Neurobiology of Suicide

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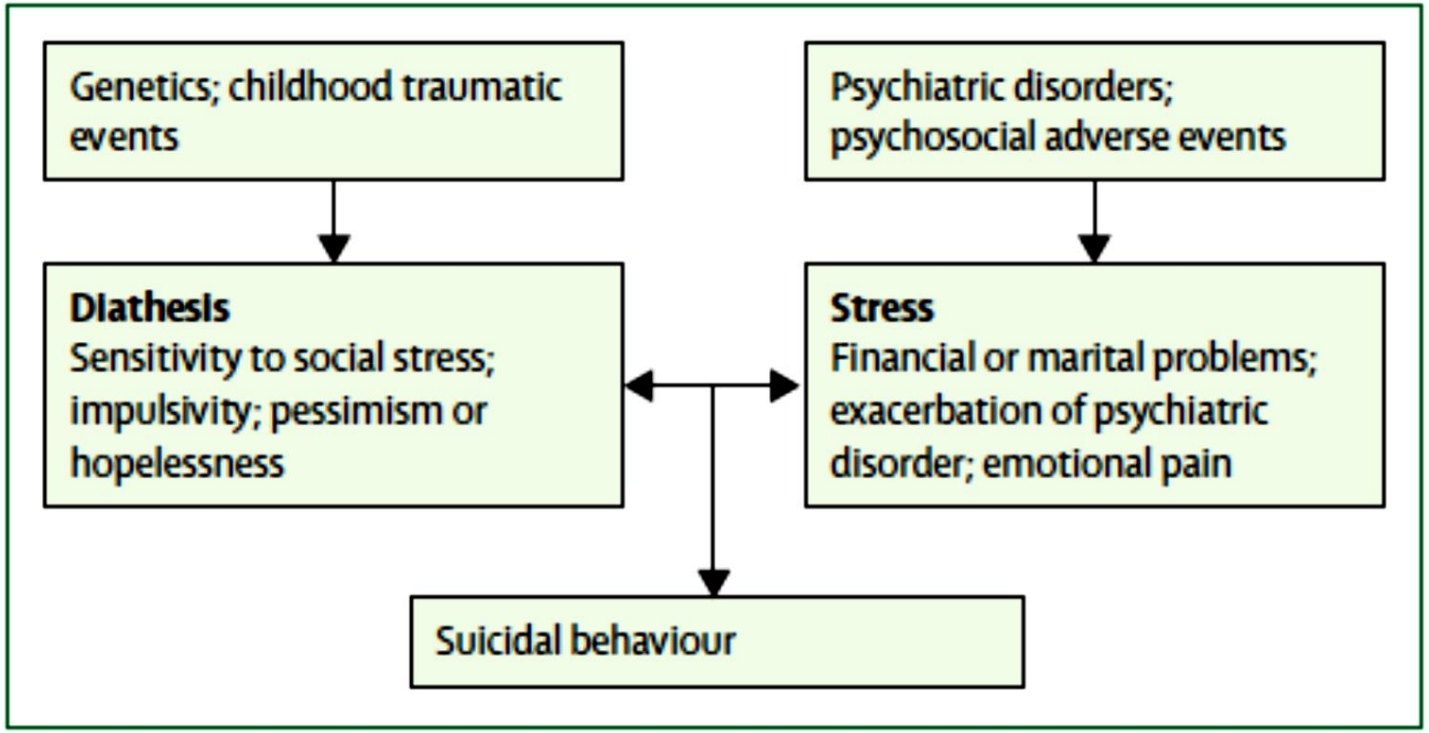
Introduction

- The World Health Organisation (WHO): more 700,000 deaths due to suicide every year.
- India: 14.04/100,000 population; 2.5 times increased in suicide deaths in men (2021 data).
- Complex multifactorial etiology.
- Advances in the fields of genetics, epigenetics, neurochemical and neuroimaging studies has help understand suicidal behaviour.
- Biomarkers (no definite markers yet) might help to inform risk-assessment procedures and treatment choice in the prevention of suicide though clinical predictors are scarce.

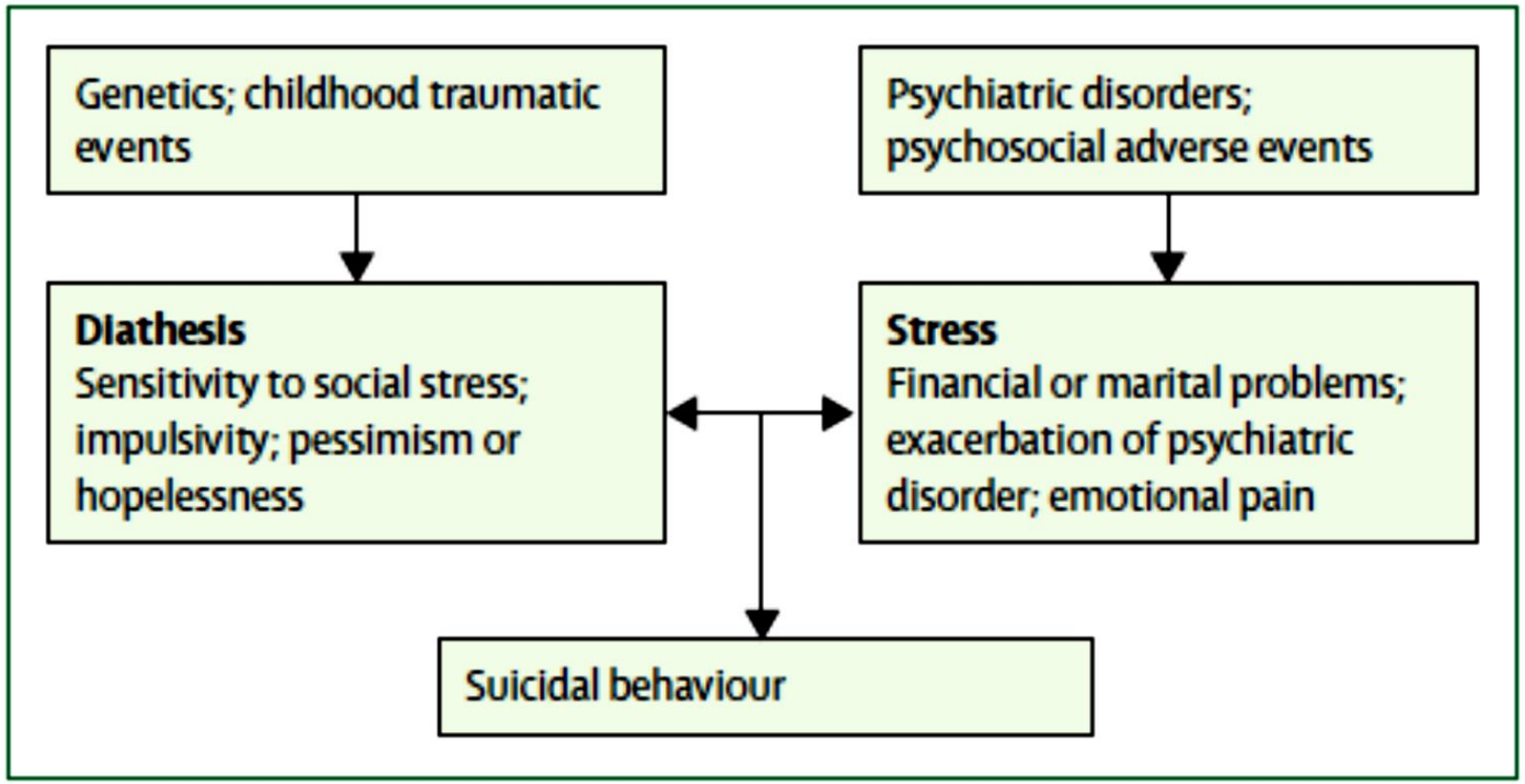


Causes of suicidal behavior: risk factors

- Stressors such as life events and psychiatric disorders are important risk factors for suicide, but the diathesis concept explains why only few individuals exposed to these stressors will take their own life.

- Stress–diathesis model of suicidal behavior: result of an interaction between stressors and a susceptibility to suicidal behavior (diathesis).
- suicidal behavior: heterogeneous and varies in degree of intent and amount of clinical damage done, suicide deaths and non-fatal but highly lethal suicide attempts are similar from demographical, clinical, and neurobiological perspectives, and therefore probably have a common diathesis
- About 50% of the risk of suicide due to diathesis is inherited, and this percentage is possibly higher in women than in men.

The stress–diathesis model of suicidal behaviour



Causes of suicidal behavior: risk factors

- Early-life adversity and epigenetic mechanisms seem to be related to causal mechanisms for this diathesis
- Experience of repeated acts of abuse, particularly physical and sexual abuse, increases risk of suicidal behaviour throughout life.
- Epigenetic mechanisms could explain the association between childhood experiences and reactivity to stressors in later life, mediated in part by the hypothalamic–pituitary–adreno–cortical axis.
- 50% of the risk for suicide or suicide attempts is heritable but specific genes are **not confirmed**.

Mental Illness/disorders as risk for suicide: BPAD

- Risk for suicide: 60 times greater than in the general population
- 25–50% of patients will commit at least one suicide attempt during their lifetime, and 10–20% will complete suicide.
- Earlier onset of the disease is associated with an increased risk of suicide attempts.
- Longer duration of illness positively correlates with a higher lethality of suicide attempts.
- Antidepressants may increase the risk of suicidality in BD patients, particularly in young patients.

Mental Illness/disorders as risk for suicide: BPAD

- Suicide attempts among individuals with BD are associated with

1. Periventricular white matter and deep white matter hyperintensities;
2. Lower grey matter volumes in regions including the ventrolateral prefrontal cortex and the dorsolateral prefrontal cortex (DLPFCx), the right orbitofrontal cortex, the right hippocampus (HIPP) and bilateral cerebellum;
3. Lower left orbitofrontal cortical thickness and white matter fractional anisotropy; and
4. Lower volume in the left ventrolateral prefrontal cortex, right DLPFCx (involved in executive function, particularly voluntary emotional regulation) and bilateral HIPP

Mental Illness/disorders as risk for suicide: BPAD

- Gene polymorphisms - tryptophan hydroxylase 1 (TPH1) and tryptophan hydroxylase 2 (TPH2), were found to be related to suicide attempts of high lethality and completed suicides, respectively.

- Polymorphisms and a low expression of the serotonin receptor 2A (5-HT2A) RNA in the prefrontal cortex have been strongly associated with suicidal behaviour.

- Expression of BDNF is significantly reduced in individuals who commit suicide independently.

Mental Illness/disorders as risk for suicide: Major Depressive Disorder (MDD)

- Mortality from suicide in individuals with MDD is more than 20 times higher compared with the general population.
- Prevalence of suicide ideation - 37.7%; prevalence of suicide plans - 15.1%.
- The increased risk of suicidality in patients with MDD has been associated with inflammatory changes - lowered BDNF or increased interleukin 1ß (IL-1ß), interleukin-6 (IL-6), interleukin-13 (IL-13), tumor necrosis factor (TNF- α), C reactive protein (CRP) and C-C motif chemokine ligand 2 (CCL2), dysfunctions of the HPA-axis, with overproduction of CRH and elevated glucocorticoid production, and structural and functional brain changes

Mental Illness/disorders as risk for suicide: Anxiety disorders

- Causal role of anxiety in suicidality remains unclear.
- Individuals with OCD are at an increased risk for suicide ideation and suicide attempts.
- One patient out of ten with OCD has a lifetime suicide attempt, and nearly half of them suicidal ideation.

Mental Illness/disorders as risk for suicide: Psychotic illnesses

- Schizoaffective disorder is associated with the highest risk of suicide attempt and completed suicide, followed by schizophrenia, first psychotic episodes, least with delusional disorders.
- F-20:

1. lifetime prevalence of suicide ideation - 19.22% to 34.5%,
2. lifetime prevalence of suicide attempts and self-harm is 14.6% to 26.8%
3. 10–22% of patients has complete suicide with the result of death, 20–40% of patients attempt suicide.

- First episode psychosis: 40% of patients experience persistent suicide ideation.

Mental Illness/disorders as risk for suicide: Psychotic illnesses

- Hyperactivity of the HPA-axis- in glucocorticoid neurotoxicity ---tissue damage of different brain regions--- could be underlying causal mechanism of suicidality in individuals with schizophrenia
- Lower cerebrospinal fluid concentrations of the serotonin metabolite 5-hydroxy-indol acetic acid (5-HIAA) and a blunted prolactin secretion in response to the D-fenfluramine test in patients with schizophrenia.
- Decreased expression levels of 2-glutamate-related genes, glutamate-ammonia ligase and glial high-affinity glutamate transporter member 3 (SLCIA3) have also been found in individuals with schizophrenia who commit suicide.
- Polymorphisms in adrenoceptor alpha 2B (ADRA2B) are associated with suicidality among patients diagnosed with schizophrenia.

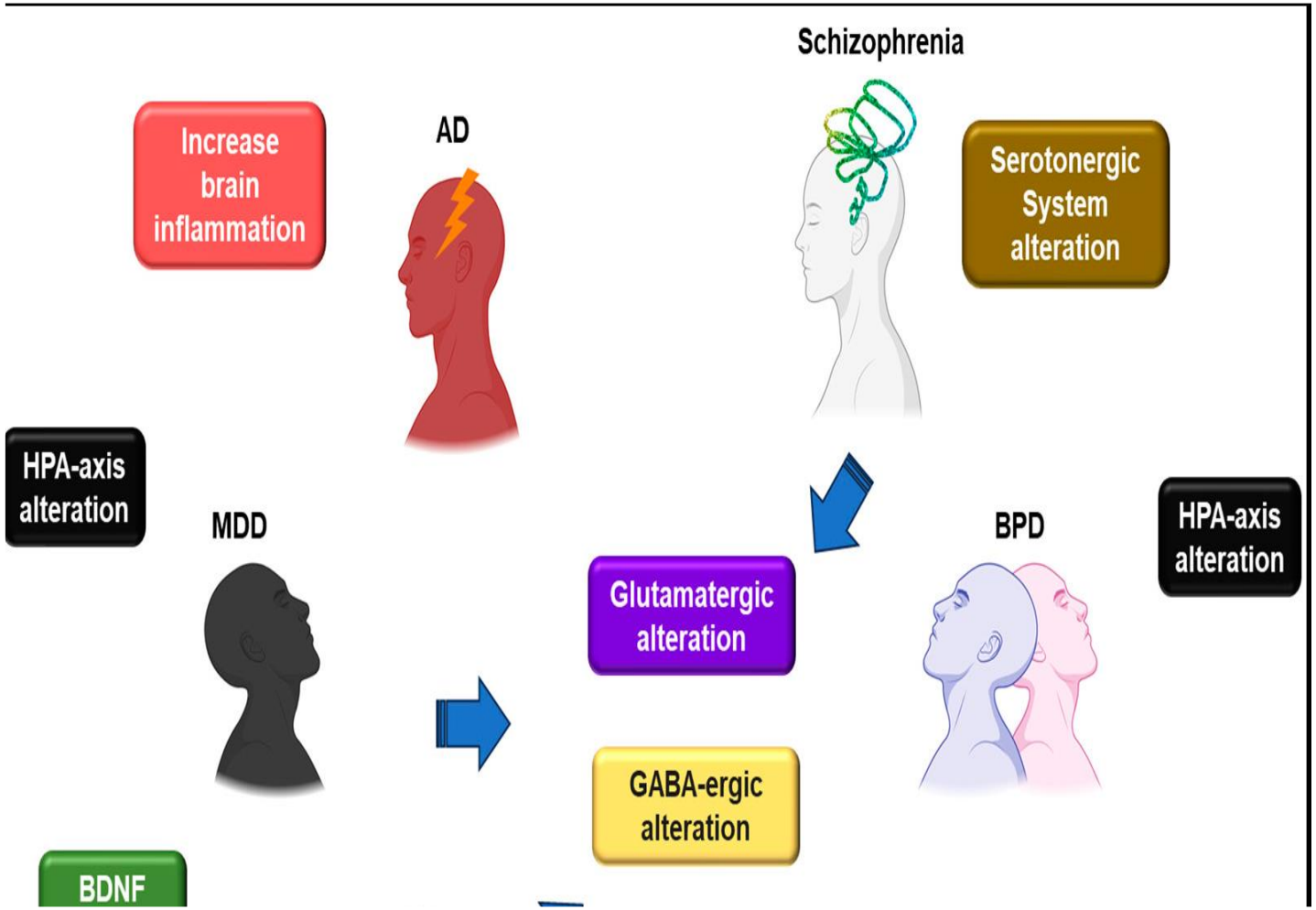
Mental Illness/disorders as risk for suicide: Borderline Personality Disorder (BPD)

- 52-fold increase in suicide rates among BPD individuals compared with the general population.
- At least 75% of patients with BPD attempt suicide.
- 6% of patients with BPD die due to suicide.
- An association exist between BPD and polymorphisms in the serotonergic system, such as TPH-1 (limiting enzyme for 5-HT biosynthesis) in females and serotonin transporter-linked promoter region (5-HTTLPR) in males.

Mental Illness/disorders as risk for suicide: Substance Use Disorder (SDU)

- Alcohol use - associated with a 94% increase in the risk of death by suicide.
- Suicide attempters with opioid and cocaine use disorders - associated with a single nucleotide polymorphism (in the BDNF gene, rs7934165), suggesting a common BDNF-related pathophysiology of suicide attempts and SUD.
- Alterations in the expression of genes involved in glial differentiation and glutamatergic neurotransmission in the dorsolateral prefrontal area were observed in suicide with SUD.

Molecular changes found in the brains of suicide victims with psychiatric disorders. In



Child abuse & early life adversities as risk for suicide

- National Epidemiological Survey on Alcohol and Related Conditions (NESARC), childhood physical and sexual abuse reported suicide attempts in 2.64% of survey respondents.

- Studies have found that children, adolescents, and adults exposed to abuse or neglect during childhood have a 2 to 4-fold increased risk for suicidality, including ideation, plans & attempts.

- Child sexual abuse correlates most strongly with suicidal behaviour.

Child abuse & early life adversities as risk for suicide

- Early-life abuse leads to persistent hyperactivity of CRF and a markedly sensitized pituitary-adrenal and autonomic response, resulting in heightened stress responses.

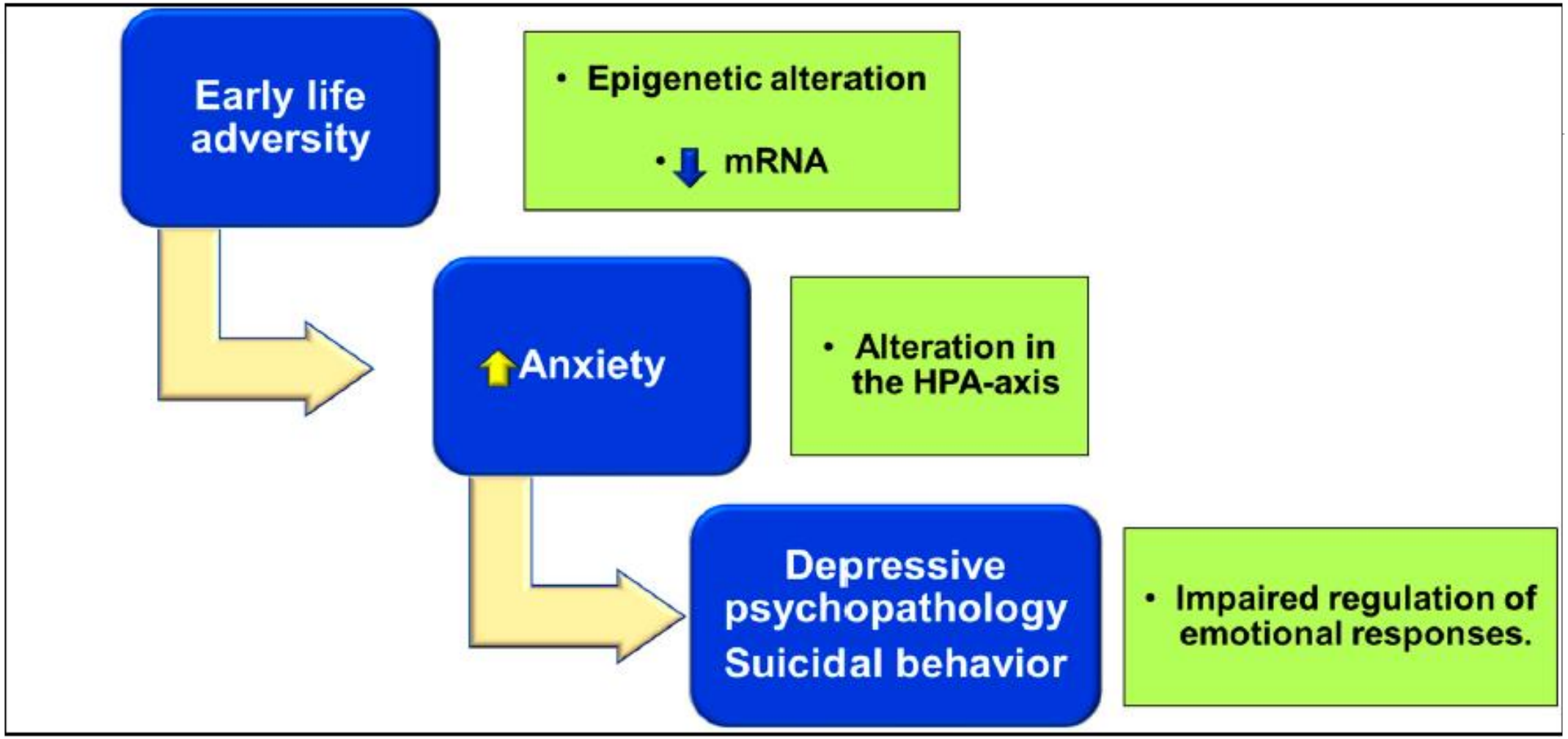
- Childhood maltreatment - lower grey matter volumes, decreased thickness, and hypoactivation in the ventral, medial, and dorsal prefrontal cortex, including the orbitofrontal and anterior cingulate cortices, HIPP, insula, and striatum.

- Disrupted white matter structural integrity - cognitive impairments, the disruption of emotional regulation, and an increased risk of suicidality.

Child abuse & early life adversities as risk for suicide

- Polymorphism of genes:

1. Corticotropin-releasing hormone receptor 1 (CRH1) and 2 (CRH2),
2. FK506 binding protein 5 (FKBP5), and
3. Corticotropin-release hormone binding protein (CRHBP); constitute specific mediators between childhood maltreatment and suicidality.



Flowchart linking early life adversity and suicidal behavior

Hypothalamic-Pituitary-Adrenal Axis and Suicide

- Early life stress has been associated with an aberrant HPA-axis activity in adulthood.
- Childhood trauma increases the risk of suicidal ideation ---linked to HPA axis dysregulation.
- Amygdala (AMY) samples used to analyse changes in the FKBP5 and Nr3c1 in suicide victims compared with controls-- found a statistically significant reduction in the targets' gene and protein expression in this brain region intensely involved in emotional regulation.
- No hard evidence of HPA axis dysregulation & suicide & early life adversities.

Neuro-inflammation and Suicide

- Higher concentrations of chemokine (C-X-C motif) ligand 1 (CXCL-1) in the serum of patients with suicide risk than non-suicidal patients.
- In these patients, the higher suicidal risk was associated with adulthood adversity and not early life stress.

Neuroinflammation: cytokines in suicide

- Cytokines - interleukins (IL), interferons (IFN), and tumor necrosis factor (TNF) play pivotal roles as signaling proteins mediating innate and adaptive immune responses
- T-cell derived cytokines from the Th1 lineage are involved in cellular mediated immune processes (IL-1α, IL-1β, IL-2, IFN-γ, TNF-β).
- Th2 lineage promote humoral immune response (IL-4, IL-6, IL-10) and are implicated in allergic reactions.
- Certain cytokines can be functionally categorized as pro-inflammatory (IL-1, IL-6, TNF-α) or anti-inflammatory (IL-4, IL-10, IL-13)
- The cytokine most frequently associated with suicidality is elevated levels of IL-6 in CSF or blood

Neuroinflammation: cytokines in suicide

- Tumor necrosis factor α: found higher TNF-α associated with suicidal behavior, suicidal ideation or suicide.
- Interleukin-2 and interleukin-2 soluble receptor (sIL-2R): IL-2 levels were lower in depressed suicide attempters than depressed non-attempters and healthy controls.
- Interferon-γ—Higher levels of IFN-γ were found in depressed patients with suicidal ideation compared to depressed non-suicidal and healthy controls.
- Decreased levels of VEGF in suicide completers.

Neuropeptides and Suicide

- Oxytocin – concentration significantly reduced in suicide attempters.
- Neuropeptide Y – resilience related peptide; potential biomarker
- There is a statistically significant decrease in the neuropeptide Y (NPY) gene expression and an increase in the gene expression of its receptors NPY1R and NPY2R in PFC & Hippocampus brain regions in depressed suicide victims.

Serotonergic System Alteration & Suicide

- In schizophrenia & depression patients with suicidal attempts: the dorsal raphe nucleus (DRN), where the primary neurons innervate the prefrontal cortex, a decrease in the total number of 5-HT1A receptors.
- The serotonin transporter (5-HTT) is responsible for the sodium-dependent serotonin reuptake, and the 5-HTT gene is located at the 17q11.1-q12 locus.
- Postmortem studies have found a significant frequency of the long allele of the 5-HTT gene in depressed suicide victims.
- Multiple studies but no concrete evidence to point solely to the serotoninergic system.

Endocannabinoid System and suicide

- The endocannabinoid system (ECS) has emerged as a potential target in psychiatric disorders because it regulates emotional responses.
- Higher frequency of single nucleotide polymorphisms (SNP) of the CB1r gene (CNR1) was found in patients with MDD and schizophrenia.
- CB2r in the central nervous system has a role as a possible anxiolytic and antidepressive target.
- G protein-coupled receptor 55 (GPR55) – target of endocannabinoids , with preliminary results suggesting that early life stress induces changes in GPR55 gene expression in mice.
- Postmortem studies: CB2r and GPR55 gene expression was significantly lower in the DLPCx of suicide victims but had higher CB2r protein expression.
- Elevated levels of anandamide (AEA) and N-palmitoylethanolamine (PEA) in the serum of suicide attempters with alcohol dependence compared to controls.

Epigenetics of Suicide

- DNA methylation is the most studied epigenetic modification in the mammalian genome.
- Covalent attachment of methyl group to cytosine residues by DNA methyltransferase enzyme renders a substantial change in information processing during gene expression.
- Stable and commonly present on adjacent CpG dinucleotide (CpG islands) in the mammalian genome.
- Repressive in nature: stops gene expression at the promoter region

Epigenetics of Suicide

- Work started with the monoaminergic system.
- Focus shifted to other molecular pathways:

1. Noradrenergic,
2. Glutamatergic and
3. Γ-aminobutyric acid (GABA) neurotransmission, polyamine system in post-mortem brains (Fiori and Turecki, 2010).

Epigenetics of Suicide: Involvement of GABAergic system

- Hyperactivity of DNA methyltransferase (DNMT-3B) gene in the frontopolar region with an observed hypermethylation status of GABAA α1 subunit in suicide brains ⟶ GABAA α1 subunit downregulation in suicide brain
- ⟶ GABAergic expression deficit ⟶ underserved hedonic and decision-making capabilities of prefrontal cortex in suicidal behavior as part of the impaired cognitive processes.

Epigenetics of Suicide: Involvement of polyamine system

- Polyamines are ubiquitous aliphatic molecules containing two, three, and four amine groups.
- Include agmatine, putrescine, spermine, and spermidine; each of which is incorporated into a highly regulated signaling pathway.
- Functions: neurotransmitter by binding to NMDA, acetylcholine, imidazoline, and serotonin receptors.
- Properties: antidepressant, anxiolytic, anticonvulsant, anti-inflammatory, and neuro-protective properties.

Epigenetics of Suicide: Involvement of polyamine system

- SAT1 gene: synthesizing spermidine/spermine N1-acetyltransferase, a rate-limiting enzyme in polyamine catabolism from polyamine system in the brain

- Promoter DNA methylation & downregulation enzyme 'SAT1' from the polyamine system across three major Brodmann Areas (BA 4, 8/9 and 11) in suicide completers.

- Other polyamine pathways related genes: ornithine decarboxylase antizymes 1 and 2 (OAZ1 and OAZ2), arginase 2 (ARG2), and AMD1; mainly in BA 44 of suicide completers with mood disorder background.

Epigenetics of Suicide: Involvement of neurotrophic system

- Initial studies- hippocampus & the dysfunctional serotonergic system with suicidal behavior.
- Orbitofrontal and dorsolateral prefrontal cortex based structural abnormalities in suicide victims with impaired neuronal plasticity.
- Brain Derived Neurotrophic Factor (BDNF) - neuronal growth, differentiation, and maintenance during brain development.
- Adult brain - pivotal role in shaping the structural, morphological, and synaptic plasticity.
- Tropomycin receptor kinase B (TRKB): is the cognate receptor of BDNF.
- Significantly diminished expression of both BDNF and TRKB genes in prefrontal & hippocampal neurons of adult suicide subjects with impaired neuronal plasticity.

Epigenetics of Suicide: Involvement of neurotrophic system

- Wernicke's area of prefrontal cortex, representing BA 21 and 22 - semantic thinking and decision making; mostly affected in suicidal behavior.

- Hypermethylation of Exon 4 promoter region of BDNF leading to deficient BDNF expression - correlates with functional impairments in associative and neurocognitive processing of suicidal brain.

- High magnitude of transcriptional repression observed for TRKB.T1 isoform in frontal cortical areas of suicide completers due to DNA methylation.

Epigenetics of Suicide: Involvement of hypothalamus-pituitary-adrenal (HPA) axis

- Dysregulated glucocorticoid receptors (GR) dampens negative feedback regulation mediated by glucocorticoid hormone in ascribing a hyperactive HPA axis response under stress environment
- Linked with early childhood adversity (childhood abuse, maternal separation or nutritional deprivation).
- Altered DNA methylation profile of GR promoter in hippocampus.
- Works as a stable epigenetic signature to heterochromatinize the conformation of GR promoter and impeded the binding of NGF1-A transcription factor in adulthood.

Epigenetics of Suicide: role of micro RNA

- 21–23 nucleotide regulatory ncRNAs that either repress translation or inhibit the stability and deployment of their target RNAs.
- Specialized roles in neural development, maintenance of mature neural traits, synaptic and neural network plasticity & memory function.
- Numerous miRNAs are expressed in specific neuronal subtypes, particularly in the neocortex and the cerebellum.
- Alterations in miRNAs have been implicated in a diverse range of neurological and psychiatric conditions, particularly those associated with prominent developmental components to pathogenesis.

Epigenetics of Suicide: microRNA

- Glucocorticoids regulate the hypothalamic-pituitary-adrenal (HPA) axis through a negative feedback mechanism while binding to soluble glucocorticoid receptors (GRs) in the pituitary and the hypothalamus; inhibit the release of corticotropin-releasing factor and adrenocorticotropic hormone.
- Expression of GRs is downregulated in depression.
- GR protein is under constant regulation by miRNAs, specifically, miR-124a and miR-18a
- There is miRNA expression downregulation in prefrontal cortex; can be a molecular signature of depressed suicidal subjects.

Way forward

- Better understanding of suicidal behavior
- Prevention of suicidal attempts
- Development of peripheral biomarkers
- Personalized treatment.

Conclusion

- Suicide is a multifaceted and multifactorial behaviour
- Impaired stress adaptation is what makes suicidal ideation appear
- Impaired stress adaptation coupled with fearlessness about death and high pain tolerance is predictive of capability of suicidal act
- A lot of neurobiological factors interact to prepare the person prime for suicide but the trigger event is probably supplied by environment (macro & micro).
- Biomakers are the way forward & personalized medicine will hold the key for prevention & treatment.

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- What could be the probable explanation for increased incidence of suicide in teens & young adults with the onset of spring?

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