a meta-analysis of the literature (Saetre et al., 2010). However, a previous meta-analysis on psychiatric disorders in general reported a positive association with suicidality (Rujescu et al., 2003). The neuronal tryptophan hydroxylase gene (TPH2) has also been associated with suicidal behaviours (Loeb et al., 2007; Perez-Rodriguez et al., 2010; Yoon & Kim, 2009; Zhou et al., 2005; Zill et al., 2004), though inconsistently (Brezo et al., 2010; Campos et al., 2010; De Luca, Hlousek et al., 2006; De Luca et al., 2004; De Luca et al., 2008; De Luca, Voinakesos et al., 2005; Mann et al., 2008; Mouri et al., 2009; Must et al., 2009; Perroud, Neidhart et al., 2010; Zill et al., 2007).
A recent work investigated eleven 5-HT genes in a large cohort of children followed for 22 years, in order to identify common and specific genetic risk factors for depressive disorders and suicide attempt, acting directly or as moderators in gene-environment interactions with childhood sexual or childhood physical abuse (Brezo et al., 2010). Two genes were found associated with suicide attempt: TPH1 in a specific way and independently from mood disorders, and 5HTR2A, that was associated with both depression and suicide attempt. Nevertheless, 5HTR2A was directly associated with depressive disorders. Briefly, suggestive evidence has been obtained for Dopamine receptor D2 (DRD2) (Finckh et al., 1997; Baca-Garcia et al., 2010) and Dopamine receptor D4 (DRD4) has been associated with completed violent suicide in females of an Asian sample (Fukutake et al., 2008). Pertain to the GABAergic system, two studies have investigated the GABA receptor A3 but negative findings were obtained (Baca-Garcia et al., 2010; Baca-Garcia et al., 2004).

Genes involved in the metabolism of monoamines have also been investigated. Suggestive evidence have been obtained for Cathechol-o-methyl transferase (COMT) as evidenced by a first meta-analysis of the literature (Kia-Keating et al., 2007), though we did not find significant evidence by a recent meta-analysis of the literature (Calati et al., 2010). Monoamine oxidase A (MAOA) has been associated with completed suicide (Du et al., 2002) and violent suicide attempt in males (Courret et al., 2005), whilst most of the studies reported negative findings (Baca-Garcia et al., 2010; Brezo et al., 2010; De Luca, Tharmalingam et al., 2006; De Luca, Tharmalingam, Sicard et al., 2005; Huang et al., 2004; Kunugi et al., 1999). To our knowledge, Mono-amine oxidase B (MAOB) has been investigated to a lower extent and two negative reports were published (Baca-Garcia et al., 2010; Brezo et al., 2010).

Other interesting genes are those related to Corticotrophin-releasing hormone (CRH), regulators of the hypothalamic-pituitary-adrenal pathway and response to stress. The CRH gene was found to be associated with suicide attempt in patients with schizophrenia (De Luca et al., 2010). Studies in other populations have, however, failed to find a positive association (Baca-Garcia et al., 2010; Wasserman et al., 2008). The Corticotrophin-releasing hormone receptor 1 (CRHR1) was found to be associated with suicide attempt in 2 studies (De Luca et al., 2010; Wasserman et al., 2009), and to interact with life stressors in increasing suicide risk in a third study (Wasserman et al., 2008), though inconsistencies have been reported (Baca-Garcia et al., 2010). The gene encoding for receptor type 2 (CRHR2) was found to be associated with severity of suicide attempt (De Luca et al., 2007) but not with suicide attempt itself (Baca-Garcia et al., 2010; De Luca et al., 2010).

Genes involved in neuroprotection and cell proliferation as well as inflammatory processes have received particular interest, given their involvement in neurodegenerative/neuropsychiatric disorders (Duman, 2009). Interesting data have been obtained for the Brain derived neurotrofict factor gene (BDNF) (Iga et al., 2007; Kim et al., 2008; Sarchiapone et al., 2008) member of the "neurotrophin" family of growth factors. Associations have been reported also with high lethality (Schenkel et al., 2010; Vincze et al., 2008) and violent suicide attempts (Neves et al., 2010), though negative reports have also been published (Baca-Garcia et al., 2010; Hong et al., 2003; Hwang et al., 2006; Kohli et al., 2010). The Nerve growth factor receptor (NGFR), a low affinity receptor for several neurotrophins including BDNF, has also been associated with suicide attempt in depressed patients (Kunugi et al., 2004), though other studies did not confirm the finding (Baca-Garcia et al., 2010; McGregor et al., 2007). Nitric oxide (NO) displays many properties of a neurotransmitter and it is involved in neurototoxicity associated with stroke and neurodegenerative diseases. The neuronal NO synthase gene (NOS1) has been found to be associated with both completed and attempted suicide (Cui et al., 2010; Rujescu et al., 2008), though findings are inconsistent (Baca-Garcia et al., 2010). Finally, the proinflammatory cytokine Tumor necrosis factor (TNF) has been reported to be associated with completed suicide in one study (Omran et al., 2009), but not in a previous one focusing on suicide attempt (Saiz et al., 2008b). In the nervous system, estrogens are involved in a number of processes which regulate synaptic plasticity including synaptogenesis and neurogenesis, and have been linked to neuropsychiatric disorders (Craig & Murphy, 2007). Attention has been focused on Estrogen receptor 1 (ESR1) (Sundermann et al., 2010). To our knowledge, three studies have so far investigated associations...
between suicidal behaviour and genetic variants in the ESR1 gene, but negative findings were reported (Baca-Garcia et al., 2010; Giegling, Rujescu et al., 2008; Tsai et al., 2003). Many other genes have been investigated in suicidal behaviour but inconsistent or poor evidence has been obtained.

**Suicide-related personality traits**

As is the case with most complex traits the role of genes in suicidal behaviour remains elusive. It has been hypothesized that genes may have an indirect effect on suicide risk through intermediate phenotypes, such as impulsive-aggressive traits (Savitz et al., 2006). It has to be underlined that a circular relationship may exist between genetic factors, suicide-related traits and suicidal behaviour. Indeed the results of candidate gene association studies suggest that genetic vulnerability factors for various related psychiatric phenotypes (major psychiatric disorders and personality traits) partly overlap with personality traits predisposing to suicidal behaviour (see also Baud, 2005). However, disentangling the effects the genetic factors influencing these different pathological conditions, appears to be a difficult task.

Studies are increasingly shifting from risk factors that predict the emergence of suicidality in the short term to such biologically determined risk factors as personality traits and temperaments. Four main constellations of personality characteristics are associated with suicidal behaviour: impulsivity, hostility-aggression, introversion, and anxiety-neuroticism. Impulsivity and aggressive traits have been long recognized as risk factors for suicidal behaviour (Eisenthal, 1967; Klerman, 1987) and seem to play a larger role among younger suicides (Gorlyn, 2005). Impulsive-aggressive traits have been linked to abnormalities in monoaminergic functioning; in particular, lowered 5-HT transmission and enhanced dopamine and noradrenalin functioning (Oquendo & Mann, 2000). Impulsive-aggressive traits have a genetic background, suggesting that it may be an endophenotype associated with the 5-HT genes and also with the emergence of suicidality (Courtet et al., 2004). The role of neuroticism, namely the tendency to experience feelings such as anxiety, anger, guilt and depressed mood, has been widely recognized as well as a trait correlated with suicidal behaviour (Brezoi et al., 2006), though it has also been linked to a variety of psychopathological conditions (Lahey, 2009), mostly characterized by high levels of suicidality. Introversion, defined as the tendency toward being predominantly concerned with and interested in one’s own mental life, and therefore to be more reflective and to enjoy limited relationships, has been postulated as a core personality trait predisposing to concomitant depression and suicidality (Janowsky, 2001). Inter-individual variability in the levels of both neuroticism and introversion has been mainly linked to the 5-HT system (Lester, 1989; Netter & Rammsayer, 1989). An early study reported the 5-HTTLPR polymorphism associated with high levels of neuroticism (Lesch et al., 1996). This finding has been the subject of numerous replication studies and several recent meta-analyses. To date, there is a substantial consensus concerning the role of the serotonin system in neuroticism and anxiety-related traits (for a review see Canli, 2008).

At the opposite, “resilience” may be a personality trait protective for suicidal behaviours. Resilience is the capacity for successful adaptation to change, to thrive in the face of adversity or recover from negative events. It is a measure of stress coping ability or emotional stamina (Connor, 2006). We have repeatedly reported of poor resilience in suicidal individuals with substance abuse (Cuomo et al., 2008; Roy, Sarchiapone et al., 2007) and suicidal prisoners (Sarchiapone, Carli et al., 2009). Measures of low resilience have also been associated with suicide risk in adolescents (Nrugham et al., 2010; Park et al., 2010), depressed elderly men (Hobbs & McLaren, 2009) and veterans (Brenner et al., 2009; Pietrzak et al., 2010). Moreover, evidence has been reported that childhood trauma may affect resilience and increase suicidal ideation, as a further link between traumatic events, personality and suicidality (Segal, 2009).
Gene-environment interaction in suicidal behaviour

Genes and life-stress

The first evidence of an interaction between genetic factors and environmental factors date back in 2003 with the publication of the study by Caspi et al. (2003). The study was performed on a large birth cohort of 847 Caucasian subjects followed from the age of 3 to 26, and genotyped for the 5-HTTLPR polymorphism. Stressful life events occurring after the 21st birthday and before the 26th birthday were assessed with the aid of a life-history calendar. Past-year depressive symptoms, suicide attempts and recurrent suicidal thoughts were assessed at age 26. Results of the analyses showed a significant interaction between 5-HTTLPR polymorphism and stressful life events on depressive symptoms, major depression and suicidal ideation/attempt. In particular, life events predicted suicide ideation/attempt among homozygous for the S-allele and heterozygous subjects, but not among homozygous for the L-allele. Nevertheless, a following study by Zalsman et al. (2006) failed to find a significant interaction between 5-HTTLPR and life events in suicidal behaviour in a sample of 191 patients affected by major depression, though succeeding in replicating the interaction on major depression and depressive severity. However, differences in samples size and characterization (847 vs. 191 subjects, population cohort vs. major depressives), genotyping (biallelic 5-HTTLPR vs. triallelic LA/LG/S subtype with rs25531), evaluation of life events and suicidal behaviour (past-year suicide attempt/ideation vs. lifetime suicide attempt) may have influenced the results obtained in this following study. In a further study on a sample of 850 school-aged children (Cicchetti et al., 2010), the 5-HTTLPR genotype has been found to be associated with suicidal ideation in maltreated children only (both emotionally abused/neglected and physically/sexually abused). Nevertheless, the effect of genotype was not significant when considering children severely abused, i.e., exposed to three or four maltreatment subtypes. On the other hand, considering more recent stressful events, these have been reported to predict 1 to 10 years later depression and suicidality on a large twin sample (Coventry et al., 2010), but interaction with 5-HTTLPR was found, neither considering the 5-HTTLPR length polymorphism nor the triallelic 5-HTTLPR sub-type with rs25531.

Of note, Zalsman et al. (2006) also investigated separately childhood and recent events reporting no significant effect on both depression and suicidal behaviour. On the other hand, an earlier study had reported a significant impact of childhood abuse on major depression in interaction with the 5-HTTLPR genotype (Kaufman et al., 2004). Therefore, Gibb et al. (2006) performed a preliminary analysis on a small sample of psychiatric patients (n=30), of which 15 (50%) had a positive history of suicide attempt. Subjects were evaluated for childhood trauma by the Childhoood trauma questionnaire (CTQ). The authors were able to demonstrate a significant interaction between the 5-HTTLPR polymorphism, physical and sexual abuse in suicidal behaviour. In a following study in substance-abuse in 26-30 year-old women (Roy, Hu et al., 2007), the risk of suicide attempt was found to increase with increasing reports of childhood trauma scores, and such increase was exaggerated among those with low expression forms of the 5-HTTLPR genotype. However, recently Brezo et al. (2010), in their longitudinal study aimed to detect specific genetic effects on mood disorders and suicide, investigated 9 single nucleotide polymorphisms in SLC6A4 and found an interactive effect between rs3794808 and childhood physical abuse on the risk for mood disorders, but not suicidal behaviour.

In 2006, Wasserman et al. (2006) focused on another 5-HT gene in suicidal behaviour: the 5HT1A. The sample under investigation was composed by 272 suicidal attempters and their parents (trios) evaluated for life events, prior suicidal behaviour and genotyped for the rs6295 (-1019C/G) polymorphism. The authors could not replicate the finding of an over transmission of the G-allele in suicide attempters (Lemonde et al., 2003), though they could detect a strong trend for its over transmission in subjects characterized by high level of previous traumatic and/or stressful life events. However, a subsequent study on suicide victims reported more life events in those homozygous for the C-allele in the same 5HT1A polymorphism (Videtic et al., 2009). As regards 5HT2A, Brezo et al. (2010) in their extensive analysis of eleven 5-HT genes in mood disorders and suicide attempt, reported a significant effect on suicidal risk but only through interaction with sexual and physical abuse.

Only a few studies have analyzed other genes involved in serotoninergic neurotransmission in interaction with stressful life events in suicidal behaviour. To our knowledge, only one and two studies respectively investigated TPH1 and TPH2. Zhang et al. (2010) reported a significant interaction between TPH2 (rs7305115) and negative life events in the preceding year on suicidal risk in a sample of patients affected by major depression, whilst Mann et al. (2008), considering another variant (rs4131347) and childhood abuse, failed to find interactive effects on suicidality in major depressive patients. To our knowledge, the only study investigating TPH1 did not find positive interaction with physical or sexual abuse (Brezo et al., 2010). Huang et al. (2004) focused on the MAOAgene and childhood adversity, but no interactive effects were detected on suicidal behaviour, though an association with childhood abuse and impulsive traits in males was detected. As stated before, a gene of recent interest for suicide is BDNF. In 2008, Perroud et al. (2008) evaluated a large sample of suicide attempters for age at onset, violence and repetition of suicidal behaviour, together with childhood trauma and the Val66Met polymorphism in BDNF. The authors reported an interaction between BDNF (Val/Val genotype) and sexual abuse on violent suicide.
They also found severity of childhood maltreatment associated with suicide repetition and younger age at onset. The same year, on a sample of 170 depressed patients, we reported a significant interaction between BDNF genotype and childhood emotional abuse on the risk of suicide attempt (Sarchiapone et al., 2008), supporting the evidence of an increased risk of suicide in Valallele carriers exposed to childhood trauma. Wasserman et al. (2008) investigated the potential interaction between life events and polymorphisms within two genes involved in the regulation to stress response of the hypothalamic-pituitary-adrenocortical (HPA) axis: the Corticotrophin-releasing hormone (CRH) and the Corticotrophin-releasing hormone receptor 1 (CRHR1) in a sample of 542 trios with suicide attempter offspring, evaluated for life events prior to a suicide attempt. No significant findings were obtained, except for a trend of over transmission of a variant in CHRH1 (rs4606) in suicide attempters exposed to low levels of stressors. Recently, Roy et al. (2010) investigated the involvement of another gene of interest which may be Regulator of G-protein signaling 2 (RGS2), encoding for a regulator factor of neuronal signaling. RGS2 was found to be associated with increased levels of suicidal ideation, indicating a potential role of this genetic variant in the risk for suicidal behaviour in stress-exposed subjects (Amstadter et al., 2009).

**Genes, suicide-related traits and life-stress**

Genes have been hypothesized acting indirectly on suicide risk through intermediate phenotypes, such as personality traits correlated with suicidal tendencies. Therefore, many studies focused on the genetic bases of suicide have investigated impulsive aggression, neuroticism and negative emotionality as potential endophenotypes of suicidal tendencies. Within the context of suicidal behaviours, violent suicide attempt and measures of violence and aggression have been mainly associated with 5-HTTLPR (Bayle et al., 2003; Zalsman et al., 2001), COMT (Baud et al., 2007; Calati et al., 2010; Rujescu et al., 2003), Mono-amineoxidase A (MAOA) (Court et al., 2005) and DOPA decarboxylase (DDC) (Giegling, Moreno-De-Luca et al., 2008). Impulsive suicide and impulsive traits have been again associated with 5-HTTLPR (Court et al., 2004) and COMT (Calati et al., 2010), but also with TPH1 (Galfalvy et al., 2009). Contrasting evidence has been obtained for SHT2A, associated, on a hand, with non-impulsive suicide (Suz et al., 2008a), low impulsive aggression (Zalsman et al., 2010) and anxiety-related traits (Serretti et al., 2007), and high levels of anger, aggression (Giegling et al., 2006) on the other. Other genes of interest are Tachykinin receptor 1 gene (TACR1) (Giegling et al., 2007), ABCG1 transporter (Gietl et al., 2007), Nitric-oxide (NOS) (Rujescu et al., 2008), and Axonal guidance gene SLIT2 (Sokolowski et al., 2010), all associated with measures of aggression. Only few studies have investigated a potential 3-way interaction between genetic predisposition, personality traits and life events. To our knowledge, only two studies have so far reported positive evidence. Huang et al. (2004) investigated the MAOA gene, childhood abuse and aggressive-impulsive traits in a sample of psychiatric patients compared with healthy controls. The authors did not find a significant association with suicide attempt, but they reported an association with a history of abuse and high impulsivity in male individuals. The authors suggest a potential interaction between this genetic variant and childhood abuse in the risk of developing impulsive tendencies in male individuals.

A recent study investigated the role of nine candidate genes (5-HTTLPR, TPH1, TPH2, 5HT1A, 5HT2A, 5HT1B, MAOA, COMT and BDNF) and childhood maltreatment in modulating anger-related traits in suicide attempters (Perroud et al., 2010). A functional polymorphism in the COMT gene was found associated with suicide attempt both independently and in interaction with childhood trauma.

A further gene of interest may be Regulator of G-protein signaling 2 (RGS2), encoding for a regulator factor of neuronal signaling. RGS2 was reported positive in suicidal behaviour in a study in the Japanese population (Cui et al., 2008). Recently, on a sample of individuals exposed to the 2004 Florida hurricane, the rs4606 polymorphism in RGS2 was found to be associated with increased levels of suicidal ideation, indicating a potential role of this genetic variant in the risk for suicidal behaviour in stress-exposed subjects (Amstadter et al., 2009).
found to modulate the association between sexual abuse and anger traits.

In the presence of sexual abuse, individuals carrying the Val high-activity allele displayed greater disposition toward anger than individuals homozygous for the Met allele. Notably, none of the serotonin-related genes influenced the effect of childhood abuse on anger traits.

Conclusions

Many different social, environmental, genetic and neurobiological factors are linked to the risk for suicide. However, on their own, these factors are unlikely to explain suicide, which is more likely to be dependent on the interaction between a genetic predisposition and exposure to environmental risk factors.

Differential pathways have been hypothesized, from indirect effects of genes on risk of developing psychiatric disorders and/or abnormal temperamental traits associated with suicidal behaviour that may be in turn elicited by acute stressors, to direct effects of early adversities on neurobiological systems regulating stress response. Recent evidence also suggests that early adversity may induce neurobiological alteration by affecting gene function via epigenetic programming. An additional contribution may be derived from behavioural traits correlated with suicide risk, such as impulsive-aggression, neuroticism and negative emotionality, which may either be explained by the genetic risk for suicide or independently interact with other genetic and environmental risk factors. To date, only few studies have addressed the complex interplay between genes, stressful events and, even less, temperamental traits.

In the present review of the literature we summarized the current knowledge of genetic factors that have been involved in suicidal behaviours and studies addressing the investigation of their interplay with environmental risk factors as well as suicide-related temperamental traits. We performed a broad search of the literature, applying only few restriction criteria (English language and reporting of any kind of genetic polymorphisms within genes), independently from study designs, size and ethnic composition of samples, and specific suicidal behaviour (i.e. completed vs. attempted). Moreover, for both brevity and clarity purposes, we have not gone into detail of specific polymorphisms, of samples investigated (all psychiatric vs. psychiatric probands compared to healthy controls, and specific composition of samples in terms of psychiatric diagnosis), and we made no assessment of the methodological quality of studies.

Therefore, the reader should take into account that both positive and negative findings reported may have different loadings depending on specific suicidal behaviour, study design, investigated populations and polymorphisms considered.

In conclusion, there is evidence of a genetic liability for suicidal behaviour, which may be modulated by environmental risk factors as well as individual psychological characteristics, such as temperamental traits. Given the complexity of suicidal behaviours and multiple sources of influence, future studies are required to address this complexity with novel methods of investigation and analysis, in order to identify the different trajectories leading to suicidal behaviour, possibly by combining evidence derived from different disciplines such as epidemiology, social science, psychology, genetics and neurobiology. Technologies and methods for studying genetics in complex disorders are evolving quickly, and an integrated approach will yield new insights.

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