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Neuropathology of Suicide: A Narrative Review Article

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Abstract

Suicide neuropathology is a multifactorial phenomenon influenced by psychological, social, and environmental factors. Researchers have primarily focused on the role of neurotransmitters, such as serotonin, in suicide. A deficiency in serotonin input to the anterior cingulate cortex and ventral prefrontal cortex is associated with suicide and suicidal behaviour and is linked to decision-making and suicide intent. The serotonin hypothesis proposed that low levels of serotonin in the brain contribute to an increased risk of suicidal behaviour. However, subsequent studies have produced mixed and inconsistent results, indicating that the relationship between serotonin and suicide is not straightforward. Recent research has expanded the focus to structural and functional brain abnormalities associated with suicidal behaviour. Advances in neuroimaging techniques have allowed researchers to investigate the brain's anatomy, connectivity, and activity patterns in individuals at risk of suicide. Genetic studies have provided insights into the genetic basis of suicide risk, with certain genetic variations associated with increased susceptibility to suicidal behaviour. Studies have found increased levels of pro-inflammatory markers in the brains of individuals who died by suicide, suggesting a link between inflammation and suicide risk. A drug targeting the glutamate pathway, ketamine, has recently drawn attention for its ability to rapidly treat depressive symptoms and holds great promise as a potential antisuicidal drug. Overall, further research is needed to better understand the neuropathological mechanisms underlying suicidal behaviour.

INTRODUCTION

Suicide is a major public health concern that is on the rise throughout the world and one of the main causes of death in our societies. It accounts for an annual global age-standardized suicide rate of 9.0 per 100,000 people with variations across age groups and countries, which translates to over 700,000 people dying by suicide every year (1). In other words, every 40 seconds someone deliberately kills her/himself. Up to one-third of individuals with suicidal ideation have a suicidal attempt within 1 year;

individuals who have had a suicidal attempt have a 16.3% risk of repeated suicidal attempts and a 1.6% risk of suicide within the year (2). Suicidal behaviour is complex and heterogeneous, presumably the consequences of several causes and is linked to multiple factors, including psychiatric/psychopathologic factors, personality traits, early-life adversity and stressful life experiences among others. Suicidal attempt or ideation is a complex behaviour resulting from intricate, multi-dimensional interactions between various social, cultural, biological, psychological, and environmental factors especially in a genetically predisposed individual (3). As suicide is often considered the worst outcome or consequence of psychiatric disorders, little attention has been paid to its independent, and likely unique, molecular genetic basis.

Over the past few decades, research in domains ranging from neuroanatomy, genetics, and molecular psychiatry has led to a model whereby behavioural dysregulation, including suicidal behaviour, develops as a function of biological adaptations in key brain areas (4). Research advances in the neuropathology of suicidal behaviours (SB) have identified distinct brain abnormalities that may hold the answer to preventing suicide. More recently, promising directions in the study of suicide have been opened by the unravelling of the distinct epigenetic processes that take place in the brain. This review article examines the many dimensions of the existing knowledge of suicidality and argues how the rapidly developing discipline of neurobehavioural epigenetics may enhance our capacity to comprehend and perhaps even prevent suicidal behaviour.

DEFINITIONS AND TERMINOLOGIES

Suicidality exists on a spectrum of severity, showing the progression from less to more severe forms of suicidal ideation (SI) and behaviour, and showing an overlap between attempted and completed suicide. Intentional self-injurious thoughts and behaviour may be suicidal or nonsuicidal. The difficulty of establishing the intent of self-harming behaviours has hindered efforts to determine and predict which individuals will go on to attempt and complete suicide. The definitions of different suicide and nonsuicide terminologies are summarized in Table 1.

EPIDEMIOLOGY / GLOBAL BURDEN OF SUICIDE

Suicide is a worldwide phenomenon. As such, it has continued to be addressed by the World Health Organization (WHO) since the 1950s. The rising trend in suicide rate is relatively skewed as 78% of all completed suicides occur in low- and middle-income countries (5). However, differences in suicide rates arise between regions and countries concerning the age, gender, and socioeconomic status of the individual and the respective country, method of suicide, and access to health care. Despite this rising trend, a significant amount of underreporting is likely to be present. Most suicides are related to a background psychiatric disease, with depression, substance use disorders and psychosis being the most relevant risk factors. However, anxiety, personality-, eating-, and trauma-related disorders, as well as organic mental disorders, also contribute. (5) There are some pervasive negative factors such as adverse childhood experiences, family breakdown, and physical or sexual abuse among others, that may predispose suicide attempters to develop these various disorders which increases their likelihood of completing suicide. Suicide rates are also high amongst vulnerable groups who experience discrimination, such as refugees and migrants; indigenous peoples; lesbian, gay, bisexual, transgender, and prisoners. By far

the single most important risk factor for suicide is a previous suicide attempt (6).

Table 1: Definitions of different suicide and nonsuicide terminologies

Terminology	Definition	Comments/Examples
Suicidal ideation	Thoughts about killing oneself or ending one's life; these thoughts may or may not include a plan.	It may be active or passive. Active suicidal ideation involves thoughts about taking action, identifying a method, having an active plan and/or having intent to act.
Suicide attempt	Self-injurious behavior that is intended to kill oneself, but is nonfatal. Self-injurious behaviour that is accompanied by any intent to die	Many individuals will acknowledge the possibility that their behaviour could have resulted in death. However, some may report that their main motivation is other than to die such as to escape an intolerable situation, or hostile environment or to get attention.
Suicide threat	Thoughts of engaging in self-injurious behaviour that are verbalized and intended to lead others to think that one wants to die, despite no intention of dying	"If you leave me, I will kill myself" "If you don't give me what I want, I will shoot myself"
Suicide gesture	Self-injurious behavior that is intended to lead others to think that one wants to die, despite no intention of dying. It is an intent to give the appearance of a suicide attempt to communicate with others.	Not following through with an attempt despite engaging in actions such as holding a bottle of pills, firearm, or knife, presumably would be considered a suicide gesture.
Suicide	Self-injurious behaviour is intended to kill oneself and is fatal.	
Non-suicidal self-injurious thoughts	Thoughts of engaging in self-injurious behaviour characterized by the deliberate destruction of body tissue in the absence of any intent to die and for purposes that are not socially sanctioned.	
Non-suicidal self-injury	Self-injurious behaviour is characterized by the deliberate destruction of body tissue in the absence of any intent to die and for purposes that are not socially sanctioned.	It most commonly consists of repetitive cutting, burning or pricking either to relieve distress, induce self-punishment or get attention.

Globally, suicides can occur throughout the lifespan and are the fourth leading cause of premature global mortality among individuals aged 15 – 29 years (7). The common suicide methods used include pesticide ingestion, hanging, firearms, drug Overdose, jumping from a great height, drowning, cutting and stabbing, starvation and dehydration, collision with or of a fast-moving vehicle and rarely electrocution. The three most common methods of suicide are ingestion of pesticides, hanging and firearms. The prevalence of use of any of these 3 methods varies with geographical location and the easy availability

of firearms or pesticides. Among individuals who commit suicide in the United States, firearms are involved in approximately 50 per cent of the deaths(8) while in the majority of other climes, hanging and ingestion of pesticides appear to be the most common methods of suicide. For instance, a recent study in Nigeria and Ghana revealed the most commonly reported methods of suicide include hanging and poisoning with pesticides or drugs(9). All nations, ethnicities, religions, genders, and social classes are affected by suicide, which occurs all over the world. Lesotho (72.4), Guyana (40.3), Eswatini - 29.4, South Korea (28.6), Kiribati (28.3), Federated States of Micronesia (28.2), Lithuania (26.1), Suriname (25.4), Russia (25.1), and South Africa (23.5) rank among the top ten countries with the highest suicide rates per 100,000 individuals. Belgium, which is ranked eleventh and has a suicide rate of 18.3 per 100,000 people, is the only country in Western Europe with an exceptionally high suicide rate. However, it is worth noting that Belgium has some of the world's most liberal laws on physician-assisted suicide, which is likely to be a contributing factor(10).

NEUROPATHOLOGY OF SUICIDE: PREVIOUS AND CURRENT UNDERSTANDING

The neuropathology of suicide is a complex and multifactorial phenomenon that has been studied extensively to gain a better understanding of the underlying biological factors contributing to suicidal behaviour. It is imperative to know that research on suicide remains very active and our understanding continues to evolve. Understanding the neuropathological basis of suicide is crucial for developing effective prevention and intervention strategies. However, suicide is a complex phenomenon influenced by a wide range of psychological, social, and environmental factors, and the neuropathological findings should be interpreted within this broader context.

Neurotransmitters implicated in suicide risk

In the past, researchers primarily focused on the role of neurotransmitters, such as serotonin, in suicide. A deficiency in serotonin input to the anterior cingulate cortex and ventral prefrontal cortex (PFC) is found in association with suicide, and non-fatal suicidal behaviour, and is linked to decision-making and suicide intent (11). Hence, hypofunction of the ventral prefrontal cortex (PFC) may lead to increased suicide risk due to the inability to restrain the self-destructive act. Likewise, the dysfunction in serotonin (5-HT) neurotransmission is detectable in the brain of suicide decedents and the cerebrospinal (CSF) fluid of nonfatal suicide attempters (12). Furthermore, cerebrospinal fluid (CSF) levels of the main serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are low in more lethal suicide attempters and predict the risk for future suicide (13). Miller et al.(14), also reported less brain serotonin transporter (SERT) in depressed suicide attempters not including depressed non-attempters compared to controls, raising the possibility that SERT is related more to suicidal behaviour than to depression.

The serotonin hypothesis proposed that low levels of serotonin in the brain contribute to an increased risk of suicidal behaviour. This hypothesis was based on the observation that individuals who died by suicide often had lower levels of serotonin or its metabolites in postmortem brain samples. A review of post-mortem brain studies of suicides has found lower levels of serotonin and/or 5-HIAA in the brainstem serotonin neurons compared with psychiatric-matched groups(15). However, subsequent studies have produced mixed and inconsistent results, indicating that the relationship between serotonin and suicide is not straightforward. Some studies find more serotonin neurons as well as increased mRNA expression and more tryptophan hydroxylase 2 in the raphe nuclei of depressed suicides(16), and others find no differences(17).

While serotonin remains a focus, researchers now recognize the involvement of other neurotransmitter systems, such as norepinephrine, glutamate and gamma-aminobutyric acid (GABA). Imbalances in these systems may contribute to the vulnerability to suicide. Alterations in neurotransmitters, such as norepinephrine, have also been investigated in relation to suicide. Imbalances in these neurotransmitter systems were proposed to contribute to emotional dysregulation and impulsivity, both of which are associated with suicidal behaviour. Increased expression of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines, including noradrenaline, has been measured in postmortem Locus Coeruleus (LC) samples from depressed suicide victims (18). Furthermore, more recent research using laser capture microdissection to examine cell-specific expression patterns in depressed suicides revealed that LC astrocytes expressed glutamate transporters less than LC neurons, while LC neurons expressed N-methyl D-aspartate (NMDA) receptor subunits more than LC astrocytes(19).

The disrupted glutamatergic and GABAergic pathway system in brain regions, particularly in the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) also play a role in suicidality. Studies revealed that in suicide patients with depression, GABA type A (GABA(A)) receptors were globally found to be upregulated but not in those without depression and comparing GABA(A) across multiple brain regions from MDD suicides found decreased GABA(A) α and δ subunits in the majority of brain areas investigated in postmortem major depressive disorder (MDD) suicide PFC tissue compared with γ subunits (20). In the glutamate pathway, several proteins (NMDA receptor GRIN2B subunit, AMPA receptor GRIA3 subunit, kainate receptor GRIK2 subunit, glutamate transporters SLC1A2 and SLC1A3, glutamate-ammonia ligase (GLUL)) are found to be associated with suicidal events which were associated with major depressive disorder (MDD) suicide in postmortem analyses of dorsolateral PFC and ACC tissue (20). A drug targeting the glutamate pathway, ketamine, has recently drawn attention for its ability to rapidly treat depressive symptoms. It thus holds great promise as a potential antisuicidal drug, rapidly decreasing suicidal ideation (SI) among patients with treatment-resistant depression and SI.(21) Ketamine acts rapidly within a few hours and has potentially long-lasting effects (up to 3 months post-infusion). However, its mechanism of action is still unclear, with suggestions that it may upregulate insulin-like growth factor 2 in the hippocampus or contribute to maintaining healthy levels of AMPA and NMDA receptor expression. (22)

Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction and Suicide risk

The dysregulation of the stress response system, particularly the HPA axis, resulting in altered stress responses has been proposed as an implicating and contributing factor to suicide. Regardless of the presence or absence of psychiatric comorbidities, HPA axis activity is involved in suicide risk (23). Elevated cortisol levels and abnormal feedback mechanisms in the HPA axis have been observed in some individuals who died by suicide. Chronic stress, traumatic experiences and early life adversities may lead to persistent chronic activation of the HPA axis, resulting in increased release of cortisol and subsequent alterations in brain function. From previous studies, it has been shown that hyperactivity of the Hypothalamic–Pituitary–Adrenal (HPA) axis increases the risk of suicidal behaviour and ideation (24,25). Also, various studies have examined the hypothalamic-pituitary-adrenal (HPA) axis, which is involved in the body's response to stress. However, these studies report inconsistent results. For example, increased levels of cortisol, a stress hormone, have been observed in individuals who died by suicide. A systematic review by Berardelli et al.,(23) revealed that the HPA axis abnormalities, mainly characterized by hyperactivity of the HPA axis, may exert an

important modulatory influence on suicide risk and impaired stress response mechanisms contribute significantly to suicide risk. Thus, targeting HPA axis dysregulation might represent a fruitful strategy for identifying new treatment targets and improving suicide risk prediction. Whereas, some studies found no association between cortisol levels and increased suicide risk (26,27) while others found decreased levels of cortisol in suicide attempters(28,29). Similarly, Roy et al.,(30) discovered that previous suicide attempters had considerably lower cortisol levels than the control group, and those who had tried suicide and had a family history of suicide had the lowest cortisol levels in response to stress. These findings are consistent with other research, demonstrating that blunted HPA axis activity is at least partially associated with suicidal behaviour.

Also, the post-mortem studies in patients who have died by suicide showed a decreased expression of glucocorticoid receptors. The association between HPA axis dysregulation in individuals who died by suicide and those who attempted suicide has also been studied in the postmortem brains of adolescents who died by suicide. The results revealed that the prefrontal cortex (PFC) and amygdala had lower expression of glucocorticoid receptor (GR)-α and GR inducible genes (31). In another study (32), only individuals who died by suicide and had experienced childhood abuse showed lower hippocampus GR expression. The dexamethasone suppression test (DST) examining the negative feedback system of the HPA axis and its dysregulation in suicidal behaviours is another area of interest. It has been shown that DST non-suppression is associated with a 14-fold higher odds of eventual suicide (33). However, the exact mechanisms underlying the HPA axis dysregulation and its relationship to suicide remain unclear. Ongoing research is focusing on refining our understanding of the HPA axis and its role in suicide risk. This includes investigating specific molecular and cellular mechanisms and exploring potential interventions that target the HPA axis to reduce suicide risk.

Neuroanatomical regions implicated in suicide risk

More recent research has expanded the focus beyond neurotransmitters and stress response systems to examine structural and functional brain abnormalities associated with suicidal behaviour. Advances in neuroimaging techniques have allowed researchers to investigate the brain's anatomy, connectivity, and activity patterns in individuals at risk of suicide. New techniques and more accessible services have driven neurobiological research in suicide in fields ranging from neuroanatomical changes linked to suicide risk to genetic bases for suicide and genomic and protein interactions contributing to suicidal behaviour.

Some studies have identified alterations in brain regions involved in emotional processing and regulation, such as the prefrontal cortex, amygdala, and hippocampus. These regions play important roles in decision-making, emotional responses, and memory and their dysfunction may contribute to suicidal behavior (34,35). (Figure 1) Other regions involved included the anterior cingulate cortex and medial orbitofrontal cortex. According to previous meta-analyses, patients with MDD have reduced hippocampal volume(36). Additionally, MDD patients with repeated or intensely strong suicide attempts further displayed significantly smaller hippocampal volumes than patients who had their first suicide attempt, non-suicidal patients, or healthy controls (37). These findings imply that decreased hippocampal volume may be a potential and useful neuroimaging marker to predict suicidality in MDD.

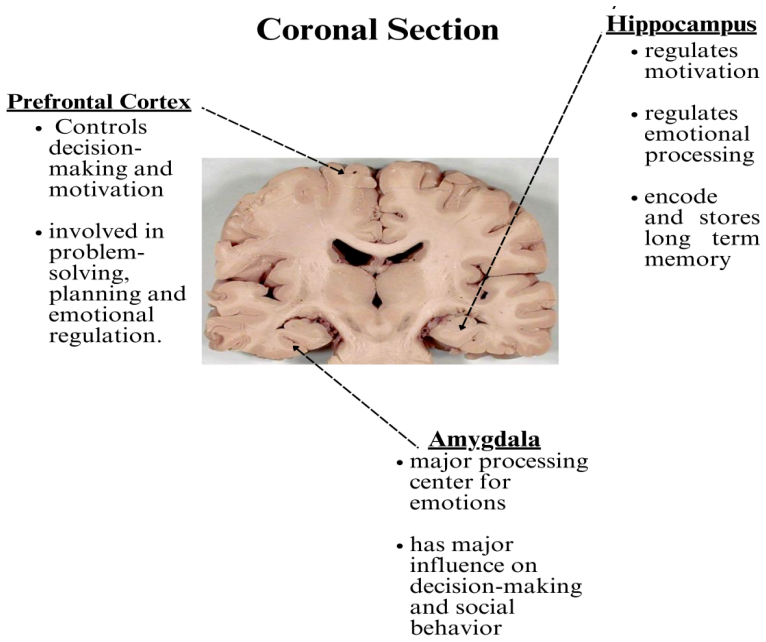

Figure I: Coronal section of the brain highlighting the functions of the prefrontal cortex, hippocampus and amygdala. Alteration in these regions has been implicated in suicidal behaviours.

Furthermore, there are differences in brain surface area and cortical volume between suicide attempters and non-attempters with MDD. A study by Kang SG et al.,(38) revealed that compared with suicide non-attempters, suicide attempters with MDD exhibited a larger surface area in the left postcentral area and left lateral occipital area and a larger cortical volume in the left postcentral area and left lateral orbitofrontal area. Suicide attempters exhibited a smaller surface area in the left superior frontal area than suicide non-attempters. In a more recent study by van Velzen LS et al.,(39) a meta-analysis of data from 21 international studies from ten countries, it was discovered that the surface area of the frontal pole was lower in young people with mood disorders and a history of actual suicide attempts than those without a lifetime suicide. Thus, a lower frontal pole surface area may represent a vulnerability for a (non-interrupted and non-aborted) suicide attempt.

The amygdala is also an important structure in emotional processing and is involved in regulating many behaviours, such as fear and aggression. Postmortem studies have reported a greater basolateral amygdala volume associated with an increase in neurovascular cells in MDD(40). Maheu et al.,(41) also published evidence that amygdala neuroplasticity appears to occur in depression but not in suicide and that proteins associated with neuroplasticity, such as doublecortin and polysialylated neural cell adhesion molecule, were upregulated in basolateral amygdala samples from depressed patients having died naturally or of accidental causes but not in depressed suicides. Thus, the inability to upregulate amygdala plasticity may therefore contribute to suicide.

Genetic factors implicated in suicide risk

Genetic studies have also provided insights into the genetic basis of suicide risk. Certain genetic variations have been associated with increased susceptibility to suicidal behaviour. These genetic factors may interact with environmental influences, contributing to the development of suicidal tendencies. The idea

that individuals may be predisposed to suicide stems in part from the observation of familial aggregation of Suicidal behaviour (SB) which has been observed in several large cohorts including a Swedish national registry-based study (83,951 probands). Offspring of probands having attempted suicide are also at a nearly fivefold higher risk of attempting suicide themselves (42). Likewise, this observation also stems from twin and adoption studies pointing to the heritability of suicidal behaviour between 30% and 50%. Identifying one or several genes or gene variants that may increase predisposition to SBs has been a challenging task. Over 200 genes have been reported as being associated with suicide attempters or suicide death. The genome-wide association analysis by Coon et al., discovered genome-wide significant areas in 43 high-risk families in Utah that suggest numerous genes associated with risk for successful suicide. A total of 207 genes were implicated by the shared genomic segments, which included 30 unique shared genomic segments with genome-wide evidence of segregation with completed suicide. Additional association studies found four significant PsychArray variations (SP110, rs181058279; AGBL2, rs76215382; SUCLA2, rs121908538; APH1B, rs745918508), increasing the possibility that these genes are associated with a higher risk of suicide. Furthermore, from the largest genetic study of suicide attempts to date, researchers have identified a region of the genome on chromosome 7 containing DNA variations that increase the risk that a person will attempt suicide. The two loci that reached genome-wide significance for suicidal attempts were the major histocompatibility complex and an intergenic locus on chromosome 7(43).

Neurotrophins and the Role of Lipid metabolism in suicide risk

The other remote factors that may also be involved in suicide include the Neurotrophins and the role of lipid metabolism. Neurotrophins such as the Brain-Derived Neurotrophic Factors (BDNF) and the mRNA expression levels of both BDNF and its receptor, tyrosine kinase B (TrkB) are decreased in postmortem suicide brains, with concomitant decreases in BDNF and TrkB full-length protein expression(44). Cholesterol has also been investigated as a potential biomarker of suicidal behaviour (SB). Evidence from studies that revealed low cholesterol as a contributor to suicide and SBs includes low cholesterol levels in the brain of people who died by suicide and in the cerebrospinal fluid of suicide attempters. Also, there are high rates of suicide and suicide attempts in individuals with disrupted cholesterol synthesis and metabolism(45).

Neuroinflammatory markers implicated in suicide risk

Emerging evidence suggests that neuroinflammation, characterized by an immune response in the brain, may play a role in suicidal behaviour. Increased levels of pro-inflammatory markers have been found in the brains of individuals who died by suicide, suggesting an association between inflammation and suicide risk. The recent findings suggest the existence of chronic low-grade inflammation in suicidal behaviour and postmortem studies demonstrated associations between suicide and inflammatory cytokines in the orbitofrontal cortex (46). One of the key markers of neuroinflammation is the activation of microglial cells. These cells play a crucial role in the immune response and can release inflammatory substances, such as cytokines and chemokines when activated. A study by Bengoechea-Fortes et al., observed increased microglial activation in the brains of individuals who died by suicide compared to individuals who died from other causes (47). Torres-Platas et al., also observed that depressed individuals who committed suicide have a greater proportion of activated microglia in the anterior cingulate cortex white matter compared with subjects without psychiatric disorders who died from other causes. The post-mortem studies of people who died by suicide found increased inflammation in the brain and cerebrospinal fluid, as well as increased levels of inflammatory cytokines. It has also been

shown that those with the highest levels of inflammatory biomarkers are up to three times more likely to commit suicide. This suggests that neuroinflammation and suicide attempts are probably also related (48). The most significant alterations in inflammatory cytokines that have been found so far concerning neuroinflammation in people who died by suicide are increased levels of interleukin 6 (IL-6), interleukin 1β (IL-1β), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 10 (IL-10), interleukin 13 (IL-13) and tumour necrosis factor (TNF-α) that are activated and produced by microglial cells and astrocytes among others (48).

Future Direction: In the future, more emphasis should be placed on suicide diagnostics and therapeutic options, particularly the interaction between genetic, molecular, environmental, and social factors and therapeutic outcomes. Research should be tailored to individualized treatment approaches based on a person's unique neurobiological profile, specific neuroinflammatory biomarkers and genetic information which could guide personalized interventions. NMDA receptor modulators and glutamate receptor antagonists such as ketamine are another area of interest for potential therapeutic interventions. Future research should be directed to extensively explore the benefits of these medications as a therapeutic option in suicide attempters.

CONCLUSION

It is important to note that the research on the neuropathology of suicide is still ongoing, and our current understanding is far from complete. Suicide is a complex and multifaceted issue influenced by a combination of biological, psychological, and social factors. Further research is needed to better elucidate the neuropathological mechanisms underlying suicidal behaviour and to develop more effective prevention and intervention strategies.

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