Suicide: Genetics and Heritability

Concepcion Vaquero-Lorenzo and Manuel A. Vasquez

Contents

Abstract Nature vs nurture is, and has been, a never stopping debate since Lamarck and Darwin exposed their corresponding theories on evolution, and even before them, such discussion already existed. Is suicide a heritable conduct? Is it learnt? Maybe the answer is both and none, at the same time. From genetic twin studies to epigenetic and environmental influence on development, this chapter aims to take a look at different points of view and most relevant theories in one of the worlds

C. Vaquero-Lorenzo
Department of Biology, Autonoma University, Madrid, Spain

M. A. Vasquez (✉)
Department of Psychiatry, Fundación Jiménez Díaz Hospital, Madrid, Spain
e-mail: alfonso.vasquezg@quironsalud.es

Curr Topics Behav Neurosci (2020) 46: 63–78
https://doi.org/10.1007/7854_2020_161
Published Online: 14 August 2020

leading causes of death, specially for young individuals. We explore different studies aiming to find biomarkers for suicide, as well as other traits frequently encountered in individuals who engage in suicidal behavior, such as impulsivity, aggressivity, and hopelessness. Finally, this chapter also looks at some of the most recent approaches in treatment and prevention of suicidal behavior, in order to highlight what they have in common and try to explain (at least partially) why they could be effective.

Keywords Cognition · Environmental · Epigenetics · Heritability · Suicide

1 Biological Correlates of Hopelessness, Impulsivity, and Aggressivity in Suicidal Behavior

In a topic as broad as suicide, and with as little answers as we've been able to gather so far, speaking about biological factors implies defining them and explaining why we consider them so. In this chapter we will discuss how some behavioral characteristics can be developed, in some cases through life experiences, and then passed down to our descendants. Further ahead, we will also talk about how a factor that hasn't been taken enough into account in heritability studies could be the one holding us back from reaching better answers. That factor is timing.

1.1 Heritability in Suicidal Behavior

Heritability is the amount of variance in biological characters that can be accounted by genetic differences between individuals.

Epidemiologic and family studies estimate that there is a genetic component in suicide with a heritability that goes from 17% to 55% (Ruderfer et al. 2019).

Additive effect of genetic factors could account for 30–50% in the development of a wide suicidality phenotype, which includes ideation, planning, and attempts, and its heritability is, mostly, independent of other psychiatric illness (most people who attempt suicide suffer from a previous psychiatric condition). Heritability in non-mortal attempts has been estimated between 17 and 45% after controlling for psychiatric illness, and family studies show higher ratios among relatives of suicidal individuals (JJ Mann et al. 2009).

For less clearly defined phenotypes, such as suicidal ideation, it is harder to establish how much of a genetic influence there is, although it clearly exists, together with environmental and other individual factors (Strawbridge et al. 2019).

Twin studies have been one of the ways of comparing the influence of the environment vs. genetics in suicide, as well as in other psychiatric illnesses. A

study on suicidal conduct performed in 1991 by Roy studied 176 couples of twins and showed a level of agreement for suicide of 11.3% between monozygotic (MZ) twins, compared to 1.8% between dizygotic (DZ) twins. For suicide attempts however, the level of correlation was even higher, reaching 38% for MZ brothers (Roy et al. 1991), showing that both, suicidal attempts, as well as suicide, have heritable factors.

Different studies have observed that when one twin develops depression, there is a risk of 50–60% of the other one developing depression as well. On suicide, however, if one of the twins dies for this cause, the risk of the same thing happening to the other is around 13% (Wasserman et al. 2007), up to 24%, depending on the study (Mann et al. 2009). In DZ twins, the risk is only 0.7% (Roy et al. 1991) up to 2.8% (Mann et al. 2009).

2 Genetic Association Studies and Polygenic Risk Scores

There still exists a problem with general population studies, and that is the lack of wide enough samples, with enough statistical power. As Ruderfer highlights (Ruderfer et al. 2019), after performing a genome-wide association analyses (GWAS), they find a very low heritability, based on single nucleotide polymorphism (SNP), only 0.035 on UK population and 0.046 on Vanderbilt's clinically predicted phenotype. They describe two polymorphic variants, chromosome 5 (rs1297617) and chromosome 19 (rs1297618), but neither was statistically significant.

For complex conditions as high blood pressure and suicide as well, SNP and GWAS have shown to be lacking, and in the same way, polygenic risk scores (PRS) have progressively gained terrain.

A PRS is a number that estimates the probability of an individual for manifesting a trait, taking into account multiple genetic variants, at the same time. In psychiatry (although not with some deterrents), this kind of study seems to be the new way to go, in what is related to heritability. Still, some studies state that PRS can only be applied to the population they derive from, and some even describe that these scores have a higher relation with ascendency, than with the condition they try to predict.

Mullins' work with PRS and suicide behavior found a relation between heritability of suicidal ideation and other psychiatric disorders, but still suggested that carrying out this thoughts had some other independent genetic factors (Mullins et al. 2014). Since they could not find significant relation among the SNPs or GWAS studied by their group, their conclusion was that suicide must be highly polygenic; therefore, PRS are a better approach to study its heritability.

3 Individual Characteristics: The Diathesis-Stress Model

Debate about "what is and what is not" suicidal behavior is widely spread and takes into consideration philosophical and semantic elements, which are far from being the purpose of this chapter.

What does seem clear though is that not all suicides are the same, as suicide attempts aren't either. Individuals who indulge in suicide behavior may have very different characteristics, although they do have some in common. Things like aggressivity or impulsivity are consistently found as risk factors for suicide behavior, so much that there is a particular subtype of suicide attempters, determined by such characteristics (Stanley et al. 2019). This kind of differences between individuals, and the presence of some particular factions that allow to group them, is what brought the hypothesis of diathesis-stress as a clinical model for suicide (Mann et al. 2009).

JJ Man et al.'s work helped show that despite environmental events that may be happening at the moment of the attempt, there are "tendencies" particular to the individual making the attempt that make him or her more prone to such behavior.

"Hopelessness" would be another one of these tendencies, and it has been related to suicide just as much as aggression or impulsivity. Different from the other two, hopelessness is a completely subjective sensation, often present in individuals suffering from depression, and it can predict future suicide (not just attempts).

Later in this chapter, we will discuss how these three tendencies, very different in the way they present themselves, find common ground in the brain prefrontal cortex (PFC). This particular region is in charge of inhibition of conduct, and at the same time, being part of the default mode network (DMN), it also plays a role in our thoughts about the past, the future, and ourselves. It is not strange at all that Arango et al. (1995), or Audenaert et al. (2006), have found changes in the number and function of serotonin receptors in this area, in individuals who engaged in suicide behavior.

4 Serotonin as a Biomarker: Why and Why Not?

The serotoninergic system is composed by 14 different serotonin receptors (found so far), the serotonin transporter, synthesis enzymes TPH1 and 2, and also catabolic enzymes MAOA and MAOB. The function of each component varies from inhibitory to excitatory, depending on the region of the brain, the exact neuron the receptor is attached to, and whether they are located presynaptically or postsynaptically. All of these variations can give place to a multitude of confounding factors to take into account, even though there is no denying that one of the most consistent findings in relation to suicide and serotonin is the low levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid of suicidal individuals.

Starting by the serotonin transporter (5HTT), it can be found in nerve endings and platelets. Its job consists mainly in retrieving serotonin (5HT) from synaptic clefts. There is a polymorphism in the promoting region proband 44 (44 bp ins/del). The short allele accounts for a lower expression of the gene and is associated with 40% less union of the transporter to serotonin.

Studies with statistical significance have shown that there is less of this transporter in cortical areas of depressive people who committed suicide (PFC, hypothalamus, raphe, etc.). Some studies have also associated the lesser union of this transporter to serotonin (specially at PFC) with depression and suicide attempts, while other studies have found the opposite.

4.1 So, How Is It That We Give People with Depression a Medication That Inhibits This Transporter Even Further? And Why Studies on 5HTT Can Be So Drastically Different?

A review carried out in 2013 focused on the relation of the different components of the serotoninergic system and their relation with suicidal behavior (Antypa et al. 2013). They report that associations between variation on the TPH1 gene and 5-HTTLPR gene and violent suicidal behavior are the most consistent findings (or, at least, the less inconsistent), but for some variations, negative results have also been reported and need further analyses. It's important to talk individually about the components of the serotoninergic system, in order to better understand where and possibly why these conflicting results emerge.

Serotonin receptor 1A (5HT1A) is an autoreceptor that regulates serotonergic synthesis and neurotransmission. Some studies have shown that there is less of this receptor in the hippocampus and amygdala of suicidal individuals. Polymorphism rs6295, as well as increased methylation of the gene promoter region in PFC, has been associated with depressed patients who committed suicide. These results have been reproduced, but there are also studies that couldn't find a significant relation between the said gene variation and suicide.

Serotonin receptor 2A (5HT2A) can be found in GABAergic neurons in the locus ceruleus. One of its functions is inhibiting noradrenergic neurons through activation of GABAergic cells. Studies on suicidal individuals haven't shown significant results, but studies on suicidal individuals with high scores of aggression show a positive correlation in all frontal areas examined. PET and SPECT studies show a reduction of union to this receptor in suicidal individuals with anxiety or depression, while there is an increase in impulsive attempters (Audenaert et al. 2006). Another study also found association between the T102C and C1354T (His452Tyr) polymorphisms of the 5-HT2a receptor gene and suicide attempts (Vaquero-Lorenzo et al. 2008). In that same study, there were no significant differences between suicide

attempters and psychiatric controls, leaving the possibility of this receptor as a common ground for both, suicide and other psychiatry conditions.

Tryptophan hydroxylase 1 (TPH1) is the enzyme in charge of peripheral synthesis of serotonin, with limited action within the brain. Although there are studies that show negative results, there are others that have related variations of this gene with completed suicide; such are the studies of Turecki et al. (2001), as well as Brezo et al. (2010), with positive results for the rs10488683 polymorphism. Other studies have also related the polymorphism A779C in the 7th intron of the gene with violent suicide attempts (Mann et al. 2001). These polymorphisms may affect the genes transcription, or the function of the enzyme, reducing its activity.

Tryptophan hydroxylase 2 (TPH2) is the rate-limiting enzyme in charge of serotonin synthesis within the brain, but studies relating this enzyme to suicide have, so far, shown conflicting results.

Ottenhof et al. (2018) reviewed in a meta-analysis 166 studies analyzing 69 *TPH2* polymorphisms, and many of these SNPs could be associated with suicide behavior, but the specific influence of these in suicide is really unclear.

Monoamine oxidase A (MAOA): As it happens with other components of the serotonergic system, there are studies that have found a positive relation between levels of this enzyme and suicide attempts, but also other studies with negative results. MAOA is the enzyme in charge of degrading norepinephrine as well as serotonin; it presents a polymorphism of the type variable number tandem repeat (VNTR) in the region 5 flanking the genes promoter, and the 4 repetition variation activates its expression, while other variants have the opposite effect. In a study by Courtet et al. (2005), they found that Caucasian males who had violent suicide attempts, had an increased expression of the allele with increased activity, as compared to nonviolent attempters.

As explained above, serotonin can carry completely different functions depending on the receptor it is activating and the location of the said receptor. That is why focusing on only one component of the system, be it the molecule itself, its transporter, or the enzymes that synthesize or degrade it, can yield conflicting results.

5 Epigenetics: When Nature Meets Nurture

We've already talked about different genetic studies related to suicide, but speaking about biology and heritability means speaking about epigenetics as well.

An article published in 2004 already stated that, as early as during pregnancy, environmental factors start having an impact on an individual's future life and that stressors during this period of time can increase the risk of suicidal behavior (Oquendo and Baca-Garcia 2004).

Epigenetics refers to the study of the epigenome, the chemical and physical modifications of the deoxyribonucleic acid (DNA) molecule that functionally regulate the collection of genes of an organism by altering the capacity of a gene to be

activated and produce the messenger ribonucleic acid (mRNA) it encodes (Petronis 2010).

It could be initially thought that epigenetics have to do exclusively with environmental influences; however, this point of view would be too reductionist, since epigenetic changes are also heritable. Twin studies (mentioned above) have been considered, as of today, the gold standard in what has to do with environment vs. heritability; the problem presents itself when we start looking at differences in genetic expression between the said twins. An article published on the *American Journal of Human Genetics* mentions a study carried out by Mill et al. (2006), where they found differences of up to 42% in methylation profile between MZ twins. "These new insights about epigenetic DNA modifications and their effects on gene expression and phenotype may increase our understanding of diverse phenotypes from personality traits to neuropsychiatric disease. The new paradigm is not one of nature vs. nurture, but complex and dynamic interaction between DNA sequence, epigenetic DNA modifications, environment, gene expression, and environmental factors that all combine to influence phenotype." To support this statement even further, there's one other study on identical twins who were discordant for schizophrenia (groups of twins where one had the disease and the other was healthy) (Mill et al. 2006). In this study, they measured epigenetic distance (the number of differences at each CpG site) and found that the patients were epigenetically more similar between them, than to their respective siblings.

5.1 So What Are These Changes "Produced by the Environment" That We Have Been Talking About?

Let's go back a little and discuss Stanley's study on suicidal subtypes. This study on impulsive and aggressive behavior used cortisol levels as a measure of response to stress. They found that suicide attempters with higher levels of impulsivity/aggression had a heightened cortisol response to stress, not seen in any of the other groups (Stanley et al. 2019).

5.2 How Are Cortisol Levels a Demonstration of Environmental Influence?

Cortisol (basal levels and reactivity) is controlled by the HPA axis. When exposed to psychological stress, the hypothalamus responds producing CRH, which stimulates production of ACTH from the pituitary gland. ACTH induces secretion of cortisol from the adrenal cortex. Cortisol performs different functions within the body, some have to do with metabolic response and some with the immune system (which in turn also affect the brain and behavior), and lastly, some of cortisol effects take place

within the brain. Glucocorticoid receptors (GR) are widely spread through the brain, and once cortisol reaches these receptors, they bind and relocate inside the cell. Once inside, they can interact with transcriptional factors and modify genetic expression of the cell (this also happens in other cells of the immune system).

Environmental factors, like childhood trauma and abuse, or maternal care, can modify HPA axis function by mediation of these receptors. There is a specific GR gene promoter that has been demonstrated to be modified by the said experiences. *NR3C1* gene is observed to have an increased methylation at the promoter region in depressed patients who experienced early sexual abuse and also in animal models with pups that received low care, leading to a lower GR expression. An increased NR3C1 has also been observed in suicide completers with a history of maternal deprivation and adults with child maltreatment. Individuals with a higher methylation of NR3C1 also show diminished cortisol responses in the dexamethasone suppression test (Chmielewska et al. 2019).

Lutz and Turecki also talked about differences in GR in an animal model of maternal grooming, where the offspring of mothers with high grooming during the first week of life had a higher hippocampal GR expression and also a lesser response to stress. This is due to an epigenetic variant of an exon 1 GR promoter, induced by maternal care (Lutz and Turecki 2014).

In his group's work, Turecki proposes a model of environmental influence on suicide based on three factors (Turecki 2014): 1 distal or predisposing factors, 2 developmental or regulating factors, and 3 proximal or precipitating factors. When these factors interact, it looks similar to Fig. 1.

There are other genetic variants related to early life stressors and adversity. *FKBP5* gene regulates a protein that allows GR receptors to translocate inside the cell, to carry its function. Hypermethylation of this gene decreases the presence of the said protein, stopping GR receptors to relocate and give negative feedback to the HPA axis.

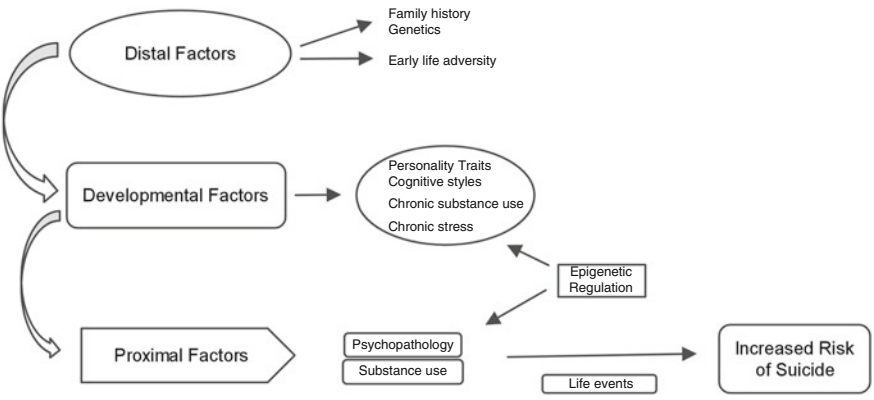

Fig. 1 Based on: Epigenetics and suicidal behavior research pathways. Gustavo Turecki. Am J Prev Med. 2014 September: 47(3 Suppl 2):S144–S151

Serotonin system may also suffer changes from early life experiences. *SLC6A4* (*5HTT*, serotonin transporter gene) has also been shown to present an increased methylation in relation to early life abuse, and in cases of hypermethylation, response of cortisol to stress was dull.

All of the above were examples of how early life experiences can shape genetic expression of individuals, making them more prone to conditions such as anxiety, or depression, and, in turn, making it more likely that they present suicide behavior.

Taking Stanley's group work on suicide subtypes (Stanley et al. 2019), and the evidence on modification of genetic expression from life events, we would like to propose a model for the subtype of stress responders, described in their work (Fig. 2).

In our model, stress responders (SR) and non-responders (NSR) would be placed at both ends of a spectrum. The closer an individual is to the SR end, the lesser a stimulus has to be to induce self-harming or suicidal behavior, while individuals on the NSR end could still act in such a way, if a strong enough stimulus appears. We also propose that life events, such as childhood trauma/abuse, parental neglect, drug abuse, damage to frontal cortex, and chronic stress (to name a few), can little by little move a NSR individual along the spectrum, toward the SR end. Since this is a spectrum, the opposite is also possible. Individuals in the SR end who receive adequate treatment, in time, would need a higher stimulus to engage in self-harming behavior.

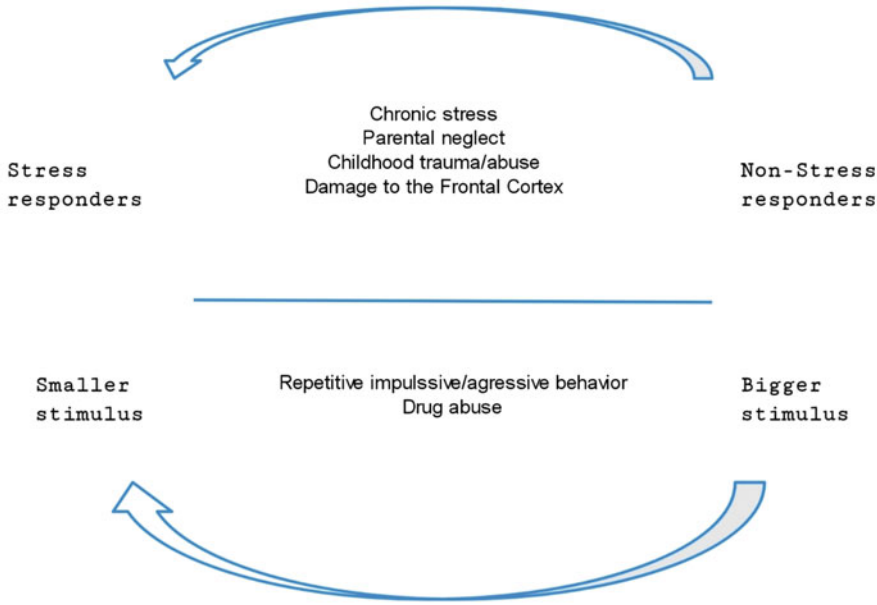

Fig. 2 Factors that contribute in transition from lesser to higher stress response

5.3 *Timing and Epigenetic Studies*

Since the very beginning of this chapter, we mentioned how timing was an important factor, probably not taken enough into account in genetic and epigenetic studies about different conditions (suicide not being an exception). The thing about epigenetics, besides their heritability, is that it changes. When an individual is studied together with their family for a genetic expression of a certain condition, that individual might not present it at the time of the test (it will make sense in a moment). Evidence suggests epigenetic changes that take place during childhood are carried all the way into adult life, and probably passed down (if they are still present), but there can also be changes that happen later into adulthood, after an individual has already had children. In this case, that person's descendants will not inherit the same pattern of gene expression that their progenitor had, giving place to additional confounding factors.

6 Prefrontal Cortex: (Maybe) the Most Important Correlate

In 2010, K. S. Kendler published an article talking about different pathways that lead to one outcome. In this article, using different risk factors (past adversity, current adversity, and psychiatric disorders, among others), Kendler showcases how ten different pathways can lead to suicide. In his closing argument, Kendler urges us to "avoid hard reductionism" but also prevents us from thinking that suicidal behavior is beyond our capacity to study or understand (Kendler 2010).

It might be possible that the ten pathways Kendler speaks about converge in a point prior to the said behavior. Through this chapter, we've already talked about most (if not all) of these pathways, in a way or another. From here on, we'll look for that "prior" convergence point, which might show us a way forward.

Ronald W Maris, in his article titled "Suicide," published in 2002, made reference to suicidal hopelessness in terms of cognitive inflexibility. Not exactly a definition, we will use his words to make sure we are not being misunderstood when speaking about hopelessness: "difficulty in believing that there are non-suicidal alternatives to life problems" (Maris 2002).

Maris hasn't been the only one relating suicide and cognition. Several articles published after his have studied the role of the prefrontal cortex in suicide. Monkul et al. (2007), Hwang et al. (2010), Wagner et al. (2012), and Keilp et al. (2013) studied different populations of suicide attempters and used different (image- or functional image-based) techniques; Keilp's group study was based on neuropsychological tests, instead of neuroimaging. Interestingly, they all found alterations in the prefrontal cortex of the population they studied.

To illustrate just how different their samples were, it would suffice to say that Hwang team's sample consisted of geriatric male patients (65 years or older)

(Hwang et al. 2010), while Monkul group's sample was formed by females, with a mean of age of 31 (Monkul et al. 2007). Both studies had different goals; the one with geriatric patients wanted to demonstrate that changes in gray matter (GM), as well as white matter (WM) (in this case due to vascular lesions), have a role in suicide behavior. They found a significant decrease in GM across several different brain areas (could be expected from their population of patients), with an even more prominent reduction in the medial frontal cortex, midbrain, cerebellum, and lentiform nucleus. They relate these findings to cognitive impairments seen in suicidal patients, including inflexibility, executive functioning, decision-making, and problem-solving.

In the study with adult female subjects, all depressed patients showed smaller orbitofrontal cortex volumes, and suicidal patients also showed larger right amygdala, than non-suicidal. It was statistically not significant (maybe due to lack of subjects), but suicidal subjects had more previous depressive episodes than non-suicidals, or an earlier age of illness onset. The explanation they give for this volume reduction also has to do with cortisol toxicity and chronic response to stress (as we already discussed above).

Orbitofrontal cortex has been described to play an important role in decision-making, and when it is damaged, subjects engage in more risky behaviors. The findings in this study correlate with previous findings showing that suicide attempters have poorer decision-making abilities. More aggressive suicidal individuals can even show a pattern of decision-making in the Iowa Gambling Task similar to that observed in patients with orbitofrontal lesions (Jollant et al. 2005).

Wagner also found reduction in cortical thickness in PFC in individuals with high risk for suicide, compared to non-high risk. His findings were in ventrolateral and dorsolateral PFC, both areas relating to inhibition of behavior.

In all, findings in these studies suggest that cognition plays a role in suicide, and its impairment, be it because of brain lesions, emotional trauma, congenital factors, or any other reason, which increases the likelihood of suicidal behavior. As Hwang expresses, in some cases it might be because of a difficulty in relocating attention away from preoccupied negative emotions or cognitions (giving way to hopelessness) (Hwang et al. 2010). In other cases, it might be because of a poorer decision-making and a lack of premeditation, as it might be the case in high aggression/impulsivity subtype described by Stanley (Stanley et al. 2019). In some cases it might be both.

Interesting enough this impaired-cognition model of suicide can also be applied to psychotic spectrum disorders. In investigations to determine psychosis biotypes, one of the most consistent findings has been brain volume reductions, with the largest effects in frontal, cingulate, temporal, and parietal cortex (Clementz et al. 2016), although these last findings on biotypes have yet to be related to suicidal behavior (Fig. 3).

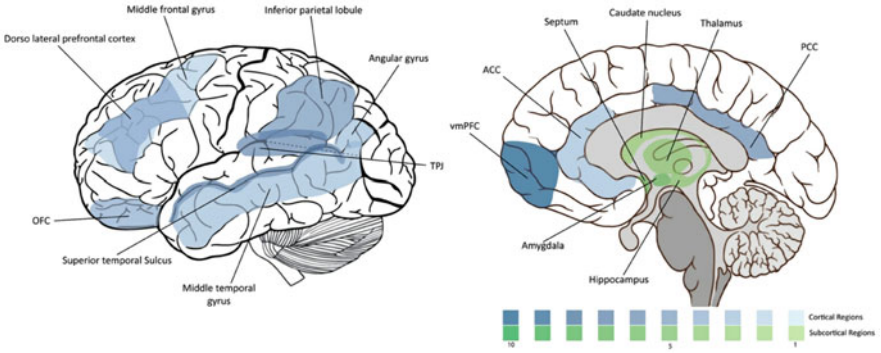

Fig. 3 Pascual L, Rodriques P and Gallardo-Pujol D (2013) How does morality work in the brain? A functional and structural perspective of moral behavior. Front Integr Neurosci 7:65. Doi: https://doi.org/10.3389/fnint.2013.00065. Image tagged for reuse

7 BDNF: Further Evidence of Cognitive Impairment in Suicide?

One more thing we have yet to talk about, but relates with the hypothesis of PFC dysfunction in suicide behavior, is the role of BDNF (brain-derived neurotrophic factor). Chmielewska's group research highlights the importance of BDNF as *1- a predictor of suicide ideation* and *2- a marker of depression* (Chmielewska et al. 2019).

Through several studies, BDNF has been related to fear conditioning, treatment response to antidepressants, and suicidal ideation and behavior. Depending on the context, and the region where BDNF is enhanced, it can act as a coding factor for memory and consolidation of fear learning. It appears that after a traumatic experience, there is an increase of BDNF in the CA1 region of the hippocampus. This would have to do with consolidation of memory. Extinction of the said conditioning also involves an increase of BDNF, but this time, it takes place in the PFC (Fuchikami et al. 2010). The same study also showed that, as it happens with cortisol, or serotonin, stressful events can also modify BDNF levels in the brain, through changes in genetic expression.

Low levels of BDNF have been related to suicidal ideation and behavior (Khan et al. 2019; Björkholm and Monteggia 2016), not only in depressed patients but also in patients with whole different conditions. One example might be a study relating *BDNF* hypermethylation in patients with acute coronary syndrome, with the presence of suicidal ideation, 1 year after the coronary event, although it is not possible knowing if the said hypermethylation already existed or was a result of the stressful situation (maybe both).

Polymorphism rs6265 (Val66Met) of the *BDNF* gene has been related with suicidal behavior as well. A study with patients who engaged in self-harming

behavior found an interaction between the said gene and the emotional environment while growing up, for homozygotic individuals, with the Val-Val variation. Homozygotic individuals, growing up in an emotionally challenging environment, were more likely to engage in harmful and life-threatening behavior. That same polymorphism has also been related to the presence of suicide thoughts (Sudol and Mann 2017).

The most important conclusion, from these and other studies, is that brain plasticity and connectivity seem to play a major role in the pathogenesis of depression and suicidal behavior (as well as other psychiatric conditions), but also in their recovery, and response to treatment. Considering these findings, if we could control in which regions BDNF is released, and enacts its function, we could open new paths for treatment.

8 Clinical Implications of an Impaired-Cognition Approach to Suicidal Behavior

At the current date, different psychological approaches and interventions for suicide prevention, in patients with borderline personality disorder, highlight the importance of mindfulness practice, some heavily relying on skills training of patients and mindfulness exercises.

8.1 Why Are We Talking About Mindfulness?

Aside from its meditation or oriental like approach (that may appeal or not to some people), mindfulness is, at its core, a style of cognitive training.

In our model, suicidal behavior would derive (in most cases) from impairments in cognition, impairments that, for some patients, would be equivalent as that seen in cases of structural brain damage. The volume reduction mentioned in the studies we already discussed would be the biological correlate of the said impairment.

Since life events and routines can negatively impact an individual brain structure, the opposite should also be true. If we believe that mindfulness training reduces risk of suicide, then individuals who undergo such training should show signs of it.

A review performed by Gotink et al. (2016) shows that after 8 weeks of mindfulness training, dorsomedial and dorsolateral PFCs show an increase in activity. There is also an increased functional connectivity of the salience network (SN), which is in charge of downregulation of the DMN, as well as directing attention to important stimuli. In all, aside from functional and volume increase in PFC, they found similar changes in the cingulate cortex, insula, and hippocampus. The amygdala also showed increased connection to the PFC and a reduction in activity and volume.

This review focused on findings after an 8-week training program, but there are studies that show changes as early as after 4 days of training. A study performed in Seoul, where they picked a group of healthy individuals, showed that after an intensive meditation program (mainly focused in mindfulness exercises) of only 4 days and 3 nights, there was increased activity in the ACC and DLPFC. They explain this finding as an improvement of functioning of the executive control network, but it is important remembering that the SN (which was not evaluated in this particular study) is responsible for directing and maintaining attention, both necessary when performing heavy focus-reliant tasks (Hwang et al. 2018).

We are not using these studies as a statement that mindfulness should be the one and only way of intervention in suicidal behavior. Quite the opposite, what we would like to relay is that interventions that increase PFC function and volume should have a positive impact in suicide prevention and that these interventions can show results in very small periods of time.

If we can accurately correlate brain volume reductions with cognitive symptoms via clinical evaluations, we could find better ways to predict suicidal behavior. Also, if we use these biological correlates as guidelines, we can pick specific interventions, better suited for each individual patient and his/her particular symptoms.

9 Conclusions

Environmental factors can modify an individual genetic expression, making them and their descendants prone to suicidal behavior.

Individuals exposed to chronic stress can become progressively less resilient to stressful situations, leading to a higher probability of them engaging in suicidal behavior.

Malfunction of the PFC, no matter the reason, could increase the probability of suicide behavior, even more so in depressed individuals.

Hopelessness, impulsivity, and aggressivity appear to have a common substrate in the PFC, although they are probably regulated by different specific areas.

In family studies of genetic expression, it is important to take timing into account.

References

Antypa N, Serretti A, Rujescu D (2013) Serotonergic genes and suicide: a systematic review. Eur Neuropsychopharmacol 23(10):1125–1142. https://doi.org/10.1016/j.euroneuro.2013.03.013

Arango V, Underwood MD, Gubbi AV, Mann JJ (1995) Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. Brain Res 688(1–2):121–133. https://doi.org/10.1016/0006-8993(95)00523-s

Audenaert K, Peremans K, Goethals I, van Heeringen C (2006) Functional imaging, serotonin and the suicidal brain. Acta Neurol Belg 106(3):125–131

Björkholm C, Monteggia LM (2016) BDNF – a key transducer of antidepressant effects. Neuropharmacology 102:72–79. https://doi.org/10.1016/j.neuropharm.2015.10.034

Brezo J, Bureau A, Mérette C, Jomphe V, Barker ED, Vitaro F, Hébert M, Carbonneau R, Tremblay RE, Turecki G (2010) Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: a 22-year longitudinal gene-environment study. Mol Psychiatry 15(8):831–843. https://doi.org/10.1038/mp.2009.19

Chmielewska N, Szyndler J, Maciejak P, Płaźnik A (2019) Epigenetic mechanisms of stress and depression. Psychiatr Pol 53(6):1413–1428. https://doi.org/10.12740/PP/94375

Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, Keshavan MS, Tamminga CA (2016) Identification of distinct psychosis biotypes using brain-based biomarkers. Am J Psychiatry 173(4):373–384. https://doi.org/10.1176/appi.ajp.2015.14091200

Courtet P, Jollant F, Buresi C, Castelnau D, Mouthon D, Malafosse A (2005) The monoamine oxidase A gene may influence the means used in suicide attempts. Psychiatr Genet 15 (3):189–193. https://doi.org/10.1097/00041444-200509000-00009

Fuchikami M, Yamamoto S, Morinobu S, Takei S, Yamawaki S (2010) Epigenetic regulation of BDNF gene in response to stress. Psychiatry Investig 7(4):251–256. https://doi.org/10.4306/pi.2010.7.4.251

Gotink RA, Meijboom R, Vernooij MW, Smits M, Hunink MG (2016) 8-week mindfulness based stress reduction induces brain changes similar to traditional long-term meditation practice – a systematic review. Brain Cogn 108:32–41. https://doi.org/10.1016/j.bandc.2016.07.001

Hwang JP, Lee TW, Tsai SJ, Chen TJ, Yang CH, Lirng JF, Tsai CF (2010) Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. J Geriatr Psychiatry Neurol 23(3):171–184. https://doi.org/10.1177/0891988710363713

Hwang WJ, Lee TY, Lim KO, Bae D, Kwak S, Park HY, Kwon JS (2018) The effects of four days of intensive mindfulness meditation training (Templestay program) on resilience to stress: a randomized controlled trial. Psychol Health Med 23(5):497–504. https://doi.org/10.1080/13548506.2017.1363400

Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R, Castelnau D, Malafosse A, Courtet P (2005) Impaired decision making in suicide attempters. Am J Psychiatry 162(2):304–310. https://doi.org/10.1176/appi.ajp.162.2.304

Keilp JG, Gorlyn M, Russell M, Oquendo MA, Burke AK, Harkavy-Friedman J, Mann JJ (2013) Neuropsychological function and suicidal behavior: attention control, memory and executive dysfunction in suicide attempt. Psychol Med 43(3):539–551. https://doi.org/10.1017/S0033291712001419

Kendler KS (2010) Genetic and environmental pathways to suicidal behavior: reflections of a genetic epidemiologist. Eur Psychiatry 25(5):300–303. https://doi.org/10.1016/j.eurpsy.2010.01.005

Khan MS, Wu GWY, Reus VI, Hough CM, Lindqvist D, Westrin Å, Nier BM, Wolkowitz OM, Mellon SH (2019) Low serum brain-derived neurotrophic factor is associated with suicidal ideation in major depressive disorder. Psychiatry Res 273:108–113. https://doi.org/10.1016/j.psychres.2019.01.013

Lutz PE, Turecki G (2014) DNA methylation and childhood maltreatment: from animal models to human studies. Neuroscience 264:142–156. https://doi.org/10.1016/j.neuroscience.2013.07.069

Mann JJ, Brent DA, Arango V (2001) The neurobiology and genetics of suicide and attempted suicide: a focus on the serotonergic system. Neuropsychopharmacology 24(5):467–477. https://doi.org/10.1016/S0893-133X(00)00228-1

Mann JJ, Arango VA, Avenevoli S, Brent DA, Champagne FA, Clayton P, Currier D, Dougherty DM, Haghighi F, Hodge SE, Kleinman J, Lehner T, McMahon F, Mościcki EK, Oquendo MA, Pandey GN, Pearson J, Stanley B, Terwilliger J, Wenzel A (2009) Candidate endophenotypes for genetic studies of suicidal behavior. Biol Psychiatry 65(7):556–563. https://doi.org/10.1016/j.biopsych.2008.11.021

Maris RW (2002) Suicide. Lancet 360(9329):319–326. https://doi.org/10.1016/S0140-6736(02)09556-9

Mill J, Dempster E, Caspi A, Williams B, Moffitt T, Craig I (2006) Evidence for monozygotic twin (MZ) discordance in methylation level at two CpG sites in the promoter region of the catechol-

O-methyltransferase (COMT) gene. Am J Med Genet B Neuropsychiatr Genet 141B (4):421–425. https://doi.org/10.1002/ajmg.b.30316

Monkul ES, Hatch JP, Nicoletti MA, Spence S, Brambilla P, Lacerda AL, Sassi RB, Mallinger AG, Keshavan MS, Soares JC (2007) Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. Mol Psychiatry 12(4):360–366. https://doi.org/10.1038/sj.mp.4001919

Mullins N, Perroud N, Uher R, Butler AW, Cohen-Woods S, Rivera M, Malki K, Euesden J, Power RA, Tansey KE, Jones L, Jones I, Craddock N, Owen MJ, Korszun A, Gill M, Mors O, Preisig M, Maier W, Rietschel M, Rice JP, Müller-Myhsok B, Binder EB, Lucae S, Ising M, Craig IW, Farmer AE, McGuffin P, Breen G, Lewis CM (2014) Genetic relationships between suicide attempts, suicidal ideation and major psychiatric disorders: a genome-wide association and polygenic scoring study. Am J Med Genet B Neuropsychiatr Genet 165B(5):428–437. https://doi.org/10.1002/ajmg.b.32247

Oquendo MA, Baca-Garcia E (2004) Nurture versus nature: evidence of intrauterine effects on suicidal behaviour. Lancet 364(9440):1102–1104. https://doi.org/10.1016/S0140-6736(04)17115-8

Ottenhof KW, Sild M, Lévesque ML, Ruhé HG, Booij L (2018) TPH2 polymorphisms across the spectrum of psychiatric morbidity: a systematic review and meta-analysis. Neurosci Biobehav Rev 92:29–42. https://doi.org/10.1016/j.neubiorev.2018.05.018

Pascual L, Rodrigues P, Gallardo-Pujol D (2013) How does morality work in the brain? A functional and structural perspective of moral behavior. Front Integr Neurosci 7:65. https://doi.org/10.3389/fnint.2013.00065

Petronis A (2010) Epigenetics as a unifying principle in the aetiology of complex traits and diseases. Nature 465(7299):721–727. https://doi.org/10.1038/nature09230

Roy A, Segal NL, Centerwall BS, Robinette CD (1991) Suicide in twins. Arch Gen Psychiatry 48 (1):29–32. https://doi.org/10.1001/archpsyc.1991.01810250031003

Ruderfer DM, Walsh CG, Aguirre MW, Tanigawa Y, Ribeiro JD, Franklin JC, Rivas MA (2019) Significant shared heritability underlies suicide attempt and clinically predicted probability of attempting suicide. Mol Psychiatry. https://doi.org/10.1038/s41380-018-0326-8

Stanley B, Michel CA, Galfalvy HC, Keilp JG, Rizk MM, Richardson-Vejlgaard R, Oquendo MA, Mann JJ (2019) Suicidal subtypes, stress responsivity and impulsive aggression. Psychiatry Res 280:112486. https://doi.org/10.1016/j.psychres.2019.112486

Strawbridge RJ, Ward J, Ferguson A, Graham N, Shaw RJ, Cullen B, Pearsall R, Lyall LM, Johnston KJA, Niedzwiedz CL, Pell JP, Mackay D, Martin JL, Lyall DM, Bailey MES, Smith DJ (2019) Identification of novel genome-wide associations for suicidality in UK biobank, genetic correlation with psychiatric disorders and polygenic association with completed suicide. EBioMedicine 41:517–525. https://doi.org/10.1016/j.ebiom.2019.02.005

Sudol K, Mann JJ (2017) Biomarkers of suicide attempt behavior: towards a biological model of risk. Curr Psychiatry Rep 19(6):31. https://doi.org/10.1007/s11920-017-0781-y

Turecki G, Zhu Z, Tzenova J, Lesage A, Séguin M, Tousignant M, Chawky N, Vanier C, Lipp O, Alda M, Joober R, Benkelfat C, Rouleau GA (2001) TPH and suicidal behavior: a study in suicide completers. Mol Psychiatry 6(1):98–102. https://doi.org/10.1038/sj.mp.4000816

Vaquero-Lorenzo C, Baca-Garcia E, Diaz-Hernandez M, Perez-Rodriguez MM, Fernandez-Navarro P, Giner L, Carballo JJ, Saiz-Ruiz J, Fernandez-Piqueras J, Baldomero EB, de Leon J, Oquendo MA (2008) Association study of two polymorphisms of the serotonin-2A receptor gene and suicide attempts. Am J Med Genet B Neuropsychiatr Genet 147B (5):645–649. https://doi.org/10.1002/ajmg.b.30642

Wagner G, Schultz CC, Koch K, Schachtzabel C, Sauer H, Schlösser RG (2012) Prefrontal cortical thickness in depressed patients with high-risk for suicidal behavior. J Psychiatr Res 46 (11):1449–1455. https://doi.org/10.1016/j.jpsychires.2012.07.013

Wasserman D, Geijer T, Sokolowski M, Rozanov V, Wasserman J (2007) Nature and nurture in suicidal behavior, the role of genetics: some novel findings concerning personality traits and neural conduction. Physiol Behav 92(1–2):245–249. https://doi.org/10.1016/j.physbeh.2007.05.061