Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2019; 11(1):1-23
doi: 10.18863/pgy.382119

Neurobiology of Suicidal Behaviour

İntihar Davranışının Nörobiyolojisi

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Abstract

Suicide is a phenomenon that is a world health priority, with multidimensional clinical appearance and with complex biological, social and psychological risk factors. Recent studies have revealed the complexity underlying the neurobiological mechanisms of suicide. The association between genetic transmission, serotonergic system dysfunction, hypothalamic-pituitary-adrenaline axis hyperactivity, stress system, lipid metabolism, noradrenergic hyperactivity, anomaly in glial cells and signaling failure and suicidal behavior has been highlighted in particular in family, twin and adoption studies. There are also considerable evidences of morphological changes in the brain neuroimaging studies, particularly in the frontolimbic nerve and differences in the cognitive functions of the suicide attempted cases. The identification of neurobiological risk factors for suicidal behavior will play an important role in the prevention of suicide, as well as the arrangement of treatment algorithms and follow-up of treatment. The aim of this review article is to evaluate the neurobiological reasons of suicidal behavior.

Keywords: Biomarker, suicidal behavior, neurobiology.

Öz

İntihar, karmaşık biyolojik, sosyal ve psikolojik risk faktörlerine ve çok boyutlu klinik görünüme sahip, dünya sağlık önceliği olan bir fenomendir. Son dönemde yapılan çalışmalar intiharın nörobiyolojik mekanizmalarının altında yatan karmaşıklığı ortaya çıkarmıştır. Özellikle aile, ikiz, evlat edinme çalışmalarında genetik geçiş, serotonerjik sistem disfonksiyonu, hipotalamo-pituiter-adrenaleksen hiperaktivitesi, stres sistemi, lipid metabolizması, noradrenerjik hiperaktivite, glial hücrelerde anomali ve sinyalizasyon hatası ile intihar davranışı arasındaki ilişkiye dikkat çekilmiştir. Ayrıca intihar girişiminde bulunan olguların bilişsel işlevlerinde farklılıklar olduğu, beyin nörogörüntüleme çalışmalarında özellikle frontolimbik ağda morfolojik değişiklikler bulunduğuna ait ciddi kanıtlar elde edilmiştir. İntihar davranışına ilişkin nörobiyolojik risk faktörlerinin belirlenmesi, intiharın önlenmesinin yanısıra tedavi algoritmalarının düzenlenmesi, tedavinin izleminde önemli rol oynayacaktır. Bu yazıda intihar davranışının nörobiyolojik nedenlerinin incelenmesi amaçlanmıştır.

Anahtar sözcükler: Biyobelirteç, intihar davranışı, nörobiyoloji.

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Submission date: 21.01.2018 | Accepted: 18.02. 2018 | Online published: 21.02.2018

SUICIDE is a complex human behavior with biological, psychological, and sociological aspects. The psychosocial aspect of suicidal behavior has been investigated in studies conducted to date. Although it has become a focus of attention among researchers in recent years, the neurobiology of suicidal behavior has not been adequately elucidated. Consistent evidence for particularly the role of genetic factors in the formation of suicidal behavior has been obtained from the studies conducted to date (Petersen et al. 2014, Mirkovic et al. 2016). Family, twin, and adoption studies have shown that suicide has a genetic dimension (Brent and Melhem 2008, Dutta et al. 2017). For example, genetic factors affect suicidal thoughts and behaviors independently of genetic factors that influence psychiatric disorders. Genetic transmission is mentioned in suicidal behavior. Even though suicide and mood disorders are clinically overlapping conditions and psychiatric disorders often increase the risk of suicide, the fact that some patients do not attempt to suicide suggests that structural predisposition or genetic tendency is important for suicidal behavior and that this situation is independent of psychiatric disorders. In other words, the 'suicide brain' is mentioned. Researches conducted over the last 30 years have shown that there is a relationship between suicidal behavior, aggression, and impulsivity.

The reasons such as serotonergic system dysfunction, HPA axis hyperactivity, noradrenergic hyperactivity, dopaminergic, glutamatergic and GABAergic system dysfunctions, glial cell abnormalities, signaling failure and microgliosis are thought to play a role in the neurobiology of suicide (García-Sevilla 1999, Merali et al. 2004, Pandey 2013). There is a limited number of neuroimaging studies on suicidal behavior. For this reason, a better understanding of the neurobiology of suicidal behavior is required. In this study, it was aimed to investigate possible neurobiological reasons and risk factors of suicidal behavior, to contribute to previous studies conducted in this field, and to emphasize the importance of the neurobiology of suicidal behavior.

Neurobiology of Suicidal Behavior

Serotonergic System

Serotonin is the most investigated neuromodulator in suicide and suicidal behavior. The fact that the serotonergic system is associated with depression and impulsive-aggressive behaviors and these two clinical conditions are related to suicide, support the role of this system in suicide (Pandey 2013). Serotonin [5-hydroxytryptamine (5-HT)] is synthesized from tryptophan via tryptophan hydroxylase (TH) in serotonergic nerve endings and other cells except for platelets. Tryptophan hydroxylase exists as two isoforms, TPH1 and TPH2. The activity of 5-HT in the synapse is terminated primarily by its reuptake into serotonergic terminals. It also undergoes enzymatic degradation and diffusion. 5-hydroxyindoleacetic acid (5-HIAA) is the degradation product of 5-HT. 5-HT plays a role in mood, anxiety, sleep, cognition, memory, and aggression (Gültekin 2005). Previous studies in this field include studies on measurement of 5-HT and 5-HIAA levels in the cerebrospinal fluid (CSF) and blood, studies on analysis of 5-HT receptor subtypes in platelets, postmortem brain studies, and neuroendocrine stimulation studies. Some studies revealed that there was a decrease or no change in 5-HT transporter binding in the prefrontal cortex of individuals with a history of suicide

attempt and that there was an increase in imipramine binding in the hippocampus (Mann et al. 2000, Arango et al. 2001, Gross-Isseroff et al. 1989).

TH is widely used as a determinant of 5-HT activity. The mRNA expression level of TH2 increased 33% in the dorsal raphe nucleus and 17% in the median raphe nucleus in depressed suicide victims compared to controls without psychiatric disorders (Bach-Mizrachi et al. 2006). Elevated mRNA expression of TH2 can explain increased TH protein levels in depressed suicides and can show homeostatic response to insufficient serotonergic transmission in the brain. It was reported that there was an increase in the area and density of TH immunoreactive neurons in the rostral part of the dorsal raphe nucleus and was a decrease in the area and density of TH immunoreactive neurons in the caudate part of the dorsal raphe nucleus in depressed suicide victims compared to controls (Boldrini et al. 2005). The levels of TH2 in the ventromedial prefrontal cortex was also found to b higher in suicide victims than in controls and was lower in suicides with violent methods than in suicides with non-violent methods (Perroud et al. 2010). It has been suggested that there is a decrease in 5-HT transmission in cortical and subcortical regions in major depression and suicide and that elevated mRNA expression of TH2 may have emerged as a compensatory mechanism for the decrease in central 5-HT transmission and/or increased stress response (Ernst et al. 2009). The presence of a large number of serotonergic neurons in the raphe nuclei of suicide victims in addition to elevated mRNA expression of TH2 has been explained as increased 5-HT synthesis capacity in response to reduced serotonergic tone. Elevated 5-HT levels in the raphe nuclei of suicide victims support this situation (Oquendo et al. 2014).

CSF 5-HIAA level is an indicator of 5-HT turnover. In a study in which depressed patients were divided into two groups according to CSF 5-HIAA level (below or above 15 ng/ml), the group with low CSF 5-HIAA level attempted suicide more frequently and used more violent methods (Asberg et al. 1976). Other studies have also demonstrated that CSF 5-HIAA levels are lower in individuals who attempt suicide (Banki et al. 1984, Jokinen et al. 2009). In a meta-analysis, this relationship was found significant (Lester 1995). It was reported that plasma 5-HIAA levels were lower in the suicide attempt group than in the control group (Spreux-Varoquaux et al. 2001). IN another study, platelet 5-HT levels were lower in the suicide attempt group than in the control group (Spreux-Varoquaux et al. 2001). The mean platelet 5-HT concentration was found to be significantly lower in patients hospitalized due to a suicide attempt than in depressed patients who did not attempt suicide; however, there was no difference compared to healthy controls. In another study, the mean platelet 5-HT concentration was significantly higher in depressed patients who did not attempt suicide than in healthy controls (Roggenbach et al. 2007). There was a negative relationship between the severity of suicidal behavior and plasma 5-HT levels in adolescents (Tyano et al. 2006).

There are seven general serotonin receptor classes with a total of 14 different receptor subtypes. 5-HT1A somatodendritic autoreceptors in the brain stem regulate 5-HT neuronal firing. There have been contradictory results in studies on autoreceptor binding in the dorsal raphe nucleus (DRN) in depressed patients who attempted suicide. In one study, there was an increase in 5-HT1A receptor binding in the rostral raphe nuclei of depressed patients who attempted suicide (Boldrini et al. 2008). It was reported that the volume distribution of 5-HT1A receptors in the dorsal raphe nuclei of

suicide victims was reduced by 40% compared to controls, and that the receptor concentration was similar to controls, and that the receptor binding capacity was reduced by 43% compared to controls (Arango et al. 2001). However in another study, there was no change in 5-HT1A receptor binding in brain regions such as the occipital cortex, hippocampus, amygdala of depressed patients who attempted suicide (Lowther et al. 1997).

Two studies reported an increase in the number of 5-HT2A receptors in the prefrontal cortex in suicide victims compared to individuals without psychiatric disorders (Mann et al. 1986, Turecki et al. 1999). Similarly Escriba et al. (2004) was an increase in 5-HT1A and 5-HT2A receptor expression. As there was also an increase in platelet 5-HT2A receptor binding in suicide victims, it has been suggested that 5-HT2A receptors can be used as a biomarker in identifying patients with suicidal tendency (Pandey et al. 1995). In a study conducted by directly measuring the platelet 5-HT2A receptor response rate, it was shown that the platelet 5-HT2A receptor response rate in patients with high-lethality suicide attempt was 41% of that in patients with low-lethality suicide attempt (Malone et al. 2007). This finding has been interpreted as that it is associated with impaired signal transmission, although patients with high-lethality suicide attempt have a larger number of 5-HT2A receptors.

Neuroendocrine Stimulation Studies

Neuroendocrine stimulation studies are used to understand the role of 5-HT in suicide. Fenfluramine is the most commonly used serotonergic agent. It causes 5-HT release and serotonin reuptake inhibition, as well as stimulation of postsynaptic 5-HT receptors. Serotonergic stimulation leads to an increase in prolactin levels in relation to dose. One of the tests assessing 5-HT function is the prolactin response to fenfluramine. The more obvious the response is, the more active the serotonergic system is. Fenfluramine reflects the decrease in the prolactin response and in the serotonergic activity. In patients with a history of major depression and suicidal behavior, the insensitivity develops in the prolactin response to fenfluramine (Mann et al. 1995). The prolactin response to fenfluramine was reduced in individuals with a history of suicide attempt compared to controls and individuals without a history of suicide attempt (Corrêa et al. 2000). Similarly the prolactin response to fenfluramine was reduced in patients with a history of fatal suicide attempt (Malone et al. 1996). In the light of these findings, it can be suggested that the insensitivity in the prolactin response to fenfluramine may be a more specific predictor of suicide rather than depression.

Dopaminergic System

In humans, catecholamine synthesis begins with the amino acid tyrosine. L-tyrosine, which is concentrated in the brain and sympathetic nervous system, is converted to L-DOPA by the enzyme tyrosine hydroxylase. L-DOPA is then converted to dopamine. Norepinephrine and epinephrine are synthesized from dopamine. Dopamine is metabolized by catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) enzymes to 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (Çuhadar and Koçak 1987). Dopamine acts by binding to five subreceptors (D1, D2, D3, D4, D5) and plays an important role in functions such as mood, aggression, motivation, reward, and attention. The number of studies on the dopaminergic system in suicide is fewer than those on the other neurotransmitter systems. Previous studies have

evaluated dopamine metabolites, dopamine receptors, and growth hormone (GH) response to apomorphine (a dopamine-receptor agonist).

There has been an increase in HVA levels in the hippocampus of patients who have attempted suicide; however, this increase could not be shown in the cortex (Crow et al. 1984). In a study conducted by Ohmori et al. (1992) who compared suicide victims with patients with physical illnesses, the level of HVA in the frontal cortex of those who attempted suicide was elevated. However, Arranz et al. (1997) found that there was no difference between controls and those who attempted suicide in terms of cortical HVA level. In studies assessing dopamine activity by measuring dopamine metabolites in CSF, it was reported that the level of HVA was lower in the suicide group than in the control group (Träskman-Bendz et al. 1993, Engström et al. 1999).

When the GH response to apomorphine was compared between 8 male depressed patients who lost their lives due to suicide in the following years and 18 depressed patients who did not attempt to suicide, the peak GH response to apomorphine was significantly lower in patients who completed suicide. These findings have been interpreted as that dopaminergic dysfunction exists in completed suicide, and more specifically that the GH response to apomorphine via D2 receptors supports the role of D2 receptors in the biology of completed suicide (Pitchot et al. 2001a). However, studies on D1 and D2 receptor binding in the nucleus accumbens, putamen, and caudate nucleus have reported no significant difference between depressed suicide victims and controls (Bowden et al. 1997, Allard and Norlén 2001). Depressed patients with a history of suicide attempt show a reduced GH response to apomorphine compared to patients who did not attempt suicide. Furthermore, when suicide attempt methods were divided into high- and low-lethality suicide attempts, it was found that there was no difference between the two groups in terms of the peak GH response to apomorphine (Pitchot et al. 2001b). From the perspective of the dopaminergic system, it is indicated that these two groups share a similar biological disorder. The GH response to apomorphine from the methods used in these studies provides information about D2 receptor sensitivity at the hypothalamic level.

Measurement of CSF HVA levels is a poor indicator of central dopaminergic activity. Therefore, these results are far from fully reflecting how the dopaminergic system in the central nervous system changes in suicide attempt. Moreover, the fact that some of these findings can be obtained postmortem and some invasive interventions are required for CSF analysis makes them difficult for clinical use. However, based on antidepressants which act via the dopaminergic pathway, it has been suggested that mesolimbic dopamine transmission is reduced in depression and suicide (Bowden et al. 1997). It was found that there was a decrease in dopamine transporter binding and an increase in the D2/D3 ratio in amygdales of depressed patients. This may suggest that there are regional changes in dopaminergic transmission in mood disorders and suicide (Ryding et al. 2006, Lindström et al. 2004).

Noradrenergic System

Adrenaline (epinephrine) is synthesized from tyrosine and phenylalanine in the adrenal gland and brain. Adrenaline has physiological effects and plays a role in cognitive function. Adrenaline plays a role in mood and suicide. Noradrenaline is synthesized by locus coeruleus (LC) neurons. There is a decrease in the mean pigment intensity and total

number of LC neurons in the left brain hemisphere of individuals who committed suicide (Arango et al. 1996). In a study investigating the binding properties of iodoclonidine (an alpha 2-adrenergic receptor agonist) and yohimbine (an alpha 2-adrenergic receptor antagonist), Agonist binding was higher in the suicide group than in the control group. But there was no difference in antagonist binding between the two groups (Ordway et al. 1994). The fact that there is no difference in the analysis of norepinephrine in LC tissue between the groups has been explained as that the difference in agonist binding may be due to differences in the involvement of the endogenous agonist noradrenaline in tissue sections.

There are two general types of adrenergic receptors, α and β. Alpha-adrenergic receptors have been studied more frequently in suicide. It has been indicated that there is an increase in the concentration of α2-adrenergic receptors in the hypothalamus and frontal cortex in depressed suicide victims compared to controls (Meana 1992). Later studies have also found an increase in α2-adrenergic receptor binding in the frontal cortex in depressed suicides (Callado et al. 1998, García-Sevilla 1999). It has also been shown that there is an increase in α2-adrenergic receptor mRNA expression in suicide victims (Escribá et al. 2004). There are also studies reporting that no difference was found in the concentration of α2-adrenergic receptors between the suicide group and the control group (De Paermentier et al. 1997, Gross-Isseroff et al. 2000). The levels of noradrenaline and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) were assessed in CSF and urine. The levels of tyrosine hydroxylase and α-adrenergic and β-adrenergic receptors were assessed in peripheral tissues and postmortem brain tissues. It has been reported that there is an increase in β-adrenergic receptor binding in the frontal cortex of suicide victims (Mann et al. 1986). It has also been indicated that there is an increase in the concentration of α2-adrenergic receptors in the cortex and hippocampus of suicide victims. There are few findings on α1-adrenergic receptors. There is found to be a decrease in the concentration of α1-adrenergic receptors in postmortem brain tissues from individuals who committed suicide (Underwood et al. 2004).

GABAergic System

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter and acts via GABA-A and GABA-B receptors (Macdonald and Olsen 1994). There is a decrease in expression of alpha1, alpha3, alpha4, and delta subunit mRNAs from GABA-A subunits in the frontal cortex of individuals who committed suicide (Merali et al. 2004). Another study has found that there is a decrease in expression of GABA-A subunits in cortical structures (Poulter et al. 2010). GABA-A receptor expression is coordinated in a particular region in the human brain and that this organization frequently undergoes changes especially in regions resistant to overstress (such as the amygdala and hippocampus) in depressive suicides and that brain region-specific inhibitory signaling, which plays a role in regulating GABA-A subunits, is associated with depression and suicide (Poulter et al. 2010).

There was no significant difference between depressed suicide victims and controls in terms of GABA-B receptor binding in the hippocampus and frontal and temporal cortices (Cross et al. 1988). However, Cheetham et al. (1988) revealed that there was an increase in GABA receptor binding in the frontal cortex in the suicide group compared to the control group, but this increase was not found in the temporal cortex. In a

study comparing GABA-A receptor binding in the LC by flunitrazepam, there was no significant difference in GABA-A receptor binding between controls, individuals with major depressive disorder (MDD), and depressed suicide victims (Zhu et al. 2006). These results have shown that GABA receptor binding sites in brains of depressed suicide victims have not changed. In postmortem studies, GABA-A receptor alpha1 and beta3 subunits were up-regulated in some areas of the cerebral cortex of patients who committed suicide (Choudary et al. 2005). There was no difference between those who committed suicide and controls in terms of GABA levels in the frontal cortex (Korpi et al. 1988). There are very few studies on the relationship between suicide and GABA. These results are inadequate to say that there is GABA system dysfunction in suicide.

Hypothalamic-Pituitary-Adrenal Axis

The HPA axis plays an important role in the human stress system. Depression and stress are major risk factors for suicide. It is known that HPA axis abnormalities exist in depression and suicide. The rate of suicide attempts was higher in depressed patients with a negative response to the dexamethasone suppression test (DST) than in depressed patients with a positive response to the DST (Yerevanian et al. 2004). While some studies have found that suicide attempt is associated with DST non-suppression, other studies have not revealed this association. In a meta-analysis, it was determined that completed suicide was associated with DST non-suppression, but suicide attempt was not related to DST non-suppression (Coryel and Schlesser 2001). HPA axis abnormalities are more strongly associated with completed suicide rather than suicide attempt.

The levels of corticotropin-releasing hormone immunoreactivity among suicides were increased in the LC, dorsolateral prefrontal cortex (DLPFC), and ventromedial prefrontal cortex (VMPFC) but were reduced at the dorsovagal complex (Merali et al. 2004, 2006). It has been suggested that the level of CRH is increased in the hypothalamus of suicide victims (Austin et al. 2003). The number of CRH receptor-binding sites is decreased due to down-regulation of CRH receptors caused by chronic CRH release. The number of CRH receptor-binding sites is found to be decreased in the frontal cortex of suicide victims (Nemeroff et al. 1988). Postmortem studies have shown CRH hyperactivity, increased number of CRH neurons, and increased CRH mRNA level in depressed individuals who committed suicide. The stress-related changes in the HPA axis can be a predictor of suicidal behavior.

Lipid Metabolism

Cholesterol is very important in the development of the central nervous system, is the building block of cortisol, and is associated with the stress system. Some studies have reported a relationship between cholesterol levels and violent behaviors. Various medications which are used to lower blood lipid levels have been reported to cause an increase in suicides and violent behaviors. Associations between low plasma cholesterol level and violence, aggression, impulsivity, suicidal behavior have been established (Ernst et al. 2009). The relationship between low serum cholesterol level and low serotonergic activity (which is associated with impulsive-aggressive behavior and suicidal behavior) has been demonstrated (Kaplan et al. 1994). Animal studies have shown a relationship between low cholesterol diet, decreased serotonergic activity, and increased aggression

level. It has been suggested that low cholesterol levels cause a decrease in neurotransmitter functioning by altering the lipid composition of the neuronal membrane, resulting in suicidal behavior. As a result, although low cholesterol levels have been found to be associated with low serotonergic activity and impulsive-aggressive behaviors, mechanisms underlying this association are not fully understood. Findings suggest that the relationship between peripheral cholesterol and suicidal behavior is also valid at the central level based on the presence of negative correlations between cholesterol levels in the frontal cortex and violent suicide attempts.

The relationship between cholesterol levels and suicidal behaviors may be due to decreased serotonergic activity (Kim and Lee 2017). In humans, the effect of cholesterol on serotonergic activity could not be proven; however, it has been reported that low cholesterol diet decreases serotonergic activity and increases aggression in non-human primates.

Brain-Derived Neurotrophic Factor

The neurotrophin family includes four structurally related proteins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). BDNF may play a role in the pathophysiology of suicide. Antidepressants increase BDNF levels in rat brain. BDNF mRNA and protein levels have been found to decrease in postmortem brain samples from suicide victims. BDNF mRNA and protein levels have been determined to decrease in the PFC and hippocampus of patients who committed suicide (Dwivedi et al. 2003). BDNF exhibits its physiological effects by binding to TrkB receptors. It has been found that mRNA and protein levels of full-length TrkB receptor are decreased in the PFC and hippocampus of suicide victims (Dwivedi et al. 2003). mRNA and protein levels of BDNF and full-length TrkB receptor are decreased in the PFC of adolescents who committed suicide. In summary, decreased mRNA and protein levels of both BDNF and full-length TrkB receptor in postmortem brain tissues from suicide victims are important findings.

Neuroimmune System (Cytokines)

Cytokines, which are considered to be the hormones of the immune system, are a different group of proteins. These molecules are released from various cells and act as signals between cells that regulate the immune response to injury and infection. Cytokine responses are mediated by cytokine receptors. The immune system plays an important role in brain-related diseases such as depression (Courted et al. 2016). There is increased microgliosis in postmortem brain tissues from patients with affective disorders and schizophrenia who committed suicide (Steiner et al. 2008). There is also a relationship between asthma, suicide ideation, and increased suicide rate (Goodwin and Eaton 2005).

There are increased mRNA expression levels of IL-3 and IL-4 in the PFC of women who committed suicide and increased mRNA expression levels of IL-3 in the PFC of men who committed suicide (Tonelli et al. 2008). There is an increase in CSF IL-6 levels in patients who attempted suicide (Lindqvist et al. 2009). Although cytokine levels in serum of depressed patients are abnormal, it is unclear whether or not cytokine levels in brain tissue are abnormal. It has been determined that there is an increase in protein and mRNA levels of IL-1β, IL-6, TNF-α in the PFC of adolescents who

committed suicide. There is a significant interaction between cytokines and neuroendocrine and serotonergic systems. These system abnormalities may be associated with suicide.

Genetics of Suicidal Behavior

Suicidal behavior is thought to be transferred from generation to generation through complex inheritance with the contribution of multiple gene-gene interactions and environmental factors (Özalp 2009). Genetic epidemiology studies in this field show that genes contribute to the risk of suicide (Brezo et al. 2008, Tsai et al. 2011, Petersen et al. 2014, Mirkovic et al. 2016). The evidence from family, twin, and adoption studies supports the belief that there is a genetic component in suicidal tendency over the past four decades. Furthermore, these studies provide evidence that suicidal behavior can be inherited, partly independent of the familial transmission of major psychiatric disorders (Roy et al. 1995, Mc Guffin et al. 2001, Petersen et al. 2014). Genetic epidemiology studies conducted to date have shown that genes contribute to the risk of suicide but the genetic contribution is weaker than the environmental contribution (Zalman 2010).

Family Studies

Suicide and suicidal behavior are highly familial. Transmission of suicidal behavior does not appear to be related to only the familial transmission of psychiatric disorders (Brent and Mann 2005, Dutta et al. 2017). Family, twin, and adoption studies support that the familial transmission of suicidal behavior is partially genetic and may be mediated by the transmission of intermediate phenotypes such as impulsivity, aggression, and neuroticism (Brent and Melhem 2008). In addition to the genetic component of familial transmission, there may be familial compelling factors (such as intergenerational transfer of familial strains, abuse, age, and separation) and environmental causes (such as imitation) (Öncü 2016).

In family studies investigating the familial transmission of suicidal behavior, the rate of suicide or suicidal behavior in the relatives of a proband with suicidal tendency is compared with the rate of suicide or suicidal behavior in the relatives of a proband without suicidal tendency (Brent and Mann 2005). However, studies conducted on this subject considerably differ methodologically from each other in terms of outcome properties such as the presence of family history of completed suicide and suicide attempt (or both of them) and in terms of other features such as the selection of probands who commit suicide or attempt suicide (Sorenson and Rutter 1991). Differences in selecting the comparison group between studies occur in the direction of the use of community samples or psychiatric disorders (Tsuang 1983, Kim 2005). File screening, family history or direct interview methods used in the assessment of family burden are other areas that differ from each other among studies (Qin et al. 2003). Despite the varieties and limitations among methods, the findings obtained from studies provide similar results in terms of demonstrating the familial transmission of suicidal behavior.

Among studies based on large community screenings, there are studies showing that the familial effect on suicidal behavior has been maintained even after the psychiatric diagnosis and treatment have been controlled. In these studies where the familial transmission of psychiatric disorders and other risk factors have been statistically adjusted, it has been observed that there is a 2- to 12-fold increase in suicide rates after this

adjustment (Johnson et al. 1998, Cheng et al. 2000, Agerbo et al. 2002, Runeson and Asberg 2003, Qin et al. 2003). Similarly, suicide rates were higher in the relatives of suicide probands than in the relatives of controls, regardless of whether the control group was composed of psychiatric patients, individuals with general medical illnesses, or a community-based sample (Foster et al. 1999, Powell et al. 2000, Tsai et al. 2002). In another study, Kim et al. (2005) compared suicidal behaviors between the relatives of suicide attempters and the relatives of community controls. They found that the risk of suicide was 10 times higher in the relatives of suicide attempters than in the relatives of community controls after adjustment for psychopathology. In the meta-analysis of Baldessarini and Hennen (2004) including 21 family genetic studies, suicide probands had a 3-fold greater risk of suicide attempts compared to controls, independent of the psychiatric history of their close relatives. In a study carried out in individuals who were hospitalized due to suicide attempt, Mittendorfer-Rutz et al. (2008) reported that the parental history of suicide or suicide attempt and the sibling history of suicide attempt increased the risk of suicide attempts in probands by 2-3 times.

In all studies, even after controlling for differences in rates of psychiatric disorders in probands, parent-child relationship problems, and rates of psychiatric disorders in family members, the rate of suicidal behaviors is higher in the relatives of suicide attempters than in the relatives of community controls. In family studies, heritability is the lowest in suicidal ideations, slightly higher in suicide attempts and the highest in completed suicides (Brent et al. 1996, Baldessarini and Hennen 2004, Kim et al. 2005, Mittendorfer-Rutz et al. 2008).

In family genetic studies, intermediate phenotypes have been identified as one of the factors that are thought to play a role in the familial transmission of suicidal behavior. According to Gottesman and Gould (2003), an intermediate phenotype should be associated with the clinical phenotype, should predict the occurrence of problems in offspring, should be inherited, and should show evidence that it mediates the transmission of the general clinical phenotype after parent-child relationships are controlled. The intermediate phenotype with the most common evidence on it is the tendency to react with impulsivity or hostility. This structure is associated with the risk of suicide attempt, can predict the occurrence of suicide attempt, is inherited, and mediates the transmission of suicidal behavior.

Another possible intermediate phenotype is neuroticism (Brent and Melhem. 2008). Impairments of working memory and executive function may constitute a neurocognitive subcomponent of insufficiency in resolving impulsive aggression and interpersonal problems. These functions alter and are inherited in adult suicide attempters and in offspring of adult suicide attempters (Jeglic et al. 2005).

In conclusion, many studies investigating the familial aggregation of suicidal behavior have revealed that genetic transmission plays an important role independently of family history of psychopathology.

Twin Studies

Unlike adoption and family based designs, twin studies investigating the genetic transmission of suicidal behavior provide a relatively detailed assessment by allowing better control of shared environmental effects. The data obtained from case reports and record-based studies carried out in this field report that the estimate for the heritability of

suicide is between 21% and 50%. Many twin studies have revealed that there is a familial transmission in the heritability of suicidal behavior, which cannot be explained by the transmission of other psychopathologies (Statham et al. 1998, Glowinski et al. 2001, Fu et al. 2002, Voracek and Loibl 2007).

Roy et al. (1995) found a higher concordance rate for suicide attempt in the surviving monozygotic twin of the co-twin's suicide in monozygotic (MZ) twins (n=26) compared to dizygotic (DZ) twins (n=9) (38% versus 0%). Roy and Segal (2001) performed a new review as a repeat of their study published in 1995. In this review, they examined 28 case reports where one of the twins had committed suicide. It was reported that the concordance rate for suicide was higher in MZ twins (n=13) than in DZ twins (n=15) (14.9% versus 0.7%). These findings support the view that the clinical phenotype for concordance includes both completed suicide and suicide attempt. In the review of Baldessarini and Hennen (2004) investigating the genetics of suicide among 7 twin studies, they found a 175 times higher relative risk among MZ twins compared to DZ twins. However, the fact that the number of suicides in DZ twins has been studied in only 2 studies and has been found at a lower rate (only 2 cases of suicide among 1486 DZ twin pairs) has led them to consider this result unreliable and uncredible. When the grief process was examined as another confounding factor in relation to the difference between suicide concordance rates in MZ and DZ twin pairs, the high concordance in MZ twins did not appear due to a more severe grief reaction. (Brent and Melhem 2008). The risk of suicide attempt in the surviving twin after one of the twins who died from causes other than suicide was found to be similar in MZ and DZ twins (3.3% versus 1.4%).

Twin studies generally provide more detailed assessment than family and adoption studies and allow for an assessment of environmental and genetic contributors to concordance. However, unless twin studies are combined with adoption studies (ie, comparison of twins adopted away to different parents), it is difficult to definitively separate genetic effects from shared environmental effects (Brent and Melhem 2008). In a study conducted in twins who were separated at birth and adopted by different families, components of maternal behavior previously considered "environment" were explained by genetic concordance of MZ twins eliciting similar maternal responses from unrelated mothers (Plomin et al. 1994). This partially reveals the difficulty and importance of combining twin studies with adoption studies.

Since case reports and case series are used in meta-analyzes, they poorly represent all twin pairs affected by suicide. The low prevalence of suicidal behavior in twins is one of the other difficulties encountered in twin studies. When these situations are evaluated together with many other factors, it should not be forgotten that findings need to be interpreted with caution.

Adoption Studies

Adoption studies provide important data supporting the role of genetic factors in suicidal behavior. There are few adoption studies. They are mostly based on Danish public health records. These studies have suggested that the risk of suicide is 7-13 times higher in the biological relatives of adoptees than in the adoptive relatives of adoptees and have emphasized that completed suicides have higher heritability compared to suicide attempts (Brezo et al. 2008).

In the review of Brent and Melhem (2008), they examined the studies performed using the Danish adoption records. Among these studies, the first study was designed to investigate the genetics of schizophrenia and mood disorders by Kety and colleagues in 1968. This study reported a higher concordance for suicide in biological, compared with adoptive relatives of adoptees who committed suicide. Subsequently, the second study was conducted by Schulsinger et al. in 1979 and compared the rates of suicide among the biological and adoptive relatives of adoptees who committed suicide versus biological and adoptive relatives of a matched living adoptee control group in Denmark. This study found a 6-fold higher rate of suicide in the biological relatives of the suicide versus those of the control adoptees. Moreover, an absence of suicide among the adopted relatives of the suicide versus control adoptees supported a genetic rather than environmental etiology. The rate of suicide was higher in the biologic relatives of suicide adoptees regardless of whether the adoptees had psychiatric disorders. However, based on these studies, it was not possible to determine whether the genetic liability to suicide was attributable to the transmission of major psychiatric disorders or to a suicide diathesis.

In the third adoption study using the same records (Wender et al. 1986), the biological and adoptive relatives of adult adoptees with mood disorder were compared, and matched unaffected adoptees were examined. This study revealed a 15-fold increase in suicide among the biological relatives of the mood-disordered adoptees versus those of the unaffected adoptees. This finding supports the role of mood disorder in the genetics of suicide. However, the greatest increased risk for suicidal behavior was found in the relatives of those probands with "affect reaction", which is a diagnosis similar to borderline personality disorder. This suggests that impulsive-aggressive personality traits may play a role in the familial aggregation of suicidal behavior (Brent and Melhem 2008).

When these findings are evaluated together, these studies support a strong role of genetics in the familial concordance of completed suicide. Limitations of these studies include limited data from countries outside Denmark, small number of adoption studies, restriction to data gathered through routine medical records, lack of systematic assessment of suicide attempts and completions, and unwell control of psychiatric confounding variables. Thus, although adoption studies show the importance of genetic factors that explain the familial aggregation of suicidal behavior, they could not reveal which environmental factors may be effective in familial transmission.

Molecular Genetic Studies

Under the guidance of twin, adoption, and family studies that indicate the presence of a genetic predisposition in suicidal behavior, molecular studies have begun to investigate specific genetic components of this predisposition. The first genetic studies that have investigated the genes associated with suicide and suicidal behavior and through which neurobiological pathways these genes contribute include linkage studies and association studies investigating specific single nucleotide polymorphisms (SNPs) (Currier and Mann 2008).

In association studies, candidate genes have been selected based on information from neurobiological studies on suicide. On the basis of neurobiological knowledge, molecular genetic studies have focused mainly on dopaminergic, serotonergic, and noradrenergic neurotransmitter systems. Neurotrophins (such as brain-derived neurot-

rophic factor [BDNF]) and HPA axis-related genes have also been investigated. (Keller et al. 2011, Oquendo et al. 2014).

In association studies conducted to determine individual candidate genes and their variants that contribute to genetic predisposition to suicidal behavior, the rather complicated findings have been obtained. Although individual SNP genetic association studies are being carried out, there are some factors that prevent these studies from being supported by repeated results. These factors include sample size, conceptual differences (such as suicide, suicidal thought, suicide attempt, and suicide tendency), ethnic factors, environmental factors, and interactions among many factors.

In conclusion, studies on the genetics of suicidal behavior are limited to information in current medical records. The assessment of psychiatric disorders is also restricted to those who receive treatment or are admitted to treatment. A better understanding of the genetic mechanisms of suicide and suicidal behavior can help determine etiological factors, identify individuals at high risk for the development of suicidal behavior, and create an approach to intervention and prevention goals.

Suicidal Behavior and Brain Imaging Studies

Structural brain imaging has been used in psychiatric disorders since the 1970s. In the first brain imaging study, cerebral ventricle dimensions of patients with schizophrenia were measured by brain computed tomography (CT). There was a relationship between increased brain ventricle size and cognitive impairment (Johnstone et al. 1976). The first brain CT study on suicidal behavior was published by Schlegel et al. (1989). This study reported no correlation between cerebral ventricle dimensions and suicidal tendencies in 44 patients with depression (Schlegel et al. 1989).

More detailed structural brain imaging is performed by magnetic resonance imaging (MRI). In the first MRI study on suicidal behavior, the relationship between psychiatric symptom frequency and deep white matter lesions in 28 patients with Alzheimer's disease was examined. There was no significant difference in deep white matter lesions between the groups with and without psychiatric symptoms (Lopez et al. 1997). However, the same study pointed out the relationship between serious psychiatric symptoms (such as suicidal ideation) and frontal white matter lesions. Structural brain imaging studies conducted to date have demonstrated evidence of white and gray matter hyperintensities and reduced subcortical volumes. In one study, major depressive disorder patients with and without suicide attempts were compared, and subcortical gray matter hyperintensities were detected in MRI findings of those who had a history of suicide attempt. Interestingly, the authors of this study mentioned that gray matter hyperintensities especially in the basal ganglia were associated with an increased risk of suicide (Ahearn et al. 2001). Another study reported that white matter hyperintensities on T2-weighted MR images were associated with a history of suicide attempt in children and adolescents receiving inpatient treatment. Especially younger patients had a high prevalence of hyperintensities in the deep white matter of the parietal lobe and past suicide attempts (Ehrlich et al. 2003). The same researchers compared 102 MDB young adult patients with and without suicide attempts who received inpatient treatment and reported that the number of periventricular white matter hyperintensities was significantly higher in those who had a previous suicide attempt (Ehrlich et al. 2005).

In the brain MRI study of Pompili et al. (2008), they evaluated 99 patients with major affective disorders (bipolar disorder types I and II and unipolar MDD), 44.4% of whom attempted suicide at least once in the past six months. They found that white matter hyperintensities were different in the presence of suicide attempts. In this study, authors reported that periventricular white matter hyperintensities were significantly associated with suicidal behaviors even when the age variable was statistically excluded (Pompili et al. 2008). In a study comparing 7 unipolar depressed female patients with suicide attempt, 10 unipolar depressed female patients without suicide attempt and 17 healthy women, it was found that gray matter volumes of the right and left orbitofrontal cortex of patients with a history of suicide attempt were smaller. This study has suggested that orbitofrontal cortex and amygdala abnormalities in suicidal patients may weaken the decision-making process and can lead to more impulsive behaviors and suicide attempts (Monkul et al. 2007). In a study examining corpus callosum areas and suicidal tendencies in patients with impulse control disorder and bipolar disorder, 10 female patients with suicide attempt, 10 female patients without suicide attempt and 27 healthy women were compared. The authors revealed that the corpus callosum size was smaller in patients with a history of suicide attempt and was negatively correlated with suicidal behavior. They have also suggested that the anterior medial prefrontal cortex may play a role in the pathophysiology of impulsivity and suicidal behavior in bipolar disorder (Matsuo et al. 2010).

In another study, 70 elderly patients with MDD and 26 healthy older individuals were compared using T1-weighted MR images. It was found that the depression group had smaller volumes in the various gray matter regions (insula and posterior cingulate cortex) and the various white matter regions (subcallosal cingulate cortex, parahippocampal region, insula, and cerebellum) (Hwang et al. 2010). This study showed that suicidal behavior in major depression was compatible with a widespread but different volume reduction in the various subcortical and cortical areas and/or cortices. Decreased volume in some brain areas has been considered as a biological predisposition to suicidal behavior. It has been suggested that depressed patients with these characteristics may be more likely to attempt suicide (Hwang et al. 2010).

Patients with mostly mood disorders were assessed in brain imaging studies for investigating suicidal behavior. However, it is important to examine cases of mood disorders as well as cases of schizophrenia or epilepsy in order to understand suicidal behavior. In a study comparing schizophrenia patients with and without suicide attempts, it was reported that schizophrenia patients with suicide attempt had larger inferior frontal white matter volumes bilaterally and that there was a significant positive correlation between rates of self-aggressive behaviors and white matter volumes in the same regions (Rüsch et al. 2008). In another study, brain gray matter volume was investigated in schizophrenia patients with and without suicide attempts. Gray matter density in the left superior temporal cortex and left orbitofrontal frontal cortex was lower in schizophrenia patients with suicide attempt (Aguilar et al. 2008). Recent studies have reported that schizophrenia patients with suicide attempt have lower gray matter density in the temporal lobes by MRI and that there is a relationship between lethality of suicide attempt and regional brain anomalies (Giakoumatos et al. 2013). Another study reported that there were decreases in the right DLPFC and superior temporal cortex thicknesses in schizophrenia patients with a history of suicide attempt (Besteher et al. 2016).

In a study conducted in 51 children with epilepsy (mean age=9.8 years), right orbitofrontal gyrus white matter and left temporal lobe gray matter volumes were significantly reduced in 11 patients with suicidal thoughts compared to 40 patients without suicidal thoughts (Caplan et al. 2010).

Structural imaging studies in individuals with borderline personality disorder may shed light on possible neuroanatomical correlations as suicidal behavior and suicidal tendency are the core symptoms of borderline personality disorder. Interestingly, one MRI study reported that there was a relationship between pituitary volume and parasuicidal behavior in young people with borderline personality disorder and that pituitary volume may be an important predictor for parasuicidal behaviors (Jovev et al. 2008). The authors have found the association between increased number of parasuicidal behaviors and larger pituitary volume and have focused on possible HPA axis hyperactivity in individuals with borderline personality disorder. Moreover, there were decreases in the anterior cingulate gyrus, hippocampus, amygdala and parahippocampal gyrus volumes in individuals with borderline personality disorder compared to healthy controls and that reduced gray matter volume in the prefrontal cortex and medial temporal cortex may be important for impulse control (Soloff et al. 2008). In a review study including 24 studies on suicidal behavior, it was reported that different results were obtained to indicate a higher prevalence of white (particularly periventricular and deep white matter) and gray matter hyperintensities mostly in the frontal, temporal and/or parietal lobes on brain imaging in patients with a history of suicide attempt and that frontal and temporal lobe volumes were reduced. The authors suggested that there was a relationship between gray matter volume reduction in the frontal lobe and suicidal behavior (Desmyter et al. 2011).

In addition to structural brain imaging, functional imaging methods (such as positron emission tomography [PET], single-photon emission computed tomography [SPECT] and functional MRI [fMRI]) that examine regional brain functions and molecular processes of the brain have been used in order to understand suicidal behavior. Functional imaging studies can include resting-state studies, activation-state studies, and studies on brain neurotransmitters, transporters, and receptors. Decreased blood flow and glucose hypometabolism in the prefrontal cortex in patients with a history of suicide attempt were common findings in resting- and activation-state functional brain imaging studies (Oquendo et al. 2003, Audenaert et al. 2006). In studies conducted with pharmacological activation, it has been found that there is an inverse correlation between prefrontal cortex metabolism and lethal suicide attempt after administration of fenfluramine (Correa et al. 2000, Soloff et al. 2003). Male patients with a history of suicide attempt recognized different and angry facial expressions faster on the basis of neuron responses in the orbitofrontal cortex (OFC) by fMRI when compared with healthy controls (Jollant et al. 2010).

In a review study including 57 brain imaging studies on suicidal behavior, it has been indicated that these studies compared patients with a specific diagnosis and with a history of suicide attempt mostly with patients with the same diagnosis and without a history of suicide attempt or healthy controls, and that these studies included mostly adult patients with diagnoses of MDD, bipolar disorder, schizophrenia, borderline personality disorder, traumatic brain injury, and epilepsy, and that there have been a limited number of studies involving children, adolescents and elderly, and that MRI

was most frequently used in the structural examination of brain gray and white matter morphology (Cox Lippard et al. 2014). This study found reduced OFC gray matter volume in patients with diagnoses of MDD, bipolar disorder, schizophrenia, and borderline personality disorder and increased amygdala gray matter volume in patients with diagnoses of MDD and schizophrenia. OFC and amygdala are effective in emotional regulation and impulse control as closely associated brain areas and that some structural problems in these areas may lead to suicidal behavior with increased impulsivity (Cox Lippard et al. 2014). In addition, the authors have reported that reduced OFC volume may be associated with lethal suicide attempts in patients with borderline personality disorder and have pointed out that MRI studies revealed abnormalities in frontotemporal white matter connections. In other words, brain white matter abnormalities may contribute to suicidal behavior, self-aggression and impulse control disorder.

In other studies, there was an increase in prevalence of cerebral white matter hyperintensities in young and middle-aged patients diagnosed with MDD and bipolar disorder who had a history of suicide attempt (Pompili et al. 2008, Ehrlich et al. 2005, Serafini et al. 2011). There are many different etiological factors (cell loss, ischemia, perivascular space enlargement, vascular demyelination) contributing to the formation of white matter hyperintensities. For this reason, the relationship between brain white matter hyperintensity and suicidal behavior needs to be examined in more detail.

In the review of Van Heeringer et al. (2014) including 12 structural and functional MRI studies on suicidal behavior, it was emphasized that structural MRI studies revealed reduced volume of the superior temporal gyrus and caudate nucleus and that functional MRI studies revealed an increased reactivity in the anterior cingulate cortex and inferior frontal cortex in intergroup comparisons. The authors have reported that brain structural deficits as well as functional overactivation of certain brain regions may contribute to the decision-making network and have suggested that these findings may lead to suicidal behavior through reduced motivational control over deliberately behavioral reaction to markedly negative stimuli (Van Heeringer et al. 2014).

There is only one study on completed suicide in the literature. In this study, regional cerebral blood flow was retrospectively compared using statistical parametric mapping between 12 MDD patients with a history of completed suicide, depressed patients without a history of suicide attempt, and healthy controls (Amen et al. 2009). Consistent with previous brain imaging studies on depression, impulse control disorder and limbic dysregulation including significant perfusion defects in the medial prefrontal, subgenual (Brodmann areas 11 and 25) and ventral tegmental areas were reported (Amen et al. 2009). Suicidal thought is important to understand the development of suicide attempt risk. In a few structural MRI studies on suicidal thought, despite the fact that reduced fractional anisotropy (FA) values in the cingulum were determined by diffusion tensor imaging (DTI) in traumatic brain injury patients with suicidal thoughts, white matter abnormalities could not be demonstrated (Pompili et al. 2008, Yurgelun-Todd et al. 2011). The absence of frontal white matter lesion findings in these individuals suggests that these findings may be closely related to suicide attempts and possibly more impulsive aspects of some suicide attempts. Although some studies have revealed similar findings in patients who have not used the same suicide methods, it is also possible that white matter lesions may be due to suicide attempts (e.g., hypoxia) that may affect the brain (Pompili et al. 2008).

The biopsychosocial characteristics of aging can cause a neurobiological risk for suicide. White matter hyperintensities and other white matter anomalies may be more common in older adult participants. Early findings of white matter hyperintensities in elderly adults have revealed that some pathological processes are more common in elderly adults (e.g., vascular disease) (Ahearn et al. 2001, Sachs-Ericsson et al. 2014). Unlike young adults, much attention has been focused on the relationship between reduced gray matter volume in the basal ganglia and reward processing and behavior control in older adult patients diagnosed with major depressive disorder who attempted suicide (Dombrovski et al. 2012, Hwang et al. 2010). Decreases in ventromedial prefrontal cortex responses to awards in elderly patients with a history of suicide attempt have been shown to be associated with impulsivity (Dombrovski et al. 2013).

Since adolescence is a critical period in the development of suicidal behavior, brain imaging studies conducted in adolescents are also important. Structural imaging studies in children and adolescents with epilepsy, bipolar disorder, and MDD show some consistency with structural imaging studies in adults. This suggests that these findings may be related to the development of suicidal thoughts and behaviors (Caplan et al. 2010, Ehrlich et al. 2003, Ehrlich et al. 2004, Goodman et al. 2011). Adolescents who attempted suicide had smaller white matter volume in the orbitofrontal cortex, and that young patients with MDD had more extensive white matter hyperintensities, and that adolescents who attempted suicide multiple times had smaller gray and white matter volumes in the anterior cingulate cortex (Ehrlich et al. 2003, Ehrlich et al. 2004, Goodman et al. 2011). The fMRI study conducted in adolescents with major depression revealed increased responses to angry faces similar to adults (Pan et al. 2013). This suggests that increased susceptibility to frontal systems associated with negative emotional processing may characterize adolescent participants with suicide attempt. A recent study has reported that the binding potential of serotonin 5-HT1A receptor in the insula, anterior cingulate cortex, and DLPFC on PET is predictive of lethality in suicide in patients followed up for two years (Oquendo et al. 2016). Another study has indicated that patients with cognitive inhibition have a predisposition to suicidal behavior (Richard-Devantoy et al. 2016). Prefrontal cortex dysfunction has been mentioned in the neuroimaging study on decision making and social threat processing in patients with a history of suicide attempt (Olie et al. 2015). There may be a relationship between volumes of the corpus callosum and nucleus accumbens and lethality of suicidal attempts in patients with bipolar disorder (Gifuni et al. 2016, Gifuni et al. 2017). There is a relationship between white matter changes and suicide attempt in patients with panic disorder (Kim et al. 2015). Prefrontal regional responses have been shown to decrease in MDD patients with a history of suicide attempt (Tsujii et al. 2017). Besides insula and orbitofrontal cortex gray matter volumes are associated with lethality of suicide attempt in patients with bipolar I disorder who had a history of suicide attempt (Duarte et al. 2017). These findings suggest that brain morphological changes in the frontolimbic network may be an indicator of previous etiopathogenic processes affecting suicidal tendency and suicide severity in patients with bipolar I disorder. There has been a growing interest in brain neuroimaging studies of suicidal behavior in recent years. To date, there has been considerable evidence especially on the frontal region and the 5-HT system. The most important limitations of the studies are the fact that few cases and heterogeneous groups have been studied, suicidal behavior is not well defined,

and the number of studies specific to age groups is insufficient. Moreover, the fact that current treatment practices for patients have not been included is one of the important limitations. There have not been studies on completed suicide. The fact that suicide methods have not been mentioned is among the limitations of the studies.

Conclusion

Despite increasing evidence, there is no biomarker available yet to prevent suicide. Although depressed patients have suicidal thoughts, every patient with suicidal thoughts may not attempt to suicide. There is serious evidence for the effects of genetic and environmental factors on suicidal behavior. Neuroscience studies will provide a better understanding of structural and functional characteristics of suicidal behavior. There is a need for large-scale studies in which new characteristics of suicidal behavior are addressed separately, confounding factors are excluded, and new neurobiological and neuroimaging techniques are applied. The obtained evidence will play an important role in the determination of risk factors for suicidal behavior and prevention of suicide as well as the arrangement of treatment algorithms and follow-up of treatment. The 'suicide brain' will be better understood in this way.

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Author Contributions: All authors attest that each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.
Peer-review: Externally peer-reviewed.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has received no financial support.