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The Neuroscience of Suicidal Behavior

KEES VAN HEERINGEN

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Nearly one million people take their own lives each year worldwide – however, contrary to popular belief, suicide can be prevented. While suicide is commonly thought to be an understandable reaction to severe stress, it is actually an abnormal reaction to regular situations. Something more than unbearable stress is needed to explain suicide, and neuroscience shows what this is, how it is caused, and how it can be treated. Professor Kees van Heeringen describes findings from neuroscientific research on suicide, using various approaches from population genetics to brain imaging. Compelling evidence is reviewed that shows how and why genetic characteristics or early traumatic experiences may lead to a specific predisposition that makes people vulnerable to triggering life events. Neuroscientific studies are yielding results that provide insight into how the risk of suicide may develop; ultimately demonstrating how suicide can be prevented.

Kees van Heeringen is Professor of Psychiatry, Chair of the Department of Psychiatry and Medical Psychology, and Director of the Unit for Suicide Research at Ghent University, Belgium. He is also the cofounder of the Flemish Expertise Centre for Suicide Prevention. Professor van Heeringen's research has been awarded the Stengel Award by the International Association for Suicide Prevention.

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The Neuroscience of Suicidal Behavior

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To all Valeries

To the one and only Myriam

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Preface

As a young psychiatrist, I was asked to see a patient at the physical rehabilitation department of the university hospital. I went to see this patient, who turned out to be a bright young girl named Valerie. She stayed at the rehabilitation department of the university hospital because she lost both her legs after having jumped from a bridge a few weeks earlier.

It was a hot summer, and later that day I was sitting on a nice terrace in the beautiful center of Ghent, enjoying a glass of beer with a couple of friends. We enjoyed ourselves, watching and discussing the girls strolling along. But, in my mind, I was trying to find an answer to this question: Why on earth had the intelligent young girl whom I met earlier that day done such a horrible thing, with such terrible and irreversible damage to her body? I could not know at that time that meeting Valerie would have such an impact on my professional life. A few years later I founded the Unit for Suicide Research at Ghent University.

Valerie told me that she had made a date with her boyfriend on the day of her suicide attempt. She wanted to talk to him because she did not feel well. So, she agreed to meet him even though she was supposed to be in school that morning. While she was talking to her boyfriend she noticed an uncle passing by. This uncle knew that she had to be at school instead of spending time with her boyfriend, and he looked very angry at her. Seeing so much anger on his face somehow urged her to take her bicycle, go to a nearby highway bridge, and jump in front of the oncoming cars. Subsequent conversations with Valerie made clear that her "not feeling well" was a manifestation of a depressive episode. She wanted to meet her boyfriend and tell him about her dark mood and the negative thoughts and painful feelings about herself and the future, which frightened her so much. Later she also told me that her father took his own life when she was 5 or 6 years old.

Crucial aspects of the story of Valerie will be discussed in this book. We will learn from intriguing brain imaging studies how reactions to angry faces may constitute a vulnerability to suicidal behavior. We will learn from genetic studies that suicide indeed may run in families and that we are now beginning to understand how our genes may make us vulnerable to suicidal behavior. We will see that depression and suicidal behavior are common, also among young people. The sad reality is that epidemiological data continue to show unacceptably high and still increasing rates of suicidal behavior among young people in many areas across the world, including the United States.

The harsh reality in the case of Valerie was that she suffered from a depressive episode that was not recognized by herself, her family, schoolteachers, or her primary care physician, and which thus was not treated. In addition, there was a family history of suicide, which should have prompted any person in her environment or any caregiver to consider a strongly increased risk of suicidal behavior in this girl. Depression and familial loading are the two major ingredients of the lethal cocktail that kills so many people every day anywhere in the world.

This book addresses the neuroscientific foundations of a model that explains suicidal behavior as the tragic outcome of an interaction between a vulnerable individual and the world in which she or he lives. Chapters 1 and 2 address the occurrence of suicidal behaviors and their risk factors, and provide a model of the interactions between these risk factors by describing the specific vulnerability to suicidal behavior and elucidating how specific stressors interact with this vulnerability to lead to self-destructive behaviors. Chapter 3 describes the neuroscience approaches to the study of these vulnerability and stress-related factors. The following chapters elaborate on these approaches in much more detail by focusing on findings from molecular (Chapter 4), cognitive (Chapter 5), and systems (Chapter 6) neuroscientific studies of suicidal behavior. Chapter 7 takes a developmental perspective, and focuses on the devastating neurobiological consequences of traumatic events during childhood, such as sexual and physical abuse. A novel understanding of brain functioning in the form of the predictive coding model is explored in relation to suicidal behavior in Chapter 8, showing that a surprisingly large proportion of neurobiological findings described in the previous chapters can be integrated in a fascinating computational model of suicidal behavior. Our limited capacity to predict suicidal behavior and treat suicide risk is a major problem in suicide prevention. Chapter 9 focuses on the implications of a neuroscientific approach for the prediction of suicidal behavior, while Chapter 10 focuses on the problems and opportunities in treating suicidal behavior from a neuroscientific point of view.

Exploring the neuroscience of suicidal behavior is an intriguing journey into the dark side of the brain. This book will show that individuals may become suicidal because of deficiencies in neurobiological mechanisms that normally provide protection to painful consequences of life. It is commonly believed that suicide is a normal response to an abnormal situation. Scientists know that the opposite is true: Suicide is an abnormal reaction to a normal situation. Suicidal behavior is commonly triggered by, for example, the breakup of a romantic relationship, the loss of a job, being bullied at school, a depression, or experiencing financial difficulties. Such terrible situations are, however, very common and lead to suicidal behavior in only a minority of exposed individuals. This book will describe why and how people may become so vulnerable that exposure to difficult circumstances may lead them to take their own life. But this book will also show that the study of these mechanisms makes it possible to prevent suicide.

CHAPTER ONE

What Is Suicidal Behavior, and Can It Be Prevented?

Learning Objectives

- What are suicidal and nonsuicidal self-injury behaviors?
- How common are suicidal behaviors?
- Why are common myths about suicide wrong?
- What is the stress–diathesis model of suicidal behavior?
- How do mental disorders such as depression relate to suicide?
- What are the three main approaches to suicide prevention?

Introduction

Every 40 seconds someone in the world takes his or her own life, and each day more than 120 Americans kill themselves (WHO, 2014; MMWR, 2017). Sadly, the number of American suicides is increasing each year. Many more individuals attempt to take their own lives, and the number of suicide attempts increase, particularly among young people. Nonsuicidal, self-injurious behaviors are even far more common than suicide attempts.

Many myths regarding suicide continue to exist, as we will see later. One of the most persistent myths is the idea that suicide cannot be prevented or that suicide risk cannot be treated. This view contributes to the continuing high number of people who kill themselves, or who try to do so. The costs of suicide are huge from an economical point of view. For example, the total cost of suicidal behavior in the United States is estimated at $93.5 billion. But also at individual levels the costs of suicide are huge. Every suicide is the tragic outcome of profound personal suffering and mental pain. But every suicide also affects the people who stay behind – with feelings of shame, guilt, and pain – and who consequently may become suicidal themselves. The lifetime prevalence of exposure to suicide is nearly 22%, indicating that more than one in five individuals will experience a suicide in their close surroundings (Andriessen et al., 2017). Stopping mental pain is commonly cited as the major motivation for suicide, but the sad reality is that suicide does not stop mental pain: suicide only transfers the pain to those left behind.

Suicide is preventable. It is estimated that every $1 spent on preventive interventions saves $2.5 in the cost of suicide (Shepard et al., 2016). Suicidal behavior never has one single cause, but the many causal factors are now well known, and insights in to the mechanisms leading to suicidal behavior have increased substantially. These insights make it possible to develop preventative strategies at various levels.

1.1 Behavioral Aspects of Suicidal Behaviors

The neologism “suicide” most probably first appeared in the seventeenth century, coming from the words *sui* (of oneself) and *caedere* (to kill). The World Health Organization defines suicide as “the act of killing oneself deliberately, initiated and performed by the person concerned in the full knowledge or expectation of its fatal outcome.” Suicide attempt is defined as “any non-fatal suicidal behavior, referring to intentional self-inflicted poisoning, injury or self-harm, which may or may not have fatal intent or outcome” (WHO, 2014).

Until the end of the 1960s, suicide attempts were considered failed suicides. Since then, several terms have been introduced that reflect the operationalization of nonfatal suicidal behavior as separate behaviors. These terms include “parasuicide,” “pseudosuicide,” “deliberate self-harm,” “self-harm,” and “nonsuicidal self-injury” (NSSI), reflecting the increasing insight that suicidal behavior is not a homogeneous phenomenon but a spectrum of self-destructive behaviors that may differ from each other in terms of lethality, planning, and intent. However, even these terms are difficult to operationalize: “lethality” may refer to medical or somatic damage due to the suicide attempt or to the methods used to attempt suicide, while there are no objective measures of “planning” or “intent.” There have been numerous approaches to classifying nonfatal suicidal, self-injurious behaviors based on theoretical, behavioral, clinical, or epidemiological characteristics, but disagreement persists (Silverman, 2016). A distinction between NSSI and attempted suicide, mainly based on suicidal intent, is now commonly made in research and in clinical guidelines, particularly in the United States. *The Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), the manual of psychiatric diseases, includes suicidal behavioral disorder and NSSI as clinical situations that require a more in-depth investigation to determine if a formal diagnosis as a mental disorder should be considered along with a proposed set of diagnostic criteria. Under suicidal behavior, specifiers are included relating to the violence of the method used, the medical consequences, and the degree of planning involved.

Table 1.1 Nonsuicidal reasons for self-harm (Edmondson et al., 2016)

Responding to distress
- Managing distress (affect regulation) – managing painful unpleasant emotional states, including making emotional pain physical, blocking bad memories
  - Interpersonal influence – changing or responding to how others think or feel; help-seeking
  - Punishment – usually of self, occasionally of or by others
  - Managing dissociation – either switching off or bringing on feelings of numbness and unreality
  - Averting suicide – nonfatal self-harm to ward off suicidal acts or thoughts

Self-harm as positive experience
  - Gratification – self-harm as comforting or enjoyable
  - Sensation seeking – through a sense of nonsexual excitement or arousal
  - Experimenting – trying something new
  - Protection – of self or others
  - Developing a sense of personal mastery

Defining the self
  - Defining boundaries – self-injury as a means of defining or exploring personal boundaries
  - Responding to sexuality – through self-harm as creating quasi-sexual feelings or expressing sexuality in a symbolic way
  - Validation – demonstrating to self and occasionally to others one’s strength or the degree of one’s suffering
  - Self as belonging or fitting in – to a group or subculture
  - Having a personal language – including one for remembrance: a means of conjuring up or acknowledging good past feelings or memories

The report of many nonsuicidal reasons by self-harming individuals supports a categorical distinction between suicide attempts and NSSI (Edmondson et al., 2016). Most common themes in studies of nonsuicidal reasons for self-harm behavior include managing distress and exerting interpersonal influence, followed by punishment and managing dissociation (see Table 1.1).

Less frequently described but nonetheless repeatedly endorsed are reasons to do with averting suicide, sensation seeking, defining personal boundaries, and coping with sexuality. There also appear to be motives for the act that are perceived as positive or adaptive, at least by the self-report of respondents, in terms of self-affirmation or validation.

Criticism regarding the use of the term NSSI is due to the fact that much of the literature on NSSI focuses on young people, and indeed few studies have been carried out in adults. Furthermore, there are obvious difficulties in labeling behaviors as definitively nonsuicidal when they greatly increase the risk of future self-inflicted death as is shown in longitudinal studies (see later discussion). Underestimation of suicide risk associated with NSSI implicates the danger that those with NSSI will be given lower priority and receive poorer treatment than others (Kapur et al., 2013). An additional problem is that suicidal intent may be difficult to assess reliably, given that individuals engaging in self-harming behaviors often report ambivalence (i.e., not caring whether they live or die) and multiple motivations. A study in adults even found that one-third endorsed experiencing suicidal thoughts while engaging in NSSI (Klonsky, 2011). Retrospective evidence suggests that the strongest risk for engaging in NSSI is a history of suicidal behavior and ideation (Brunner et al., 2007), while other studies show that NSSI frequently precedes suicidal thoughts and behaviors, suggesting that NSSI may act as a "gateway" to suicidal behavior, whether or not via the enabling of the capability for suicide (Whitlock et al., 2013; Grandclerc et al., 2016). An alternative view is to regard NSSI and suicide attempts as dimensional variants of self-injurious behavior, with the presence or absence of suicidal intent not representing a categorical distinction (Orlando et al., 2015). Such an interpretation is supported by the apparent similarity of neurobiological underpinnings for NSSI and suicidal thoughts (Maciejewski et al., 2014). Such an underlying and possibly common neurobiological vulnerability, i.e., a shared so-called diathesis, is the major topic of this book.

1.2 Epidemiological Aspects

1.2.1 Occurrence of Suicidal Behaviors

Suicide rates vary greatly according to regions and countries, as shown in Figure 1.1 (WHO, 2017).

According to the most recent global estimations, 804,000 suicide deaths occurred worldwide in 2012, representing an annual global age-standardized suicide rate of 11.4 per 100,000 individuals in the population (WHO, 2014). This means that in 2012, every 40 seconds someone in the world took their own life. In the same year, suicide accounted for 1.4% of all deaths worldwide, making it the fifteenth leading cause of death. Globally, suicides account for 56% of all violent deaths: More

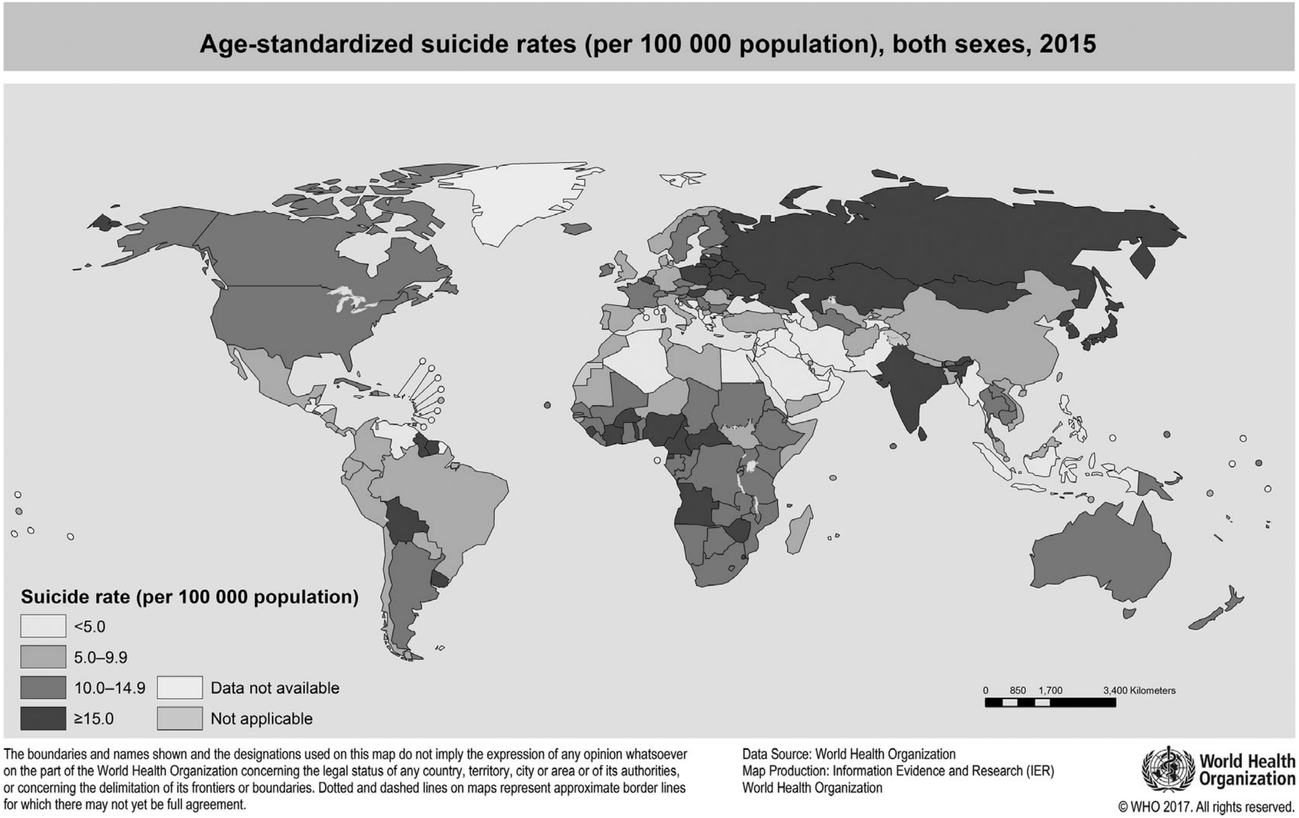
Age-standardized suicide rates (per 100 000 population), both sexes, 2015
Suicide rate (per 100 000 population)
<5.0
5.0–9.9
10.0–14.9
≥15.0
Data not available
Not applicable
0 850 1,700 3,400 Kilometers
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization
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Figure 1.1 Suicide rates in the world. See color plate 1. Age-standardized suicide rates (per 100 000 population), both sexes, 2015
http://gamapserver.who.int/mapLibrary/app/searchResults.aspx

people die from suicide than from crimes and war combined. In general, Asian and Eastern European countries have the highest rates, Central and South American and eastern Mediterranean countries have the lowest rates, and rates in the United States, Western Europe, and Africa are somewhere in between. But the situation is changing rapidly, with, for instance, strong increases in the United States in recent years, as we will see later. Although differences in rates between countries and regions may to a certain extent reflect differences in case ascertainment and in the availability and recency of reported data (Windfuhr et al., 2016), they more probably are genuine, and influenced by differences in the prevalence of specific risk and protective factors (see later discussion) and broader societal factors (such as social deprivation and political change).

Despite an increase in the global population, the absolute number of suicides has fallen by about 9%, from 883,000 to 804,000 between 2000 and 2012. The global suicide rate has fallen 26% (23% in men and 32% in women) during the 12-year period from 2000 to 2012, which is faster than the 18% decrease in overall mortality. Unfortunately, increases in suicide rates (these are the number of death by suicide per 100,000) have been reported in many countries. For example, suicide rates have increased in the United States in recent decades more than 30%, from 10.5 in 1999 to 13.0 in 2014, and thus are now higher than the global average (Curtin et al., 2016).

Self-injury mortality (SIM), a combination of known suicides by any method and estimated deaths from drug self-intoxication that have been classified by medical examiners and coroners as accident or undetermined, also increased substantially in the United States. There were an estimated 40,289 self-injury deaths in 1999 and 76,227 in 2014. The estimated crude rate for SIM thus increased 65% between 1999 and 2014. The SIM rate thereby continuously exceeded the kidney disease mortality rate and surpassed the influenza and pneumonia mortality rate by 2006. By 2014, the SIM rate converged with the diabetes mortality rate. Also by 2014, SIM accounted for 32 and 37 years of life lost for male and female decedents, respectively (Rockett et al., 2016).

Increases in rates of suicide and self-injury mortality have been related to many factors, ranging from adverse economic changes to reductions in the availability of psychiatric beds (Bastiampillai et al., 2016). Concerning economic factors, a study of 63 countries estimated that an excess of 5,000 suicide deaths worldwide in 2009 were related to the global financial crisis, with the effect of unemployment on suicide rates being stronger in countries with lower pre-crisis unemployment rates

(Nordt et al., 2015). In the United States, economic downturns such as the 2007/2008 recession were associated with an increase of 1.22 deaths per 100,000 population among those with lower educational levels, compared with an increase of 0.17 per 100,000 in those with more than 12 years of education (Harper et al., 2015). Careful analysis of epidemiological data suggests that recession may hurt but that austerity kills, particularly via increased suicide rates (Stuckler & Basu, 2013). An increase in unemployment rates, however, may not explain the effect of financial crises on suicide rates, and the causal relationship between the increase in unemployment and increase in suicide has indeed been questioned for both the United States and Europe (Fountoulakis, 2016). When unemployment rates are low, the suicide rate among unemployed persons is high, but when unemployment increases and the composition of unemployed persons shifts to include more mentally healthy persons, the suicide rate of unemployed persons decreases. In addition, it appears that the number of suicides increases several months before unemployment increases. The most likely explanation is that mental health care deteriorates during periods of economic crisis and austerity. Also, patients constitute a specifically vulnerable group, which is hit harder by a crisis in a selective and accumulated way. This accumulation of stressors might be the cause behind the increase in suicide rates (Fountoulakis, 2016).

There are few regional or national data on the occurrence of nonfatal suicidal behavior or NSSI in the general population. Most data regarding suicide attempts come from studies of visits to general hospitals following self-injurious behavior, a few providing data that enable the calculation of national rates. Between 2006 and 2013 approximately 3.5 million visits to US emergency departments for attempted suicide and self-harm were reported, suggesting an annual population-based rate of approximately 170 per 100,000 (Canner et al., 2016). In Europe, Ireland has a national registry of such visits to general hospitals countrywide, based on which the rate of self-harm (with varying levels of intent and various underlying motives) was estimated at 204 per 100,000 in 2015 (NSRF, 2016). Nationwide individual-level register data on the entire population living in Denmark from 1994 to 2011 revealed an average incidence rate of self-harm of 131 and 87 per 100,000 among females and males, respectively. Among women in the 15–24 age group, an almost 3-fold increase in rates was observed during the study period (Morthorst et al., 2016). Based on data from the WHO World Mental Health (WMH) Survey Initiative, involving 17 countries from different parts of the world, the estimated lifetime prevalence of suicide attempts in the overall cross-national adult general population sample is 2.7% (Nock et al., 2008). A systematic review of studies of the prevalence of NSSI and deliberate self-harm (DSH) in adolescent samples across the globe shows a mean lifetime prevalence of 18% and 16%, respectively (Muehlenkamp et al., 2013). The number of emergency department visits for self-inflicted injury among adolescents has increased substantially from 2009 to 2012 in the United States (Cutler et al., 2015). Noteworthy is the increasing use over the last decade of potentially more lethal methods such as hanging and jumping from heights as a method of self-harm (Vancayseele et al., 2016). Research clearly shows that the use of more lethal methods increases the risk of future fatal suicidal behavior.

1.2.2 Demographic Influences

Three times as many men die of suicide as women (though in low- and middle-income countries the male-to-female ratio is much lower, at 1.5 men to each woman). Globally, suicide rates are 15.0 for males and 8.0 for females, and suicides account for 50% of all violent deaths in men and 71% in women (WHO, 2014). Rates of attempted suicide are generally higher among females than among males. For example, the Irish national registry report shows that rates in 2015 were 186 and 222 for males and females, respectively (NSRF, 2016).

The proportion of all deaths due to suicide and the rank of suicide as a cause of death vary greatly by age. In high-income countries suicide is most common among middle-aged and elderly men, but rates among young people are increasing. Globally, among young adults 15–29 years of age, suicide accounts for 8.5% of all deaths and is ranked as the second leading cause of death (after traffic accidents). Among adults aged 30–49 years, suicide accounts for 4.1% of all deaths and is ranked the fifth leading cause of death. Rates of nonsuicidal self-harm are highest in young age groups. In the United Kingdom, for example, two-thirds are younger than 35 years (Geulayov et al., 2016). Figure 1.2 clearly shows that suicide is a leading cause of death in young people, particularly those aged between 10 and 35 years.

Seasonal variation in suicide rates has also been reported, with peak incidences in spring and summertime, and suicide rates appear to correlate with latitude and exposure to sunshine (Christodoulou et al., 2012). In the next chapter, neurobiological effects on the geographic distribution of suicidal behaviors will be discussed, ranging from genetic factors to lithium concentrations in drinking water.

Rank	10–14	15–24	25–34	35–44	45–54	55–64	65+
1	**Unintentional Injury 763**	**Unintentional Injury 12,514**	**Unintentional Injury 19,795**	**Unintentional Injury 17,818**	Malignant Neoplasms 43,054	Malignant Neoplasms 43,054	Heart Disease 507,138
2	Malignant Neoplasms 428	**Suicide 5,491**	**Suicide 6,947**	Malignant Neoplasms 10,909	Heart Disease 34,248	Heart Disease 76,872	Malignant Neoplasms 419,389
3	**Suicide 409**	**Homicide 4,733**	**Homicide 4,863**	Heart Disease 10,387	**Unintentional Injury 21,499**	**Unintentional Injury 19,488**	Respiratory disease 131,804
4	**Homicide 158**	Malignant Neoplasms 1,469	Malignant Neoplasms 3,704	**Suicide 6,936**	Liver Disease 8,874	Respiratory disease 17,457	Cerebro-vascular 120,156
5	Congenital Anomalies 156	Heart Disease 997	Heart Disease 3,522	**Homicide 2,895**	**Suicide 8,751**	Diabetes Mellitus 14,166	Alzheimer's Disease 109,495
6	Heart Disease 125	Congenital Anomalies 386	Liver Disease 844	Liver Disease 2,861	Diabetes Mellitus 6,212	Liver Disease 13,728	Diabetes Mellitus 56,142
7	Respiratory disease 93	Respiratory disease 202	Diabetes Mellitus 798	Diabetes Mellitus 1,986	Cerebro-vascular 5,307	Cerebro-vascular 12,116	**Unintentional Injury 51,395**
8	Cerebro-vascular 42	Diabetes Mellitus 196	Cerebro-vascular 567	Cerebro-vascular 1,788	Respiratory disease 4,345	**Suicide 7,739**	Influenza & Pneumonia 48,774
9	Influenza & Pneumonia 39	Influenza & Pneumonia 184	HIV 529	HIV 1,055	Septicemia 2,542	Septicemia 5,774	Nephritis 41,258
10	Benign Neo, or Septicemia 33	Cerebro-vascular 186	Congenital Anomalies 443	Septicemia 829	Nephritis 2,124	Nephritis 5,452	Septicemia 30,817

Figure 1.2 Ten leading causes of death, United States, 2015. See color plate 2.

1.2.3 The Suicidal Process

Self-injurious thoughts and behaviors are risk factors for future suicide attempts and for death by suicide (Ribeiro et al., 2016). The strongest risk factor for suicide is a previous suicide attempt, and there might be a 70-fold increase in the likelihood of a subsequent attempt and close to a 40-fold increase in the likelihood of death following a suicide attempt (Harris & Barraclough, 1997). Characteristics of prior attempts – including number, recency, intent, and lethality – thereby appear to be important indicators of risk of subsequent suicide.

Early research focused heavily on distinguishing NSSI from suicidal outcomes, but more recent findings indicate that the longitudinal effects of NSSI on suicidal behavior may be much stronger than originally anticipated (Asarnow et al., 2011; Wilkinson et al., 2011). Individuals engaging in DSH have a substantially increased risk of suicide (Beckman et al., 2016). For example, based on a median 5-year follow-up of a large cohort, the suicide rate was estimated at 278 per 100,000 in self-poisoning patients versus 7 per 100,000 in controls. The median time from hospital discharge following self-poisoning to suicide was nearly 600 days (Finkelstein et al., 2015).

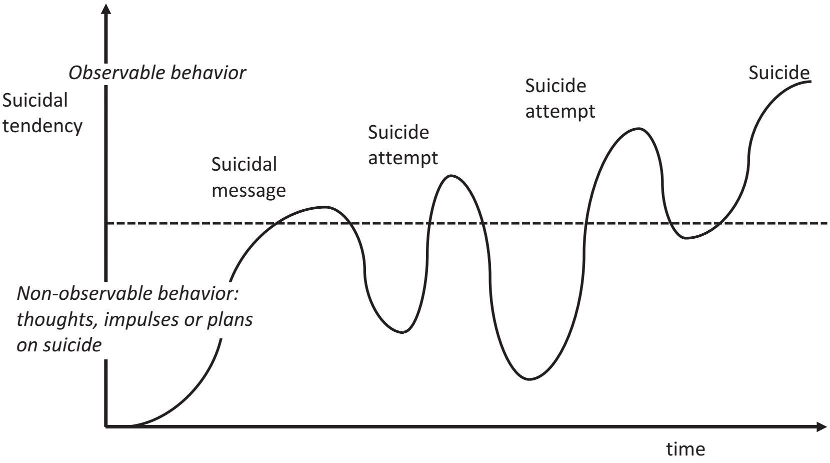

Figure 1.3 The suicidal process (adapted from Retterstøl, 1993).

Findings from longitudinal epidemiological studies thus suggest a relationship between suicidal thoughts, nonfatal suicidal behaviors including NSSI, and suicide. Such findings support the concept of the suicidal process, which is also apparent from psychological autopsy studies of individuals who died due to suicide. The suicidal process is defined as the development and progression of suicidal thoughts and behaviors as a process within an individual and in interaction with their surroundings. The process may evolve through thoughts about taking one's own life, which may grow through often repeated nonfatal suicidal behaviors with increasing lethality and suicide intent, and end with death by suicide (van Heeringen, 2001).

Figure 1.3 shows an example of such a suicidal process that may start with fleeting thoughts about suicide or with a wish for a temporary oblivion or escape from emotional pain, which may precipitate suicidal behaviors. Stressors such as adverse life events and major depressive episodes may thus precipitate suicidal behaviors in the course of the process (Oquendo et al., 2014a; see also Chapter 2). Only small parts of the process – above the dotted line – may become known to those closest to the person (Retterstøl, 1993). The general population National Comorbidity Survey in the United States shows cumulative probabilities of 34% for the transition from suicidal thoughts to a plan, 72% from a plan to a suicide attempt, and 26% from thoughts to an unplanned attempt. About 90% of unplanned and 60% of planned first suicide attempts occur within 1 year of the onset of suicidal thoughts (Kessler et al., 1999). A recent study in the United States in Rochester, MN, documented that, first, approximately 60% of individuals succumbing to suicide died on their index attempts. While men were more likely than women to use firearms, females using guns were just as likely as their male counterparts to die on an index suicide attempt. Second, more than 80% of subsequent suicides occurred within a year of initial attempt. One in 19 (males 1 in 9, females 1 in 49) suicide attempters died during a follow-up of 3–25 years. Of dead index attempters, 72.9% used guns, yielding an odds ratio for gunshot death, compared with all other methods, of 140 (Bostwick et al., 2016).

Epidemiological data, including studies in twins, provide support for an interaction between life events and a common vulnerability, or shared diathesis, in suicidal ideation and nonfatal and fatal suicidal behaviors (see, e.g., Maciejewski et al., 2014). Stress–diathesis interaction models of suicidal behavior will be described in more detail in Chapter 2.

1.3 Risk Factors for Suicidal Behaviors

Further support for a stress–diathesis interaction model of suicidal behavior is found in studies of risk factors in suicidal behavior, showing that such factors may be proximal or distal (see Table 1.2).

Table 1.2 Risk factors for suicidal behavior (Hawton & van Heeringen, 2009)

Distal
- Genetic loading
- Early traumatic life events
- Restricted fetal growth and perinatal circumstances
  → Personality characteristics (such as impulsivity, aggression)
  → Neurobiological disturbances (such as dysfunction of the serotonin and stress-response systems)

Proximal
- Psychiatric disorder
- Physical disorder
- Psychosocial crisis
- Availability of means
- Exposure to models

The next sections will address known proximal and distal risk factors. It should be noted that the term "risk factor" in quoted studies commonly is an umbrella term. A distinction should be made between "correlates" (characteristics associated with suicidal behavior), "risk factors" (a correlate that precedes suicidal behavior and can be used to divide the population into high- and low-risk groups), and "causal risk factors" (a risk factor that is identified when its manipulation of a risk factor systematically changes the probability of suicidal behavior). The discussion of the prediction and treatment of suicide risk in Chapter 9 will make clear that the distinction between these three terms is crucial: Causal risk factors are predictors and valuable treatment targets; non-causal risk factors are predictors, but less effective treatment targets; and correlates may be poor predictors and ineffective treatment targets.

1.3.1 Distal Risk Factors

Distal or predisposing factors that may increase the risk of suicidal behaviors include genetic influences and early-life adversity, which will be discussed in detail in Chapters 4 and 7. Twin and adoption studies show that the heritability of suicidal behaviors (the extent to which genetic individual differences contribute to individual differences in suicidal behavior) is between 30% and 50%. When the heritability of psychiatric conditions is considered, the specific heritability of suicide attempts is estimated as 17% (Turecki & Brent, 2016). The identification of specific genes remains elusive, despite a wealth of candidate gene and genome-wide association studies, as we will see in the next chapters. Early-life adversity involving childhood abuse and parental neglect may exert its risk-increasing effect via the neurocognitive deficits (involving, e.g., decision making and problem solving) that are associated with suicidal behaviors, whether or not via changes in the reactivity of the stress-response system and detrimental effects on brain structures (see Chapter 7).

Impulsivity appears to play a role in a substantial proportion of self-harming behaviors including NSSI (Lockwood et al., 2017). For example, the goal of relief from a terrible state of mind may drive impulsive behavior for short-term gain over long-term objectives. Hence, impulsivity may increase the vulnerability to engage in a readily accessible though maladaptive behavior, such as self-harm, to moderate affect. Successful implementation of this strategy in alleviating distress may lead to negative reinforcement of self-harming behavior. However, while this line of reasoning intuitively appears to be correct, study findings are difficult to interpret because of large variances in the conception and measurement of impulsivity and the precision with which self-harm behaviors are specified. For example, the effects of cognitive impulsivity (relating to difficulties maintaining focus or acting without forethought) may differ from those of behavioral impulsivity. The impulsivity of self-harming behaviors does not appear to correlate well with the impulsivity as a personality trait. Elevated trait impulsivity may also lead to the experience of more painful and provocative experiences over time. Through habituation, individuals may have a dampened response to the aversive nature of self-harm, which contributes to the maintenance of the behavior. Taken together, and despite methodological issues, the findings suggest that distinct impulsivity facets confer unique risks across the life-course of self-harm (Lockwood et al., 2017).

A combination of increased levels of impulsivity and aggression is common in suicide attempters, but the contribution of both trait characteristics to suicide risk appears to differ. For example, aggression is a better predictor of suicidal behavior than impulsivity among depressed individuals (Keilp et al., 2006). A history of impulsive-aggressive behaviors is indeed commonly found in suicides, and particularly among young suicides (Turecki, 2005). In fact, part of the familial liability to suicide may be transmitted through impulsive-aggressive behaviors. These behaviors aggregate in families, and first-degree relatives of suicides and attempted suicides are more likely to exhibit aggression than relatives of controls (Turecki, 2005). Impulsive-aggressive behaviors may thus play a role in mediating familial transmission of suicidal behavior and, as such, may be considered as a behavioral endophenotype in genetic studies of suicide, as will be discussed in Chapter 4. Impulsive-aggressive behaviors are linked to both suicidal behaviors and reduced activity of brain neurotransmitters such as serotonin, which may act as a common distal neurobiological risk factor.

The association between changes in brain neurotransmission and the occurrence of suicidal behaviors is among the most replicated findings in biological psychiatry. Many studies link suicidal behaviors to alterations in the serotonin neurotransmission system, most probably as a distal risk factor that may become manifest via personality characteristics (such as impulsivity and harm avoidance) or neurocognitive deficits. Other neurotransmitters implicated in suicidal behaviors are glutamate and GABA (see Chapter 4).

Blunted cortisol reactivity to stress may well be a trait marker of suicide risk. First-degree relatives of individuals who took their own lives show a blunted cortisol response to an acute laboratory stressor (McGirr et al., 2010). In addition, suicide attempters with and without a family history of suicide show a lower cortisol response to stress in the laboratory when compared with individuals with suicidal thoughts and controls, but the lowest cortisol reactivity to stress is observed in suicide attempters with a family history (O'Connor et al., 2017). Findings like these suggest that blunted cortisol reactivity to stress as a trait may be a heritable marker of suicide risk. The reality, however, is more complicated, as we will see in Chapter 4.

Interestingly, increasing evidence points at infection with the brain-tropic parasite *Toxoplasma gondii* as a distal neurobiological risk factor for suicidal behaviors. Seropositivity is associated with increased risks of suicide attempts and suicide, possibly via immunologically induced changes in neurotransmitter activity (Pedersen et al., 2012; Flegr, 2013). In addition, there appears to be an additive effect of IgM (but not IgG) class antibodies to *T. gondii* and *Cytomegalovirus* on the odds of a suicide attempt (Dickerson et al., 2017). The association between infections and suicide was confirmed in a nationwide, population-based, prospective cohort study in which more than 7 million individuals were observed during a 32-year follow-up period. An increased risk of death by suicide was found among individuals hospitalized with infection in prospective and dose–response relationships, and the population-attributable risk (the reduction in incidence that would be observed if the population were entirely unexposed to infection, compared with its actual exposure pattern) associated with hospitalization with infection accounted for 10% of suicides. The strongest associations with suicide occurred in patients with human immunodeficiency virus and viral hepatitis (Lund-Sørensen et al., 2016). The findings indicate that infections may have a relevant role in the pathophysiological mechanisms of suicidal behavior, although the nature of the mechanisms remains unknown. For example, it remains to be demonstrated to what extent infections and their antibiotic treatment may lead to altered brain function and suicidal behavior via changes in the gut microbiome. Immunological aspects of suicidal behavior will be discussed in more detail in Chapter 4.

1.3.2 Proximal Risk Factors

Proximal risk factors act as precipitants of suicidal behaviors, and include adverse life events (discussed in Chapter 2) and psychopathology. Depressed mood, mental pain, and hopelessness are crucial ingredients of the suicidal state of mind, and nearly all suicidal behaviors occur