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Neuropathology of suicide: recent findings and future directions

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Abstract

Suicide is a major public health concern and a leading cause of death in most societies. Suicidal behaviour is complex and heterogeneous, likely resulting from several causes. It associates with multiple factors, including psychopathology, personality traits, early-life adversity and stressful life events, among others. Over the last decades, studies in fields ranging from neuroanatomy, genetics, and molecular psychiatry have led to a model whereby behavioural dysregulation, including suicidal behaviour, develops as a function of biological adaptations in key brain systems. More recently, the unravelling of the unique epigenetic processes that occur in the brain has opened promising avenues in suicide research. The present review explores the various facets of the current knowledge on suicidality, and discusses how the rapidly evolving field of neurobehavioural epigenetics may fuel our ability to understand, and potentially prevent, suicidal behaviour.

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General model of suicide risk

The last decade has seen intensified research on suicide and suicidal behaviours (SB). Despite an increased understanding of the factors at play, suicide continues to place a great burden on all societies. Global prevalence of suicide continues to be high, with an annual global age-standardized suicide rate of 11.4 per 100,000 people, which translates to approximately 800,000 people dying by suicide every year.[1] This number does not take into account the other forms of suicidality, such as suicide attempts (SA) and suicidal ideation (SI) (12-month prevalence approximately 25 and 175 times the prevalence of suicide fatalities, respectively[2]). While the extent and characteristics of the relationship between these phenotypes and suicide are not entirely established, they also represent a burden and public health concern in their own right. Up to one third of individuals with SI have a SA within one year; individuals who have had a SA have a 16.3% risk of repeated SA and 1.6% risk of suicide within the year.[3] Anxiety disorders, impulse-control disorders, mood disorders, and alcohol abuse or dependence may partially facilitate the transition from SI to SA,[4,5] and axis I psychiatric disorders are present in the vast majority of suicide fatalities at the moment of death, as determined by medical records and/or psychological autopsy reports.[6,7] Psychiatric disorders are thus key proximal factors in building suicide risk,[5] with various disease characteristics being associated with increased risk, but particularly depressed mood. For example, in patients with schizophrenia (SCZ), suicide risk is associated with depressive features and insight.[8] In bipolar disorder (BD), risk of suicide is heightened during mixed episodes and major depressive episodes, as well as during the early stages of illness,[9] while in the case of major depressive disorder (MDD), the number, duration, and intensity of major depressive episodes are determinants of suicide risk.[10-12] Depression therefore represents a major confounder in all suicide studies, particularly in biological analyses of SBs, where discrete disease-related contributions to suicide risk have not been clearly identified, and the majority of studies include samples derived from individuals with depression and SB, often without non-depressed suicide controls.

The recent call to action by the World Health Organization[1] has given additional momentum to the field of suicide research, and multiple models have been proposed to describe the events leading to a suicide. The relative contributions of distal versus proximal factors, as well as the strength of association of individual factors, such as early-life adversity (ELA),[13,14] and mediating factors, such as anxious or impulsive personality traits,[15,16] are described differently depending on the model favoured.[17-21] Despite their differences, these models have many commonalities, highlighting the complex, multifactorial nature of suicide and SB.[5,21] (Figure 1) A key consideration in explaining the impact of psychological traits and experience on suicidality is that biological changes underpin behavioural changes.[22] Efforts to understand the biological factors that contribute to suicide focus on describing the processes involved in eliciting behavioural change and identifying potential targets to alter unhealthy behaviours. An important research avenue has been the search for clinically-applicable biomarkers for suicide, as these would allow healthcare practitioners to specifically address SB in those most at risk.[23] New techniques and more accessible services have driven neurobiological research in suicide in fields ranging from neuroanatomical changes linked to suicide or heightened suicide risk to genetic bases for suicide, and genomic and protein interactions contributing to SB.

Genetic contributors to suicide risk

Most accepted models of suicide risk distinguish between predisposing (distal, or diathesis) factors and precipitating (proximal, or stress) factors.[21] The idea that individuals may be predisposed to suicide stems in part from the observation of familial aggregation of SB, which has been documented since the 1980s,[24] and which has been observed in a number of large cohorts including a Swedish national registry-based study (83,951 probands)[25] and twin and adoption studies pointing to a heritability of SB between 30–50 %.[26-28] Offspring of probands having attempted suicide are also at a nearly 5-fold higher risk of attempting suicide themselves.[29] Although many other psychiatric conditions associated with SB are also heritable, severe SBs (suicide and SAs) appear to be transmitted independently of Axis I and Axis II disease.[15,16,30,31] When heritability is corrected for transmission of psychiatric disorders, specific heritability is between 17–36%.[26] Such evidence for family clustering of SB, even after correction for transmission of other psychiatric conditions, suggests there is a genetic predisposition to SB and has fuelled research into genes associated with SB.

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 SA or suicide death, with the rate of discovery of new SB candidate genes increasing exponentially in the last decade.[32] Pre-existing knowledge of biological systems likely to be associated with SBs, such as rate of serotonin synthesis, decreased serotonergic neurotransmission, and neurotrophic factors, have driven extensive candidate-gene studies.[33-36] Results from these studies have generally not been consistent, leading to decreased enthusiasm for genetic variation studies focusing on single genes over the last decade in favour of genome-wide association studies (GWAS), which use a less-biased, gene-discovery based approach.[37] Despite major technical developments in our capacity to effectively and quickly investigate the genome, a major challenge in GWAS is the tremendous number of samples required to detect genetic variants that account for a very small proportion of the total phenotypic variance. As a result, genome-wide significance of GWAS studies of SB has remained elusive. The existing GWAS studies that have directly or indirectly examined SB[38-49] have nonetheless pointed to a number of variants that, while not achieving genome-wide significance, may be interesting targets for future studies of SB. (Supplementary Table 1)

Due to the relative rarity of death by suicide, suicide was not often used as a phenotype in GWAS studies of SB. The first of two studies using suicide as a primary phenotype[38] compared single nucleotide polymorphisms (SNPs) in 68 suicides vs. 31 psychiatrically healthy controls, and identified suggestive evidence for SNPs in or around 19 genes. Seven of these genes were differentially expressed in brain tissue of a partially overlapping sample of 18 suicides and 21 controls.[38] The second study investigated SNPs in a larger sample comprising both completed suicides and live subjects with SA (N = 577) compared with psychiatric or healthy controls without a history of SA (N = 1,233).[39] Although no result reached genome-wide significance, seven of the nine suggestive SNPs observed in the analysis comparing suicides versus individuals without SB (N = 317 Cases vs. 1,233 Controls) mapped to the TBX20 gene, which among other functions is a transcription factor with identified roles in the CNS.[39,50] Among the other GWAS studies published, SAs and/or SI were used as phenotypes. Among the numerous SNPs identified through these studies, 15 SNPs have shown evidence of at least a trend

toward significance between case and control groups (*P*-values<10^{-6}; see shaded cells in Supplementary Table 1). Of note, only SNPs in or near three genes appear to have reached genome-wide significance, one located near the *ACP1* gene,[45] one located within *ABI3BP*,[41] and one located within *PAPLN*,[40] and all of these have been described to regulate the extracellular matrix and collagen-binding. Among the other hits that did not reach genome-wide significance, genes had ascribed functions in cellular assembly and organization, nervous system development and function, cell death and survival, immunological disease, infectious disease, and inflammatory response.[39]

An outstanding concern regarding the results from GWAS studies is the lack of reproducibility of results. To a large degree this may be explained by the generally small samples investigated by GWAS studies of SB. Recently, attempts have been made to describe polygene effects,[46,48] and a recent study identified 750 genes linked to neurodevelopment that appeared to selectively drive SBs, independently from schizophrenia or MDD diagnosis.[48] Analysis of genes associated with psychopathologies and SB identified several pathways of interest (cell adhesion/migration, small GTPase and receptor tyrosine kinase signalling) and identified genes that have been independently associated with SBs, such as BDNF and NTRK2, among others. If replicated, these results could support using polygenic analyses to bridge results from GWAS studies with other studies that have already provided suggestive evidence of genetic associations with SBs.

Collectively, GWAS studies show that despite a great deal of enthusiasm and the potential to uncover novel genetic contributors to SBs, as observed for other psychiatric phenotypes, individual gene variants are likely to account only for a very small proportion of the total phenotypic variability. Other factors, such as the environment, behavioural traits, life trajectories, and coping mechanisms, are essential regulators of suicide risk, and likely to account for more sizeable effects.[5]

Functional genomics of biological circuits implicated in suicide

Our understanding of how the genome is regulated, in particular through a variety of epigenetic mechanisms, has contributed to one of the most meaningful changes to the neuroscience landscape in the past 15 years.[51] The investigation of biological processes underlying SB has greatly benefitted from the study of these mechanisms (Figure 2), which allow for a fine-tuning of biological responses, and offer an intuitive explanation for the impact of experiences into altered behavioural phenotypes. Adjusting physiological and behavioural responses to environmental cues is essential for adaptation, but in cases of childhood maltreatment or abuse, such adaptations can have detrimental effects.[52,53] Early-life adversity (ELA), defined as neglect or physical or sexual abuse during childhood, has profound and long-lasting effects on the development of psychological and cognitive traits associated with increased risk of suicidality.[54,55] Further, a significant proportion of individuals exhibiting SB have a history of ELA.[52,56-58] Biological mechanisms for the translation of such traumatic experiences into behaviour have been proposed to be principally regulated by altered DNA methylation and histone modifications.[59] Such regulation of expression and function of molecules has the potential to drive pathological processes, partly because they change over the life course. Global study of methylation in brain tissues indicates

that suicide is associated with widespread changes in methylation patterns of neurotrophic and neuroprotective factors in the hippocampus and prefrontal cortex.[60,61] Continued technological improvements have made sequencing approaches more affordable and are bringing high-resolution whole-methylome analysis within reach.[62]

Mechanisms that affect the architecture and expression of the genome as a function of life experiences differ among brain regions and cell types. Accordingly, understanding suicide neurobiology requires integrating brain region- and cell type-specific processes into global patterns of brain activity dysregulation. Structural and functional alterations affecting depressed patients mainly derive from neuroimaging studies, and histological investigations of postmortem brain samples. These studies have provided evidence that some brain cells and circuits are selectively associated with suicide. In the following sections, we aim at articulating changes in genomic and epigenomic functions within brain regions most consistently implicated in mood disorders and suicide, most notably: brainstem monoaminergic systems, the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the amygdala, and the hippocampus (Figure 3).

Neurotransmitters and neuromodulators

New findings on monoaminergic systems, hippocampal function and suicide

The entire brain receives monoaminergic innervation from 5-HT and noradrenergic neurons located in raphe nuclei and the locus coeruleus (LC), respectively. 5-HT neurons have long been implicated in depressive disorders and suicide,[63] with substantial evidence suggesting impaired serotonergic function,[64-66] as summarized in recent exhaustive reviews.[23,35,67,68] Among other findings, studies found that depressed suicide completers show in dorsal raphe nucleus decreased levels of the serotonin metabolite, 5-HIAA,[35] as well as more 5-HT neurons[19,69] and increased mRNA expression and protein levels of tryptophan hydroxylase (TPH, the rate-limiting enzyme in the synthesis of 5-HT[70-73]). Upregulation of TPH activity and increased numbers of 5-HT neurons, have been interpreted as mechanisms compensating for an overall reduction in 5-HT transmission, a finding that has been supported by imaging studies.[74,75] In addition to brain tissue, several studies have shown that low levels of 5-HIAA can also be observed in the CSF in the context of SB.[76]

Due to their high rate of co-occurrence, a major obstacle has been isolating factors specifically responsible for SB, rather than depression.[13] Some studies have successfully distinguished changes associated with depression from those associated with suicide, identifying small changes in serotonin transporter (SERT) and receptor expression (5-HT_{1A}), as well as indications of serotonin genotypes and expression patterns that may be specifically linked to suicidality.[13,74,77,78] The characterization of personality traits linked to suicide has shown that impulsive/aggressive phonotypes may be associated with altered serotonin levels, especially in the context of ELA.[79] Recently, studies have pointed towards epitranscriptomic dysregulation of serotonin signaling in suicide and SB (see below, and [80,81]). In the future, researchers will face the challenge of exploring the psychopathological significance of complex interactions between multiple serotonin and other monoamine receptor types (e.g. 5-HT_4, 5-$HT_{1B,}$ 5-

HT_{2B}), and associated adaptor proteins (p11, S100α), that are currently emerging from animal research.[82-86]

Deficits in noradrenergic transmission have similarly been recognized in depression for decades[87]. In analogy with aforementioned findings regarding 5-HT neurochemistry, increased expression of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines, including noradrenaline, has been measured in postmortem LC samples from depressed patients[88,89] (see also [90]). Although one report has indicated significant reductions in the total number and average density of pigmented LC neurons in the left side of the brainstem in suicide completers,[91] most morphological studies of the LC have found no differences between MDD and control subjects.[90,92,93] Recent studies using laser capture microdissection to analyze cell-specific patterns of expression in depressed suicides showed decreased expression of glutamate transporters by LC astrocytes,[94] as well as upregulated expression of NMDA receptor subunits by LC neurons. As proposed by the authors, this increased glutamatergic activity in the LC may account for the fast-acting antidepressant properties of NMDA antagonists.[95]

At the neuroanatomical level, the role of monoamines in depression and suicide has been largely investigated in the context of its relationship to hippocampal neurogenesis, a major substrate of mood regulation and antidepressants mode of action. Stockmeier et al.[96] have reported increases in the mean densities of pyramidal neurons and glial cells in cornu ammonis (CA) regions and in the DG granule cell layer, with accompanying reductions in the mean soma size of these cells in samples from MDD subjects versus controls. In MDD patients, hippocampal volume is reduced,[97] and this phenomenon can be partly counteracted by antidepressant treatment.[98] Hippocampal shrinkage has been hypothesized to result in part from decreased adult neurogenesis in the dentate gyrus (DG). Abundant preclinical research has shown that adult animals exposed to chronic stress and displaying depressive-like behaviours have decreased hippocampal neurogenesis.[99] Inversely, ECS,[100] a model of ECT, or conventional antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs), potently increase neurogenesis in the DG.[101] In turn, this improves stress regulation[102] and is sufficient to reduce anxiety- and depressive-like behaviours in mice.[103] Postmortem studies have also suggested that progenitor proliferation is increased by antidepressant treatment, while the expression of proliferative markers in DG samples was similar between untreated depressed patients and controls.[104,105] The same group reported significant reductions in DG granule cell numbers in anterior (but not posterior) hippocampal samples of untreated MDD patients compared to matched controls.[106] In the absence of changes in numbers of progenitor cells, these results suggest depression-associated impairments in granule cell neuron maturation or survival, and support the notion that decreased adult hippocampal neurogenesis contributes to hippocampal volume loss in depression.

The GABAergic and glutamatergic systems

Transcriptomic studies designed to identify dysregulated genes in individuals who died by suicide have repeatedly pointed towards disrupted glutamatergic and GABA-ergic pathways in several brain regions,[62,107-113] particularly in the PFC and the ACC. These two brain regions have been consistently

implicated in MDD by spectroscopic,[114-116] structural,[117-119] and functional studies.[120-122] The PFC is essential for executive function,[123,124] while the ACC plays important roles in stress responses [125] and the integration of cognitive activity with affective experience. Ultimately, changes affecting excitatory and inhibitory transmission in these structures are thought to underlie abnormalities documented in neuroimaging (e.g. hypoactivity[126-128] and loss of grey matter volume[129] in the PFC), and neuroanatomical (e.g. reduction in third-order branching of basilar dendrites of layer VI pyramidal neurons in dACC[130]) studies.

In microarray studies, GABA type A [GABA(A)]receptors were globally found to be upregulated in suicides with depression, but not those without depression.[111,112] However, a study 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,[131] and a recent study identified a transcript for the GABA(A) receptor γ2 subunit (GABRG2) that was downregulated in postmortem MDD-suicide PFC tissue.[132] Of interest, GABA(A) receptor expression may be differentially regulated through altered DNA methylation levels and downregulated DNA methyltransferase (DNMT) in the frontopolar cortex of suicide brains.[133] Follow-up studies focusing on these receptors are required to better interpret their relationship with SB.

In the glutamate pathway, a number of proteins are found to be associated with suicidal events, including the NMDA receptor GRIN2B subunit, which was found to be associated with SA in a GWAS,[48] the AMPA receptor GRIA3 and the kainate receptor GRIK2 subunits, which were associated with treatment-emergent suicidal ideation (TESI) in a GWAS,[40] the glutamate transporters SLC1A2 and SLC1A3, and the glutamate-ammonia ligase (GLUL), which were associated with MDD-suicide in postmortem analyses of dorsolateral PFC and ACC tissue.[111,112] In studies distinguishing between MDD and MDD-suicide, GRIN2B, GRIK3 and GRM2 were specifically upregulated in the dorsolateral PFC of suicides,[134] while astrocytic components of the glutamate pathway in this same brain region, including GLUL, were downregulated.[135] In the ACC, neuronal components of the glutamate pathway were upregulated.[135]

A drug targeting the glutamate pathway, ketamine, has recently drawn attention for its ability to rapidly treat depressive symptoms.[136-138] It also holds great promise as a potential anti-suicidal drug, rapidly decreasing SI among patients with treatment-resistant depression and SI.[139-141] Ketamine acts rapidly (within a few hours) and has potentially long-lasting effects (up to 3 months post-infusion).[141] However, its mechanism of action is still unclear, with suggestions that it may inhibit astrocyte secretion of BDNF,[142] upregulate insulin-like growth factor 2 in the hippocampus,[143] or contribute to maintaining healthy levels AMPA and NMDA receptor expression.[144] Although ketamine is an NMDA antagonist, recent studies in rodents show that its antidepressant-like effects appear to be mediated by an activation of AMPA signalling.[145] Activation of AMPA receptors by ketamine may occur through inhibition of glycogen synthase kinase-3 (GSK3),[146] which could be partially mediated by the ketamine-induced upregulation of mouse microRNA clusters miR448-3p and miR764-5p, miR1264-3p, miR1298-5p and miR1912-3p, all of which are linked to the serotonergic (5HT)-2C receptor (5HTR2C).[147] Ketamine may therefore act in part through microRNA modulation, but the impact of such an effect on SB remains to be determined.

Finally, it is worth noting that overall modifications of the excitatory/inhibition imbalance in the context of depression and suicide may also stem from changes in cellular phenotypes, a form of cellular plasticity that has been recently documented in the amygdala. The amygdala is important in emotional processing and is involved in regulating many behaviours, such as fear and aggression.[148] Neuroimaging studies have associated MDD with increases in amygdalar blood flow and glucose metabolism,[126] as well as altered volume.[149,150] Postmortem studies have reported a greater basolateral amygdala (BLA) volume associated with an increase in neurovascular cells in MDD.[151] Maheu and colleagues also published evidence that amygdalar neuroplasticity appears to occur in depression, but not in suicide.[152] Proteins associated with neuroplasticity, such as doublecortin (DCX) and PSA-NCAM, were upregulated in BLA samples from depressed patients having died naturally or of accidental causes, but not in depressed suicides.[152] The inability to upregulate amygdalar plasticity may therefore contribute to suicide. In agreement with this, numbers of somatostatin neurons are decreased in the amygdala of women with MDD, possibly attributable to a change in phenotype rather than to cell loss.[153]

Glial and immunological contributors to suicide risk

While glial cells account for the majority of cells in the human brain, their potential association with suicide has been investigated relatively recently. Overall, findings point towards reductions in macroglial cell (mainly astrocytes and oligodendrocytes) densities[109,154,155] or soma size,[156] while microglial cells appear to show enhanced activation and recruitment.[157] In the subgenual ACC and in the amygdala, an overall glia reduction was initially documented.[158] Comparable findings in the dorsal ACC (dACC) were subsequently made by some investigators but not by others.[159] The latter study found similar glial densities between samples from depressed suicides and controls, but significantly increased density in samples from individuals with co-morbid alcohol dependence.[159]

In the amygdala, reductions in overall glial cell densities have been found[160] (see also [151]), an observation subsequently attributed to lower numbers of oligodendrocytes.[161] It is tempting to speculate that this phenomenon is related to the altered glial cell line-derived neurotrophic factor (GDNF) signalling recently evidenced in the BLA of depressed suicides,[162] as this neurotrophic factor has been shown to be expressed by mature oligodendrocytes.[163]

Astrocytes are polyfunctional glial cells whose roles include supporting neurons, regulating the supply of nutrients, metabolites and growth factors, and availability of neurotransmitters and ions, as well as maintaining the blood-brain barrier and playing a key role in immunity.[164,165] In studies using animal models of mood disorders, astrocyte and glial functions are disrupted, particularly in relation to glutamatergic signalling.[166,167] Further to this, in suicide, astrocyte morphology and function appear to be altered in discrete brain regions of depressed suicides. In the PFC[168,169] and dACC white matter, hypertrophic astrocytes,[170] as well as increased proportions of priming and perivascular macrophages,[168] have been described, all suggestive of low-level neuroinflammation in these regions (reviewed in [171]).[170,172,173] A microarray expression study conducted in postmortem suicide brains identified decreased mRNA expression of the astrocyte connexins (Cx) 30 and 43,[173] which are key factors in maintaining the blood-brain barrier.[174] Subsequent analysis of histone methylation profiles of astrocyte-related genes

confirmed that Cx30 and Cx43 are downregulated and provided evidence of epigenetic control of connexin genes.[134] Some recent evidence suggests that the permeability of the blood-brain barrier may be increased in individuals having recently attempted suicide,[175] which also suggests that inflammatory processes occur in the brains of suicide attempters. Transcriptomic analyses of the PFC of depressed suicides revealed that a number of astrocytic genes are downregulated compared to healthy controls, with the most significant alterations in aldehyde dehydrogenase 1 family member L1 (ALDH1L1) and glial fibrillary acidic protein (GFAP).[62] Similar downregulation of GFAP expression has also been identified in the PFC in animal models (mRNA)[166] and in several subcortical regions of depressed suicides (mRNA and protein).[94,172] Finally, decreased density of glial fibrillary acidic protein (GFAP)-immunolabelled astrocytes was reported in the DG of women, but not men, with depression.[176] Of note, the same parameter measured in CA2/3 was reported to be inversely correlated with the duration of depression in suicides.[177]

Evidence has been accumulating to support a relationship between inflammation and depressive states.[178-180] High levels of comorbidity are observed in the clinic between inflammatory autoimmune diseases and depression,[181,182] and a substantial proportion of patients receiving cytokine therapy develop depression.[183,184] Conversely, depressive states associate with increased levels of pro-inflammatory cytokines, including tumour necrosis factor, interleukin‐6 (IL‐6),[185] IL-2, IL-8,[186] and IL-1β.[187,188] Available evidence further suggests a specific association between those inflammatory markers and SB, with results showing increased levels of IL‐6 and decreased levels of IL‐2 in patients with SB,[189] as well as decreased levels of vascular endothelial growth factor (VEGF)[190] and changes in levels of quinolinic acid or kynurenic acid.[181,191,192]

A related line of evidence comes from the proposed role of the brain-tropic parasite, *Toxoplasma gondii,* in raising suicide risk.[193,194] In a sample of 45,745 women systematically tested for this parasite, seropositivity increased risk of all forms of self-directed violence, and the increased risk of SA and suicide was correlated with concentrations of anti-toxoplasma antibodies.[193] Toxoplasma seropositivity may also be linked to gender-specific alterations in personality traits associated with SB, specifically increased aggression in women and increased impulsivity in young seropositive men.[195] These intriguing associations may result in part from the immune response to *T. gondii*, particularly the inflammatory response in the brain, and the modulation of tryptophan availability, which, in addition to slowing parasitic replication, decreases serotonin production and increases levels of the NMDA antagonist, kynurenic acid.[196] A potential link between increased kyurenic acid, *T. gondii* infection, and SB has also been reported in cohorts of patients with schizophrenia,[197] but the overall contribution of *T. gondii* to SB is not universally accepted.[198]

Although most studies investigating inflammatory markers in SB have used blood samples, studies carried out in CSF[191,199] or postmortem brain tissue,[157,168,200,201] have led to the suggestion that suicide might be associated with the recruitment of immune cells and low-grade inflammation in the brain. At the pathophysiological level, it has been proposed that low-grade brain inflammation might modulate glutamatergic neurotransmission. Accordingly, inflammation-induced changes in levels of kynurenic and quinolenic acid (which act as antagonist and agonist at glutamatergic NMDA receptors, respectively)

may ultimately alter the net stimulation of NMDA receptors, in line with recent report about the antidepressant and anti-suicidal effects of the glutamatergic NMDA receptor antagonist ketamine.

The opioid system – promising avenues

The peptidergic opioid system is composed of a family of opioid peptides and four opioid receptor types (mu, delta, and kappa, as well as the non-canonical N/OFQ receptor) that critically controls pain,[202] reward,[203] and mood processes.[204] Post-mortem studies have examined the μ-opioid receptor (MOR) binding in suicide victims who were mainly diagnosed with depression. Compared with controls, MOR density was increased in frontal and temporal cortices,[205-207] as well as in caudate nuclei.[206] Furthermore, positron emission tomography (PET) studies with a MOR selective radiotracer showed that the induction of a sadness state in healthy individuals,[208] as well as depressed mood in clinical cohorts,[209] associated with adaptations in MOR neurotransmission across several brain regions. The dynorphin-kappa opioid receptor signaling pathway has also been linked to suicide, with increased[210] and decreased[211] expression reported in the caudate nucleus and amygdala, respectively. Interestingly, one the first PET studies on the kappa opioid receptor recently conducted in a dimensional Research Domain Criteria approach found significant relationships between trauma-related psychopathology and bioavailability of this receptor,[212] with potential implications in the context of ELA and suicide. Finally, a recent report found decreased expression of the N/OFQ receptor in the ACC of suicides.[213]

An emerging line of investigation suggests that the opioid system may be involved in the regulation of emotional pain and social attachment,[204,214] particularly in relation to SB.[215] Accordingly, patients typically report that self-injurious behaviors decrease their emotional pain, and this has been proposed to be related to endogenous opioid signaling.[216-218] In addition, a recent study reported that buprenorphine, an opiate classically used for maintenance therapies in addicted individuals, may decrease severe SI in patients without substance use disorder.[219] Future studies will be required to explore the relative contributions of distinct opioid receptors and peptides in these effects, as opioid modulatory therapies gain momentum in the management of depressive conditions.[220]

Neurotrophic pathways

Neurotrophins

In important studies examining the expression of the key brain-derived neurotrophic factor (BDNF) in postmortem suicide brains, mRNA expression of both BDNF and its receptor, tyrosine kinase B (TrKB), were shown to be decreased, with concomitant decreases in BDNF and TrkB full-length protein expression.[221,222] The link between BDNF expression and suicide has since been extensively explored, and despite some conflicting reports regarding serum BDNF levels in suicide attempters,[223-225] BDNF expression is generally altered in the suicide brain. Some insight into this association has come in part from evidence of increased BDNF promoter/exon 4 DNA methylation in suicide brains,[226] a finding that is consistent with those observed in depressed patients with a history of SA, or with SI during treatment,[227] and with evidence of hypermethylation of BDNF exons 4 and 9 induced by ELA in an animal model,[228]

which further supports the biological impact of ELA on suicide risk. Finally, there is evidence that treatment of MDD patients with antidepressants relieves epigenetic repression of BDNF,[229] pointing to its role in mediating depressive phenotypes, and potentially SB. The main receptor of BDNF, TrkB, is also regulated through epigenetic changes that appear to have an impact on suicide risk. In brain tissue from individuals who died by suicide, mRNA expression of the astrocyte-enriched TrkB truncated variant, TrkB-T1, is significantly decreased in association with increased methylation at the TrkB-T1 promoter, and appears to be regulated by the microRNA miR-185.[230-232]

Efforts to describe the impact of BDNF on suicide risk have also focused on a gene polymorphism that produces a Val instead of a Met in codon 66 (Val66Met). Many publications have shown evidence that the BDNF-Met variant is associated with a heightened risk of SB (reviewed in [37]), with its effect on suicide risk mediated in part by experiences of child abuse.[233,234] Importantly, differences between study results have highlighted the importance of considering the particular contributions of sex,[235] psychiatric diagnosis,[236,237] and type of SB[236,238,239] when interpreting the degree of regulation of SB by a single polymorphism.

Lipid metabolism

Following strong initial evidence of an association between low peripheral cholesterol levels and suicidality, cholesterol has been investigated as a potential biomarker of SB (reviewed in [240]). Evidence that low cholesterol may contribute to suicide and SBs includes low cholesterol levels in the brain of suicides[241] and in CSF of suicide attempters,[242] and high rates of suicide and SA in individuals with disrupted cholesterol synthesis and metabolism.[243,244] However, certain studies provide conflicting evidence as to the relationship between cholesterol and SB. [245-247] An important consideration is that different forms of cholesterol (LDL vs. HDL) may have differing roles in brain function and suicidality, and a number of other important confounders, such as age, sex, and nutritional status, may also have significant contributions to suicide risk. Nevertheless, cholesterol represents a potentially important player in brain function as nearly one quarter of the body's cholesterol is located in the CNS,[248] where it is a key component of lipid rafts, acts as a precursor for neurosteroids, is regulated by BDNF, and regulates neural plasticity.[240,249] Additional evidence suggests that cholesterol may have important implications in neurotransmitter signalling.[240]

Beyond cholesterol, there is evidence that triglyceride levels[250,251] and regulators of fatty acid composition may also influence suicide risk, particularly in the case of violent SA and suicides.[252] Of interest, a recent report indicates a potential role for epigenetic regulation of polyunsaturated fatty acid (PUFA) biosynthesis through differential DNA methylation of elongation of very long-chain fatty acids protein 5 (Elovl5) in subjects with MDD with or without a history SA.[253] The effect of this differential methylation is unclear, however, since the levels of circulating PUFA were not significantly different between groups.[253] This is also consistent with a previous study reporting no change in fatty acid composition of postmortem brain tissue of suicides with or without MDD, as compared to healthy controls.[254] Such evidence of the role of lipids in suicide has led to speculation as to the potential for modulating lipid profiles in patients deemed "at-risk",[255] but the evidence to support such interventions is still insufficient.

Stress response systems

The polyamine stress response system

In addition to the HPA stress response system, the polyamine system, another stress response pathway, has been extensively characterized in relation to suicide risk. Polyamines, aliphatic compounds with multiple amine groups, have been implicated in a host of cellular functions, including the regulation of gene expression at transcriptional and post-transcriptional levels, most notably regulating the function of several neuromodulators (primarily glutamate receptors, but also nicotinic receptors and ion channels), and acting as neurotransmitters themselves.[256] In particular, there is evidence that the polyamines agmatine, spermine, and spermidine are released at synapses on depolarization.[257-259] In conditions of physical, hormonal, or emotional stress, the polyamine stress response is activated, with increased expression of putrescine and agmatine in both central and peripheral tissues.[260,261] Growing evidence suggests that elevated levels of these two polyamines in the brain have antidepressant and anxiolytic effects, potentially through regulation of inflammation.[262-264] Additionally, agmatine may mediate the activity of pharmacological antidepressants, in part through binding to NMDA receptors.[265-267]

Polyamines may play a particular role in the context of suicide, as studies investigating postmortem suicide brains show that expression levels of gene products associated with the polyamine stress response system are dysregulated.[268-273] Expression of the rate-limiting enzyme spermine N1-acetyltransferase (SAT1), as well as of several other polyamine-associated enzymes (SMOX, ODC, SMS, AMC-1), are altered in the cortex of postmortem suicides.[270,273,274] Individual isoforms of SAT1 may partially explain the decreased SAT1 expression in brain tissue of suicides,[268,270,275,276] and there is some evidence that microRNAs can target polyamine transcripts including SAT1.[277] Another important contributor to SAT1 downregulation is through epigenetic control, with studies identifying promoter DNA methylation of SAT1 that inversely correlated with SAT1 expression, and evidence for histone modifications affecting key enzymes in polyamine synthesis.[278-280] SAT1 has emerged as a potential biomarker for suicide, topping the lists of candidates in several studies.[281-283]

Early-life adversity and the HPA stress axis

One of the best investigated examples of epigenetic changes in response to ELA is that of the hypothalamic–pituitary–adrenal (HPA) axis, a key regulator of cortisol release and stress response.[284] Animal models of ELA have long shown that stressful events during early life disrupted glucocorticoid function and altered behavioural responses to stress challenges.[285] Glucocorticoid release, triggered by stress, is regulated by a negative feedback loop in which secreted steroids activate glucocorticoid receptors (GR) in the hypothalamus, thereby shutting off further production. Ground-breaking studies conducted in rats showed that GR exon 1_7 expression in pups is epigenetically regulated by the early-life environment. [286-288] In a subsequent postmortem brain study from individuals who had died by suicide and were severely abused during childhood, compared with individuals without a history of child abuse

(suicide or healthy control), the GR exon 1_F variant (human homolog to the rodent exon 1_7) was also epigenetically regulated in humans by their early-life environment.[289] As in rodents, the methylation of exon 1_F was associated with the quality of care in early life,[289] and its methylation status seems to regulate the binding of the NGFI-A transcription factor associated with GR expression.[288,289] These findings have since been confirmed in the context of ELA and of parental emotional stress, with increased GR 1_F/GR1_7 methylation in both central nervous system and peripheral tissues.[290] In contrast, results of studies examining other GR exons or examining adult psychopathology have yielded mixed results.[290] In addition to this direct decrease of GR expression, there is evidence that GR function may also be altered through the FK506-binding protein (FKBP5), which downregulates GR signalling. Particular sequence variants of FKBP5 have been associated with increased suicidality,[291-295] particularly in individuals with a history of ELA.[296-299] Disrupted GR function results in inadequate control of the HPA axis in these individuals, possibly leaving them with hyperactive cortisol secretion, and the development of anxiety traits. In turn, anxiety mediates the relationship between ELA and SB.[21,55]

An exciting new candidate in the relationship between cortisol regulation and suicide is the spindle and kinetochore associated protein 2 (SKA2), a gene that has been implicated in GR signalling.[300] Recent reports have converged on identifying differential methylation of SKA2 at the level of a single CpG.[301,302] Increased SKA2 3'UTR methylation, and concomitantly decreased SKA2 mRNA, was detected in suicide brain samples, as well as in peripheral blood samples of individuals with both SI and SA, compared to controls.[302] Peripheral samples that were available at time points preceding the onset of SI also displayed altered SKA2 methylation, pointing to a predictive effect of this marker. A second study confirmed these findings in saliva and blood samples, showing that increased methylation of the SKA2 site correlated with impaired cortisol suppression.[301] Additionally, combining SKA2 methylation status with history of childhood abuse allowed for a stronger prediction of SA.

Future directions and current challenges for functional genomic research in SB

Accumulating evidence indicates that epigenetic processes present unique properties in the brain compared to other organs of the human body, as revealed by a unique pattern of non-CG methylation,[303] high levels of hydroxymethylation,[304] or the complexity of non-coding RNAs,[305] among others (Table 1). Brain epigenetics is therefore a distinct field that requires the development of specific analytical tools to address unique experimental challenges.

We can speculate that the brain may have evolved as the most sensitive organ to process changes in environmental conditions to improve adaptation to the environment. Accordingly, over evolutionary time this functional specialization may have required particular, potentially more complex, molecular and epigenetic processes mediating the interplay of the environment and the genome. In addition, because epigenetic changes can be long-lasting (potentially over generations, although this is debated[306]), they represent a form of genomic plasticity that could help explain psychiatric phenotypes, such as depressive illness and SB, that associate with distal environmental stressors such as exposure to

early-life adversity.[307] We detail below immediate and long-term research opportunities for brain functional genomic studies investigating SB.

DNA CH methylation

While DNA methylation is largely restricted to sequences composed of cytosines followed by guanines (known as CG dinucleotides), recent results have identified a non-canonical form of DNA methylation in non-CG, or CH, contexts (where H stands for A, C or T). While high levels of CH methylation (mCH) were first identified in embryonic stem cells (ESCs),[308] recent findings have revealed that the highest levels of mCH across mammalian tissues are in the brain.[303,309] Results also showed that mCH accumulation is much more pronounced in neurons than in glial cells,[303,310] and that mCH levels measured at the whole tissue level (below 5%) are considerably lower than for the CG context (70-80%). Nevertheless, the large number of cytosines in CH, compared to CG, contexts, has led to estimates that mCH may ultimately account for as much as a quarter of all methylated cytosines.[309,310]

Similar to mCG, mCH tends to negatively associate with transcriptional activity. It is therefore possible that differences in gene expression associated with suicide might partly result from differential mCH levels, particularly for genes that are dysregulated in cells with high mCH levels (i.e., neurons rather than glial or other cell types). Importantly, mCH may be particularly relevant to so-called 'sensitive periods', defined as time-windows in brain development during which critical processes must take place to achieve proper maturation of essential physiological functions. This concept, which was primarily investigated for sensory-motor functions[311] and more recently in relation to emotional regulation,[312] may partly explain the relationship between ELA and suicide.[313] As mentioned above, ELA is an important predictor of SB, and its effects are thought to be mediated partly through DNA methylation. Considering that mCH progressively accumulates in neurons during the first few years of life in human,[310] it is tempting to speculate that this newly identified epigenetic mark may be particularly sensitive to ELA.

Compared with DNA methylation in the canonical CG context, mCH transcription regulation is only starting to be explored.[314] Recent reports have established an intriguing link between the length of genes along the DNA sequence and levels of CA DNA methylation.[315,316] A proposed model[317] suggests that expression of long genes, as a population, is enriched in the brain and is tightly regulated by enhanced MeCP2 binding due to high mCA levels. While these results were obtained in relationship to Rett syndrome, a neurodevelopmental disorder due to mutations in the MeCP2 gene, they uncover a specific epigenetic function of mCH that may be relevant to psychopathology and suicide.

Hydroxymethylcytosine

While methylcytosine is sometimes described as the fifth DNA base, a sixth base has been recently identified[304,318] that corresponds to a further oxidation step (mediated by Tet-translocation enzymes, Tet1, 2 and 3) from methyl- (5mC) to hydroxymethylcytosine (5hmC). This new epigenetic mark appears to be stable in vivo[319] and to occur in CG – but not CH – contexts, indicating that mCG is uniquely

susceptible to Tet-mediated oxidation. Similarly to mCH, 5hmC predominantly accumulates in neuronal cells, and its levels are higher in the brain than in any other human tissue.[304,320] Most techniques used to measure levels of DNA methylation (including the popular bisulfite conversion) do not distinguish between 5mC and 5hmC, although several methodologies have now been developed to address this (including oxBS-Seq,[321] TAB-Seq[322] or Aba-Seq[323,324]). 5mC and 5hmC seem to have opposite relationships with transcriptional activity, with 5mC negatively correlating with gene expression,[325] and 5hmC positively correlating with expression in rodent[326] and human[324] brains. A similar positive relationship was observed for dendritic cells of the immune system,[327] while gene bodies and enhancer regions in ESCs display a more subtle dual pattern.[328] There is currently some debate about the specific proteins that dictate this divergent transcriptional regulation.[316,329] Such complexity again emphasizes the importance of tissue-, or even cell type-specific epigenetic regulatory processes. While 5hmC has begun to be investigated in neurodegenerative disorders such as Alzheimer's and Huntington's diseases,[330,331] its potential implication in the understanding of SB remains unknown.

Histone marks

Histones are essential protein complexes that control chromatin structure and activity and are regulated by post-translational modifications of their N-terminal tails. Distinct histone modifications associate with genomic features, for example, active promoters and enhancer regions are associated with histone 3 lysine 4 (H3K4) trimethylation and H3K27 acetylation, respectively, whereas repressed promoters are associated with H3K9 and H3K27 dimethylation and trimethylation. While histone modification represents a ubiquitous mechanism for regulating gene transcription, specific contributions of histone modification to the emergence of suicide-related phenotypes have only been explored at the level of candidate genes,[230,280] and genome-wide approaches should be conducted.

RNA modifications and non-coding RNA

Transcription, translation and degradation of RNA molecules are well-controlled processes that are regulated by RNA modifications (RNA methylation and pseudouridine), RNA editing, and RNA structure (see [305,332] for recent reviews). These mechanisms result in complex relationships between RNA and protein levels in the brain as, for example, it has been suggested that only 40% of the variance in protein levels could be attributed to RNA abundance.[333] In the mouse brain, RNA methylation primarily corresponds to N6-methyladenosine (6mA), frequently referred to as an epitranscriptomic mark, which affects messenger and non-coding RNAs and is dynamically regulated during brain development.[334] It has been shown to regulate RNA degradation kinetics and to accumulate in the prefrontal cortex during learning and memory processes at specific loci associated with synaptic function.[335] In humans, SNPs in two RNA demethylases, FTO and ALKBH5, which are responsible for 6mA processing, have been associated with MDD.[336,337] This suggests that N6-methyladenosine may contribute to the control of mood and emotional responses, and potentially to suicide pathophysiology.

Another RNA modification is pseudouridine (Ψ), which has been shown to affect hundreds of messenger RNAs.[338,339] While changes in levels of pseudouridine have been described across tissues and following cellular stress, its potential role in transcriptomic regulation and in brain function remains unexplored.

Conversion of adenosine to inosine residues by deamination (RNA A-to-I editing) relies on an enzymatic pathway[340] to promote RNA functional diversity (by modulating alternative splicing and microRNA targeting), thereby leading to qualitatively different proteins and potentially fine-tuning genomic responses to rapidly changing environmental demands.[341] Recently, an association between suicide and a SNP in the adenosine deaminase ADARB1 was reported.[342] In suicide, dysregulated RNA editing has been reported for the serotonin 5-HT_{2C} receptor, with evidence that increased 5-HT_{2C} editing in suicide[80,343] could lead to decreased receptor signalling. In rodent models, ELA has also been associated with increased 5-HT_{2C} editing.[344]

Another promising type of epigenetic regulation of gene expression is the role of non-coding RNAs. A large proportion of the transcriptome is composed of regulatory RNAs that do not encode proteins but regulate mRNA transcription, function and availability, and interact directly with DNA regulatory proteins and enzymes.[345] Among non-coding RNA species, long non-coding RNAs are of particular interest as they are enriched for brain expression[346] and developmentally regulated,[347] but less evolutionarily conserved than other RNA species. While preclinical studies start to unravel how lncRNAs may contribute to emotional control,[348] their role in SB is currently unknown. On the other hand, microRNAs, which are small non-coding RNA molecules between 19-24 nucleotides long, have been implicated in the pathophysiology of mental illness, including MDD. The specific dysregulation of miR function in suicide is just beginning to be appreciated, as reviewed recently.[349]

Cell-type specificity

Several distinct cell-types are physically intermingled in the brain, and large-scale single-cell RNA-sequencing studies have recently started to uncover the transcriptomic underpinnings of cellular diversity.[350,351] A similar diversity also emerges at the epigenetic level: while all neurons share common genetic material, their distinct gene-expression patterns are regulated by epigenetic processes.[352] The heterogeneity of neuronal cell types and their physical entanglement represent experimental challenges that severely hamper the detection of potentially subtle cell-type specific adaptations driving complex emotional responses.[353] Recent rodent studies have demonstrated that depressive-like behaviours[354] and behavioural responses to antidepressants[83] may result from molecular adaptations in a minority population of neuronal and non-neuronal cells in a given brain region. Such discrete adaptations are likely missed by studies performed with tissue homogenates, therefore cell-type specific strategies are needed in suicide research. FACS-sorting of nuclei from postmortem tissue recently enabled the study of cell-type specific epigenetic mechanisms of ELA and suicide, and recent technological achievements suggest that similar studies are now feasible at the level of gene expression using either FACS (followed by analyses of nuclear messenger RNAs[355]) or laser microdissection.[356]

Brain imaging of epigenetic processes

PET-scan ligands allowing for the visualization of epigenetic enzymes in the human brain have recently been developed.[357,358] Although the spatial resolution of such approaches will be inherently limited, they should enable longitudinal studies (e.g., of SB) of human brain epigenetic processes that are not feasible with existing biochemical approaches which by definition only capture single epigenetic postmortem 'snapshots'.

Therapeutic perspectives

Tools are currently being developed to enable potent and specific manipulation of the epigenome with long-term therapeutic potential in the field of molecular psychiatry. Experimental manipulations of the human DNA sequence have been revolutionized over the last few years by the discovery of the Cas9 system.[359] The power of Cas9, and other gene targeting strategies, is now being harnessed to manipulate the epigenome. Accordingly, recent reports have shown that enzymes responsible for the methylation of the human DNA (DNMT3a) can be directed to specific loci in vitro[360,361] in order to modify site-specific DNA methylation patterns. Very recently, similar approaches have been used in vivo[362] to mediate targeted epigenetic reprogramming in the brain,[363] with the potential for inheritance.[364] Importantly, the first experimental approach to take advantage of these recent technologies demonstrated in rodent models that targeted epigenetic modulation of histone methylation (H3K9me2) controlled drug- and stress-induced transcriptional and behavioural responses.[362] Such tools may eventually allow for epigenetic interventions in psychiatric patients, but a series of major obstacles and challenges remain that are notably related to specificity, safety and efficiency, similar to those that have been encountered historically for gene therapies in other medical fields.[365]

Current challenges in suicide research

Our understanding of the factors and pathways involved in mediating suicide risk has greatly benefitted from the advances in the last decade. As we improve our ability to investigate more discrete changes, it becomes increasingly important to disentangle the relative contributions of psychopathology from changes specific to suicide. The high rate of co-occurrence of MDD and suicide constitutes a major challenge in identifying selective determinants of suicide and SB. Recent work examining the transmission of violent behaviours and SA also show substantial overlap between these phenotypes,[366] which may be partly explained by the co-transmission of impulsive-aggressive and SB.[10,16] Such confounding factors suggest that distinguishing between the etiological factors of distinct psychopathologies and SB may be more complex than was originally anticipated. A further complication stems from the emergence of SI during antidepressant treatment, which has been reported in a small proportion of patients receiving SSRIs.[367] Although some studies have investigated genetic correlates of treatment-emergent SI,[40,368] we have yet to adequately describe the clinical and biological features associated with treatment-emergent or treatment-worsening SI.

The wide range of phenotypes that may be considered in studies investigating suicide or suicidal behaviour further complicates identification of clear markers for suicide and SB. SI and SA may at times

be studied concurrently, and even within these accepted categories, phenotypes may be distinguished on the basis of passive or active engagement, on the presence or absence of planning (SI), and according to the potential lethality, intent and violence (SA).[5] These phenotypes are often considered to exist on a spectrum and as a result are frequently studied and reported on together. However, reports have also shown specific differences between non-violent and violent SA,[185,235,241] and similar questions may be asked about the biological similarities between SI, SA and suicide. Given the relatively high prevalence of SI, compared to SA and suicide,[5] reliable indicators of progression to SA or suicide would be of clear clinical benefit. Psychological constructs have been proposed to aid in our understanding of these transitions,[369] and strengthening this understanding with clearly defined biological mechanisms will provide a crucial opportunity to act before suicide occurs.

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Conflict of interest

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Figure legends

Figure 1. Modelling suicide risk

Several models have been proposed to describe suicide risk. These models seek to describe the factors that lead individuals to transition from non-suicidal self-injury or SI to other forms of SB, including death. Estimated global prevalence rates are indicated in each circle. The Biopsychosocial Model for Suicide Risk describes the various elements that cause clear biological changes that act as distal, mediating, or proximal factors to increase suicide risk. The Motivational-Volitional Model includes the premotivational, motivational, and volitional phases and describes de psychological changes that occur when an individual transitions from non-lethal behaviours to potentially lethal SB. The Acquired Capability Model proposes psychological changes that can lower an individual's aversion to self-harming behaviour and psychologically prepare them to carry out lethal SB.

Figure 2. Biological pathways leading to suicidal behaviour

Many biological factors have been proposed as contributors to suicide risk. ELA, a key contributor to SB, affects stress response systems (HPA axis and polyamine system), which may affect behaviour (anxiety, impulsivity, cognitive ability, social integration, and depressed mood). Changes have also been reported in neurotransmitter and neurotrophic signalling pathways as well as in neuroinflammation and lipid metabolism. These individual factors, as well as their many interactions and overlapping phenotypes (not shown in diagram) work together to modulate the likelihood of engaging in SB.

Figure 3. Brain regions implicated in depression and suicidal behaviour

Several brain regions have been implicated in MDD and SB. Changes to the prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, raphe nuclei, and locus coeruleus include changes to volume, cellular morphology and density, potential inflammation, altered function, and changes to mRNA and protein expression levels.

Tables

Table 1. Main features of epigenetic plasticity: current knowledge and gaps

Molecular substrate	Mark	Enrichment in brain	Enrichment in a specific cell-type	Developmental pattern	Behavioural experience-dependent plasticity	Implication in depression & suicide
Epigenetic (DNA)	5mCG	No	No	No	Yes	Yes
	5mCH	Yes [309]	Yes neurons >> glia [310]	Yes Strong accumulation during early life [310]	?	?
	5hmCG	Yes [304]	Yes mature neurons > progenitors [370]; varies also across neuronal types [326,371]	Yes Genomic pattern formed in utero [310], with postnatal dynamics [372]	Yes [373]	?
Epitranscriptomic (RNA)	6mA	No [334]	?	Yes [334]	Yes [335]	?
	Pseudouridine (Ψ)	No [338]	?	?	Yes Cellular stress [338]	?
	A-to-I editing	No [374]	?	?	Yes [344]	Yes [80,343,375]

Supplementary Table 1. Summary of key findings from GWAS Studies

Supplementary Table 1 includes SNP reference sequence ID, official gene name and functional annotation for SNPs identified in GWAS studies with *P*-values below 10^{-5}. Shaded cells indicate *P*-values below 10^{-6}.

Associated gene	Functional annotation (determined using https://david.ncifcrf.gov/home.jsp unless otherwise indicated)	Top SNPs identified by authors	Genome-wide significance	Reported *P*-value	Comments
A1CF	**APOBEC1 complementation factor(A1CF)** mRNA processing, mRNA localization resulting in posttranscriptional regulation of gene expression, cytidine to uridine editing, mRNA modification, protein stabilization nucleoplasm, cytoplasm, endoplasmic reticulum, apolipoprotein B mRNA editing enzyme complex nucleotide binding, RNA binding, double-stranded RNA binding, single-stranded RNA binding, protein binding	rs72787049[48]	No	1.1×10^{-6}	SA, observed in imputed and genotyped SNPs
ABI3BP	**ABI family member 3 binding protein** positive regulation of cell-substrate adhesion, extracellular matrix organization interstitial matrix, extracellular space, extracellular matrix collagen binding, heparin binding,	rs2576377[41]	**Yes**	**2.55×10^{-8}**	SA in MDD (Discovery cohort)
ADAMTS14	**ADAM metallopeptidase with thrombospondin type 1 motif 14** Inflammatory response[39] proteolysis, collagen fibril organization, collagen catabolic process extracellular region, proteinaceous extracellular matrix metalloendopeptidase activity, zinc ion binding,	rs6480463[39]	No	1.70×10^{-6}	SA/Suicide vs. Non-attempter live/non-suicide postmortem
APOO	**Apolipoprotein O** lipid transport, cristae formation Golgi membrane, extracellular region, extracellular space, mitochondrion, endoplasmic reticulum membrane, integral component of mitochondrial inner membrane, very-low-density lipoprotein particle, low-density lipoprotein particle, high-density lipoprotein particle, MICOS complex protein binding	rs2520237[44]	No	9.57×10^{-6}	TWSI; genotype × drug interaction
		rs2707159[44]	No	4.50×10^{-6}	TWSI; genotype × drug interaction
		rs2707159[44]	No	7.58×10^{-6} in females; n.s. in males	TWSI; genotype × drug interaction; potential gender-dependent effect
ATL2 (ARL6IP2)*	**Atlastin GTPase 2** ER to Golgi vesicle-mediated transport, endoplasmic reticulum organization, Golgi organization, protein homooligomerization endoplasmic reticulum, endoplasmic reticulum membrane, membrane, integral component of membrane GTPase activity, protein binding, GTP binding, identical protein binding	rs6737169[41]	No	8.86×10^{-6}	SA in MDD (Discovery cohort)
BRINP3 (FAM5C)	**BMP/retinoic acid inducible neural specific 3** Inflammatory disease[39] cell cycle arrest, positive regulation of neuron differentiation, negative regulation of mitotic cell cycle, cellular response to retinoic acid extracellular region, mitochondrion, endoplasmic reticulum, dendrite, neuronal cell body	rs17375108[39]	No	2.66×10^{-6}	SI in depressed subjects
C8orf74	**Chromosome 8 open reading frame 74** protein binding (?)	rs7011192[39]	No	3.9×10^{-6}	Suicide vs. non-SB
CAPN13	**Calpain 13** proteolysis intracellular, cytoplasm	rs6548036[41]	No	7.37×10^{-6}	SA in BD (Discovery cohort)

	calcium-dependent cysteine-type endopeptidase activity, calcium ion binding				
CCDC7*	**Coiled-coil domain containing 7** Unknown function	rs10740855[47]	No	7.66×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs10827069[47]	No	6.52×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs12359568[47]	No	7.41×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs1831771[47]	No	7.48×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs1831774[47]	No	6.97×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2947080[47]	No	6.89×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2990980[47]	No	7.18×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2990984[47]	No	6.78×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2990986[47]	No	7.10×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs3006713[47]	No	5.22×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs3006726[47]	No	8.14×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7075553[47]	No	4.45×10^{-6}	Suicide behaviour severity; meta-analysis of three sample sets
		rs7090007[47]	No	9.42×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7910275[47]	No	7.04×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs9338709[47]	No	8.12×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs944823[47]	No	6.52×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs1413977[47]	No	4.58×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs1832048[47]	No	4.34×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs1832048[47]	No	4.34×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2184486[47]	No	4.49×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2947059[47]	No	5.17×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2992079[47]	No	6.92×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets

		rs4749744[47]	No	5.91×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7078469[47]	No	2.43×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7079041[47]	No	2.35×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7089887[47]	No	5.31×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7899433[47]	No	4.15×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7899442[47]	No	4.31×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7899680[47]	No	4.18×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7900825[47]	No	3.69×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7905328[47]	No	6.37×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs7914502[47]	No	2.89×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs9663143[47]	No	6.36×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs980117[47]	No	4.44×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs1333222[47]	No	7.34×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
DPP10	**Dipeptidyl peptidase like 10** Associated with asthma[39] proteolysis, protein localization to plasma membrane, positive regulation of establishment of protein localization to plasma membrane, regulation of potassium ion transmembrane transport plasma membrane, membrane, integral component of membrane serine-type peptidase activity, dipeptidyl-peptidase activity, potassium channel regulator activity	rs1374268[39]	No	5.69×10^{-6}	Live SA vs. Depressed non-SA
		rs4308128[39]	No	3.67×10^{-6}	Live SA vs. Depressed non-SA
EPB41L4A	**Erythrocyte membrane protein band 4.1 like 4A** actomyosin structure organization cytoplasm, cytoskeleton, extrinsic component of membrane structural constituent of cytoskeleton, cytoskeletal protein binding	rs13358904[39]	No	4.96×10^{-6}	SI in depressed subjects
FBXL18	**F-box and leucine rich repeat protein 18** F-box domain, cyclin-like Alternative splicing, Complete proteome, Leucine-rich repeat, Polymorphism, Proteomics identification, Reference proteome, Repeat, Ubl conjugation pathway	rs4724701[43]	No	2.00×10^{-6}	TESI vs. non-TESI; Best empiric associations calculated with Fisher Product Method over both allelic and genotypic tests
GDA	**Guanine deaminase** Guanine catabolic process – zinc ion binding – guanine deaminase activity – hydrolase activity[‡]	rs11143230[44]	No	8.28×10^{-7}	TWSI; whole sample; potential effect on females treated with escitalopram

	nucleobase-containing compound metabolic process, guanine catabolic process, purine nucleotide catabolic process, nervous system development, guanine metabolic process intracellular, cytosol, extracellular exosome zinc ion binding, guanine deaminase activity				
GFRA1	**GDNF family receptor alpha 1** MAPK cascade, cell surface receptor signaling pathway, nervous system development, glial cell-derived neurotrophic factor receptor signaling pathway, positive regulation of GTPase activity intracellular, plasma membrane, extrinsic component of membrane, anchored component of membrane, extracellular exosome Ras guanyl-nucleotide exchange factor activity, receptor binding, glial cell-derived neurotrophic factor receptor activity	rs4751955[42]	No	7.75×10^{-7}; RADIANT analysis	MDD; quantitative trait analysis (SCAN Suicidality used to determine SI and SA) ; $P=2.84\times10^{-5}$ in meta-analysis
IL28RA (IFNLR1)	**Interferon lambda receptor 1** regulation of immune effector process, regulation of response to biotic stimulus, negative regulation of cell proliferation, regulation of cell proliferation, regulation of multi-organism process, regulation of defense response to virus, regulation of defense response to virus by host plasma membrane, integral to plasma membrane, integral to membrane, intrinsic to membrane, intrinsic to plasma membrane, interleukin-28 receptor complex, receptor complex, plasma membrane part cytokine receptor activity, cytokine binding	rs10903034[40]	No	3.02×10^{-6}	TESI
		rs1416834[40]	No	3.6×10^{-6}	TESI
Intergenic	Unknown function	rs10043093[44]	No	7.59×10^{-6}	TWSI; whole sample
Intergenic	Unknown function	rs11852984[39]	No	1.52×10^{-6}	SA/Suicide vs. Non-attempter live/non-suicide postmortem
Intergenic	Unknown function	rs1219615[47]	No	6.51×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
Intergenic*	Unknown function	rs12751302[42]	No	1.61×10^{-6}; RADIANT analysis	MDD; discrete trait: SA; $P=1.16\times10^{-4}$ in meta-analysis
Intergenic	Unknown function	rs1368607[44]	No	1.76×10^{-6}	TWSI; genotype × drug interactions; potential gender effects
Intergenic	Unknown function	rs1418811[39]	No	1.32×10^{-6}	SI in depressed subjects
Intergenic	Unknown function	rs1433412[44]	No	2.22×10^{-6}	TWSI; genotype × drug interactions; potential gender effects
Intergenic*	Unknown function	rs143371100[47]	No	6.19×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
Intergenic*	Unknown function	rs1451195[47]	No	6.19×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
Intergenic	Unknown function	rs1473995[44]	No	7.37×10^{-6}	TWSI; whole sample
Intergenic	Unknown function	rs17790430[48]	No	2.5×10^{-6}	SA, observed in imputed and genotyped SNPs
Intergenic	Unknown function	rs1879390[44]	No	6.93×10^{-6}	TWSI; escitalopram-treated subjects
Intergenic	Unknown function	rs2419374[39]	No	9.76×10^{-7}	SI in depressed subjects
Intergenic	Unknown function	rs2846685[44]	No	4.71×10^{-6}	TWSI; genotype × drug interactions; potential gender effects
Intergenic	Unknown function	rs2905346[44]	No	9.47×10^{-6}	TWSI; genotype × drug interactions

Intergenic	Unknown function	rs320461[39]	No	3.7×10^{-6}	Suicide vs. non-SB
Intergenic	Unknown function	rs3851150[47]	No	4.60×10^{-6}; meta-analysis of 3 studies	Suicide behaviour severity in BD; meta-analysis of three sample sets
Intergenic	Unknown function	rs4254432[44]	No	7.09×10^{-6}	TWSI; genotype × drug interactions
Intergenic	Unknown function	rs6812841[44]	No	7.70×10^{-6}	TWSI; nortriptyline-treated subjects
Intergenic	Unknown function	rs7019771[44]	No	3.81×10^{-6}	TWSI; genotype × gender interaction
Intergenic*	Unknown function	rs720903[47]	No	4.37×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
Intergenic; closest genes ACP1, FAM110C, SH3YL1*	**ACP1: Acid phosphatase 1, soluble** Tyrosine phosphatase that influences Wnt signalling; Lithium-sensitive[45] protein amino acid dephosphorylation, phosphorus metabolic process, phosphate metabolic process, dephosphorylation cell fraction, soluble fraction acid phosphatase activity, phosphoprotein phosphatase activity, protein tyrosine phosphatase activity, phosphatase activity, identical protein binding **FAM110C** positive regulation of cell migration, positive regulation of protein kinase B signaling, regulation of cell projection assembly spindle pole, nucleoplasm, cytoplasm, microtubule organizing center, microtubule, cell cortex protein binding, alpha-tubulin binding **SH3YL1: SH3 and SYLF domain containing 1**[§] phosphatidylinositol biosynthetic process regulation of ruffle assembly ruffle membrane	rs300774[45]	**Threshold**	**5.07×10^{-8}; (combined analysis of 2 datasets)**	SA; Bipolar disorder subjects; *P*-value (combined analysis of 2 datasets) at threshold of GW significance; *P*-value primary dataset = 1.09×10^{-6}
Intergenic; closest gene ANKRD7 (476kb)	**Ankyrin repeat domain 7** male gonad development	rs6466675[48]	No	3.0×10^{-6}	SA, observed in SNP-by-SNP GWAS
Intergenic; closest genes ANXA2 (129kb), FOXB1 (212kb)*	**Annexin A2** cellular growth and signal transduction[43,§] skeletal system development, angiogenesis, blood vessel development, vasculature development, body fluid secretion, regulation of blood coagulation, negative regulation of blood coagulation, extracellular matrix organization, collagen fibril organization, regulation of response to external stimulus, fibrinolysis, extracellular structure organization, secretion, blood vessel morphogenesis, regulation of coagulation, negative regulation of coagulation, regulation of body fluid levels, negative regulation of multicellular organismal process cell fraction, extracellular region, proteinaceous extracellular matrix, basement membrane, soluble fraction, endosome, early endosome, plasma membrane, cytoplasmic membrane-bounded vesicle, extracellular matrix,	rs1630535[43]	No	1.3×10^{-7}	TESI vs. non-TESI; Best empiric associations calculated with Fisher Product Method over both allelic and genotypic tests

	cytoplasmic vesicle, vesicle, membrane-bounded vesicle, sarcolemma, melanosome, extracellular matrix part, extracellular region part, perinuclear region of cytoplasm, pigment granule enzyme inhibitor activity, phospholipase inhibitor activity, small GTPase regulator activity, calcium ion binding, phospholipid binding, calcium-dependent phospholipid binding, phosphatidylinositol-4,5-bisphosphate binding, cytoskeletal protein binding, lipid binding, Ras GTPase binding, Rab GTPase binding, enzyme binding, GTPase regulator activity, small GTPase binding, phosphoinositide binding, ion binding, cation binding, metal ion binding, GTPase binding, lipase inhibitor activity, nucleoside-triphosphatase regulator activity				
Intergenic; closest gene AVPR1A (22kb), PPM1H (189kb)	**AVPR1A: Arginine vasopressin receptor 1A** regulation of systemic arterial blood pressure by vasopressin, maternal aggressive behavior, positive regulation of systemic arterial blood pressure, generation of precursor metabolites and energy, G-protein coupled receptor signaling pathway, activation of phospholipase C activity, positive regulation of cytosolic calcium ion concentration, negative regulation of female receptivity, grooming behavior, blood circulation, positive regulation of cell proliferation, positive regulation of heart rate, positive regulation of glutamate secretion, myotube differentiation, calcium-mediated signaling, telencephalon development, positive regulation of cell growth, positive regulation of prostaglandin biosynthetic process, positive regulation of cellular pH reduction, cellular response to hormone stimulus, social behavior, positive regulation of renal sodium excretion, cellular response to water deprivation, maternal behavior, sperm ejaculation, penile erection, positive regulation of vasoconstriction, response to corticosterone, negative regulation of transmission of nerve impulse, response to peptide endosome, plasma membrane, integral component of plasma membrane, integral component of membrane, cytoplasmic vesicle vasopressin receptor activity, protein kinase C binding, protein binding, peptide hormone binding, V1A vasopressin receptor binding, peptide binding **PRM1H: Protein phosphatase, Mg2+/Mn2+ dependent 1H** protein dephosphorylation nucleus, cytoplasm phosphoprotein phosphatase activity, protein serine/threonine phosphatase activity	rs10747978[48]	No	6.2×10^{-6}	SA, observed in SNP-by-SNP GWAS
Intergenic; closest genes B3GALT5, C21orf88*	**Beta-1,3-galactosyltransferase 5** protein amino acid glycosylation, glycoprotein metabolic process, glycoprotein biosynthetic process, biopolymer glycosylation, glycosylation endoplasmic reticulum, Golgi apparatus, integral to membrane, intrinsic to membrane galactosyltransferase activity, UDP-galactose:beta-N-acetylglucosamine beta-1,3-galactosyltransferase activity, UDP-galactosyltransferase activity, beta-1,3-galactosyltransferase activity	rs10854398[41]	No	6.06×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
		rs8132770[41]	No	7.15×10^{-6}	SA in all mood disorders (random-effects meta-analysis)

	C21orf88/B3GALT5 antisense RNA 1 Unknown function				
Intergenic, closest ELP3	**Elongator acetyltransferase complex subunit 3** neuron migration, tRNA wobble uridine modification, regulation of transcription from RNA polymerase II promoter, transcription elongation from RNA polymerase II promoter, central nervous system development, positive regulation of cell migration, histone H3 acetylation, histone H4 acetylation, regulation of protein kinase activity histone acetyltransferase complex, nucleolus, cytoplasm, transcription elongation factor complex, Elongator holoenzyme complex RNA polymerase II core binding, protein binding, N-acetyltransferase activity, phosphorylase kinase regulator activity, H3 histone acetyltransferase activity, H4 histone acetyltransferase activity, metal ion binding, iron-sulfur cluster binding	rs4732812[44] (intergenic)	No	3.35×10^{-6}	TWSI; escitalopram-treated subjects; potential gender-dependent effects in escitalopram-treated subjects
Intergenic; closest genes MIR3977 (243kb), ATP6AP1L (FLJ41309; 279kb)*	**MIR3977 microRNA 3977** Unknown function **FLJ41309/ ATP6AP1L ATPase H+ transporting accessory protein 1 like** ATP hydrolysis coupled proton transport integral component of membrane, proton-transporting V-type ATPase, V1 domain proton-transporting ATP synthase activity, rotational mechanism, proton-transporting ATPase activity, rotational mechanism	rs7720861[48]	No	6.1×10^{-6}	SA, observed in SNP-by-SNP GWAS
Intergenic, closest genes FLJ42117 (C3orf67; 322kb), FHIT (377kb)*	**Chromosome 3 open reading frame 67** Unknown function **FHIT** *See above*	rs11130703[41]	No	9.37×10^{-6}	SA in BD (Discovery cohort)
Intergenic; closest genes IL7, STMN2	**Interleukin 7** B and T cell development T cell lineage commitment, immune response, humoral immune response, cell-cell signalling, positive regulation of cell proliferation, organ morphogenesis, regulation of gene expression, positive regulation of B cell proliferation, negative regulation of apoptotic process, negative regulation of catalytic activity, bone resorption, positive regulation of T cell differentiation, positive regulation of organ growth, homeostasis of number of cells within a tissue, negative regulation of extrinsic apoptotic signalling pathway in absence of ligand extracellular region, extracellular space **STMN2: Stathmin 2** intracellular signaling cascade, neuron differentiation cell fraction, membrane fraction, soluble fraction, insoluble fraction, plasma membrane, internal side of plasma membrane, axon, growth cone,	rs10448042[47]	No	3.65×10^{-6}; meta-analysis of 3 studies	SA in BD; meta-analysis of three sample sets
		rs10448044[47]	No	2.81×10^{-6}; meta-analysis of 3 studies	Suicide behaviour severity in BD; meta-analysis of three sample sets

	site of polarized growth, cell projection, neuron projection, plasma membrane part, perinuclear region of cytoplasm				
Intergenic, closest genes IRX2, IRX4*	**Iroquois homeobox 2** regulation of transcription, DNA-templated, specification of loop of Henle identity, proximal/distal pattern formation involved in metanephric nephron development nucleus sequence-specific DNA binding **Iroquois homeobox 4** regulation of transcription, DNA-templated, heart development, establishment of organ orientation nucleus DNA binding, sequence-specific DNA binding	rs924134[41]	No	6.12×10^{-6}	SA in BD (Discovery cohort)
Intergenic; closest genes KIAA1462, MTPAP*	**KIAA1462** Unknown function **MTPAP: mitochondrial poly(A) polymerase** transcription, RNA processing, mRNA processing, mRNA metabolic process mitochondrion nucleotide binding, nucleoside binding, purine nucleoside binding, RNA binding, polynucleotide adenylyltransferase activity, ATP binding, nucleotidyltransferase activity, purine nucleotide binding, adenyl nucleotide binding, ribonucleotide binding, purine ribonucleotide binding, adenyl ribonucleotide binding, adenylyltransferase activity	rs2462021[41]	No	8.30×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
		rs1360550[41]	No	8.95×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
Intergenic; closest genes LOC100507632/ LINC00968, IMPAD1*	**LINC00968: long intergenic non-protein coding RNA 968** Unknown function **IMPAD1: Inositol monophosphatase domain containing 1** integral to membrane, intrinsic to membrane magnesium ion binding, inositol or phosphatidylinositol phosphatase activity, inositol-1(or 4)-monophosphatase activity, phosphatase activity, ion binding, cation binding, metal ion binding	rs2609990[47]	No	7.61×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2582384[47]	No	8.76×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
		rs2610025[47]	No	4.61×10^{-6}	Suicide behaviour severity in BD; meta-analysis of three sample sets
Intergenic, closest gene LRRIQ3 (LRRC44, 73kb)	**LRRC44/LRRIQ3 leucine rich repeats and IQ motif containing 3** protein binding	rs1417259[41]	No	3.17×10^{-6}	SA in MDD (Discovery cohort)
Intergenic; closest genes SFRP2 (113kb), DCHS2 (331kb)*	**SFRP2: Secreted frizzled related protein 2** patterning of blood vessels, chondrocyte development, outflow tract morphogenesis, cardiac left ventricle morphogenesis, apoptotic process, G-protein coupled receptor signaling pathway, cell-cell signaling, multicellular organism development, response to nutrient, positive regulation of cell proliferation, negative regulation of cell proliferation, male gonad development, negative regulation of gene expression, negative regulation of cardiac muscle cell apoptotic process, negative regulation of epithelial to mesenchymal transition, positive regulation of endopeptidase activity, regulation of neuron projection development, Wnt signaling pathway,	rs1993423[48]	No	3.6×10^{-6}	SA, observed in SNP-by-SNP GWAS

	negative regulation of Wnt signaling pathway, collagen fibril organization, positive regulation of cell growth, negative regulation of cell growth, negative regulation of cell migration, negative regulation of BMP signaling pathway, cellular response to extracellular stimulus, positive regulation of peptidyl-serine phosphorylation, positive regulation of cell adhesion mediated by integrin, positive regulation of catenin import into nucleus, non-canonical Wnt signaling pathway, post-anal tail morphogenesis, response to drug, negative regulation of mesodermal cell fate specification, embryonic digit morphogenesis, positive regulation of apoptotic process, negative regulation of cysteine-type endopeptidase activity involved in apoptotic process, negative regulation of JUN kinase activity, positive regulation of fat cell differentiation, positive regulation of osteoblast differentiation, positive regulation of angiogenesis, negative regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, digestive tract morphogenesis, negative regulation of epithelial cell proliferation, negative regulation of peptidyl-tyrosine phosphorylation, convergent extension involved in axis elongation, bone morphogenesis, sclerotome development, negative regulation of dermatome development, hematopoietic stem cell proliferation, cellular response to X-ray, negative regulation of canonical Wnt signaling pathway, planar cell polarity pathway involved in neural tube closure, Wnt signaling pathway involved in somitogenesis, positive regulation of canonical Wnt signaling pathway, negative regulation of extrinsic apoptotic signaling pathway via death domain receptors, negative regulation of intrinsic apoptotic signaling pathway in response to DNA damage, regulation of midbrain dopaminergic neuron differentiation, regulation of stem cell division, negative regulation of planar cell polarity pathway involved in axis elongation extracellular region, extracellular space, integral component of membrane, extracellular matrix fibronectin binding, G-protein coupled receptor activity, integrin binding, Wnt-protein binding, Wnt-activated receptor activity, receptor agonist activity, endopeptidase activator activity **DCHS2: Dachsous cadherin-related 2** homophilic cell adhesion via plasma membrane adhesion molecules plasma membrane, integral component of membrane calcium ion binding				
Intergenic, closest gene TBX20*	**T-box 20** *See below*	rs12538684[39]	No	6.9×10^{-6}	Suicide vs. Non-suicide postmortem
		rs990633[39]	No	5.6×10^{-6}	Suicide vs. Non-suicide postmortem
Intergenic, closest gene TMX3 (126kb)*	**TMX3** Calcium ion binding and protein disulfide isomerase activity; association with ADHD and neural development platelet degranulation, protein folding, peptidyl-cysteine oxidation, response to endoplasmic reticulum stress, cell redox homeostasis cell, endoplasmic reticulum membrane, plasma membrane, cell	rs7244261[47]	No	4.10×10^{-6}; meta-analysis of 3 studies	Suicide behaviour severity in BD; meta-analysis of three sample sets

	surface, integral component of membrane, platelet alpha granule membrane				
Intergenic, closest gene ZFAT (ZNF406, 390kb)	**ZNF406/ZFAT: zinc finger and AT-hook domain containing** hematopoietic progenitor cell differentiation, transcription from RNA polymerase II promoter, multicellular organism development, positive regulation of transcription from RNA polymerase II promoter, spongiotrophoblast layer development nucleus, cytosol RNA polymerase II regulatory region sequence-specific DNA binding, transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding, nucleic acid binding, transcription factor activity, sequence-specific DNA binding, metal ion binding	rs1457463[41]	No	8.45×10^{-6}	SA in BD (Discovery cohort)
KCNIP4	**Potassium voltage-gated channel interacting protein 4** cardiac conduction, potassium ion transmembrane transport, protein localization to plasma membrane, regulation of potassium ion transmembrane transport cytoplasm, endoplasmic reticulum, cytosol, plasma membrane, voltage-gated potassium channel complex voltage-gated ion channel activity, potassium channel activity, calcium ion binding, potassium channel regulator activity	rs358592[44]	No	2.5×10^{-6}	TWSI; escitalopram-treated subjects; potential gender-dependent effect
KIAA1244 (ARFGEF3)	**ARFGEF family member 3** negative regulation of phosphatase activity, regulation of ARF protein signal transduction, positive regulation of GTPase activity integral component of membrane, transport vesicle membrane ARF guanyl-nucleotide exchange factor activity	rs203136[42]	No	1.74×10^{-7}; RADIANT analysis	MDD; discrete trait: SA; $P=6.24\times10^{-5}$ in meta-analysis
KIAA1549L (C11orf41)	**KIAA1549 like** integral component of membrane	rs10437629[45]	No	3.77×10^{-6}; (combined analysis of 2 datasets)	SA; Bipolar disorder subjects; *P*-value primary dataset = 8.56×10^{-5}
MIR548AA1 **MIR548D1***	**microRNA 548aa-1** Unknown function **microRNA 548d-1** Unknown function	rs6677272[48] rs6679943[48]	No No	8.6×10^{-7} 8.6×10^{-7}	SA, observed in imputed and genotyped SNPs SA, observed in SNP-by-SNP GWAS
NCAM1	**Neural cell adhesion molecule 1** MAPK cascade, cell adhesion, axon guidance, neuron projection development, positive regulation of GTPase activity, viral entry into host cell, regulation of synaptic plasticity, interferon-gamma-mediated signaling pathway Golgi membrane, cytoplasm, plasma membrane, external side of plasma membrane, cell surface, membrane, integral component of membrane, anchored component of membrane, extracellular exosome virus receptor activity, Ras guanyl-nucleotide exchange factor activity	rs3781878[46]	No	1.98×10^{-6}	SA, Meta-Analysis of RADIANT, GSK-Munich, and BACCs
NEBL	**Nebulette** cardiac muscle thin filament assembly stress fiber, Z disc, I band, extracellular exosome	rs703088[42]	No	9.01×10^{-6}; RADIANT analysis	MDD; discrete trait: SA; $P=5.37\times10^{-4}$ in meta-analysis

	protein binding, tropomyosin binding, cytoskeletal protein binding, zinc ion binding, structural constituent of muscle, filamin binding, actin filament binding				
PAPLN	**Papilin, proteoglycan like sulfated glycoprotein** proteolysis, negative regulation of endopeptidase activity proteinaceous extracellular matrix metalloendopeptidase activity, serine-type endopeptidase inhibitor activity, peptidase activity, zinc ion binding	rs11628713[40]	**Experiment-wide**	**6.2×10^{-7}**	TESI
PLCB1	**Phospholipase C beta 1** Social and communication difficulties in childhood and adolescents[39] G2/M transition of mitotic cell cycle, signal transduction, G-protein coupled acetylcholine receptor signaling pathway, glutamate receptor signaling pathway, Wnt signaling pathway, calcium modulating pathway, brain development, memory, regulation of G-protein coupled receptor protein signaling pathway, lipid catabolic process, cerebral cortex development, positive regulation of interleukin-12 production, intracellular signal transduction, interleukin-12-mediated signaling pathway, interleukin-15-mediated signaling pathway, positive regulation of embryonic development, positive regulation of GTPase activity, inositol phosphate metabolic process, fat cell differentiation, positive regulation of myoblast differentiation, negative regulation of transcription, DNA-templated, positive regulation of transcription, DNA-templated, positive regulation of JNK cascade, phosphatidylinositol metabolic process, insulin-like growth factor receptor signaling pathway, positive regulation of developmental growth, regulation of cell cycle, activation of meiosis involved in egg activation, interleukin-1-mediated signaling pathway, regulation of fertilization, positive regulation of G1/S transition of mitotic cell cycle, positive regulation of acrosome reaction, negative regulation of monocyte extravasation, positive regulation of CD24 biosynthetic process nuclear chromatin, nucleus, cytoplasm, cytosol, nuclear speck, nuclear membrane, myelin sheath, extracellular exosome phosphatidylinositol phospholipase C activity, signal transducer activity, GTPase activator activity, calcium ion binding, protein binding, calmodulin binding, lamin binding, phosphatidylinositol-4,5-bisphosphate binding, enzyme binding, protein homodimerization activity	rs6055685[39]	No	8.31×10^{-7}	SI in depressed subjects
PRKCE	**Protein kinase C epsilon** macrophage activation involved in immune response, protein phosphorylation, apoptotic process, cell cycle, cell adhesion, signal transduction, activation of phospholipase C activity, positive regulation of epithelial cell migration, positive regulation of fibroblast migration, positive regulation of cell-substrate adhesion, peptidyl-serine phosphorylation, platelet activation, positive regulation of actin filament polymerization, negative regulation of protein ubiquitination, lipopolysaccharide-mediated signaling pathway, positive regulation of insulin secretion, positive regulation of synaptic transmission, GABAergic, positive regulation of cytokinesis, intracellular signal transduction, locomotory exploration behavior, TRAM-dependent toll-like receptor 4 signaling pathway, Fc-	rs12373805[41]	No	9.20×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
		rs4953249[42]	No	7.30×10^{-6}; RADIANT analysis	MDD; discrete trait: SA; $P=7.15\times10^{-3}$ in meta-analysis

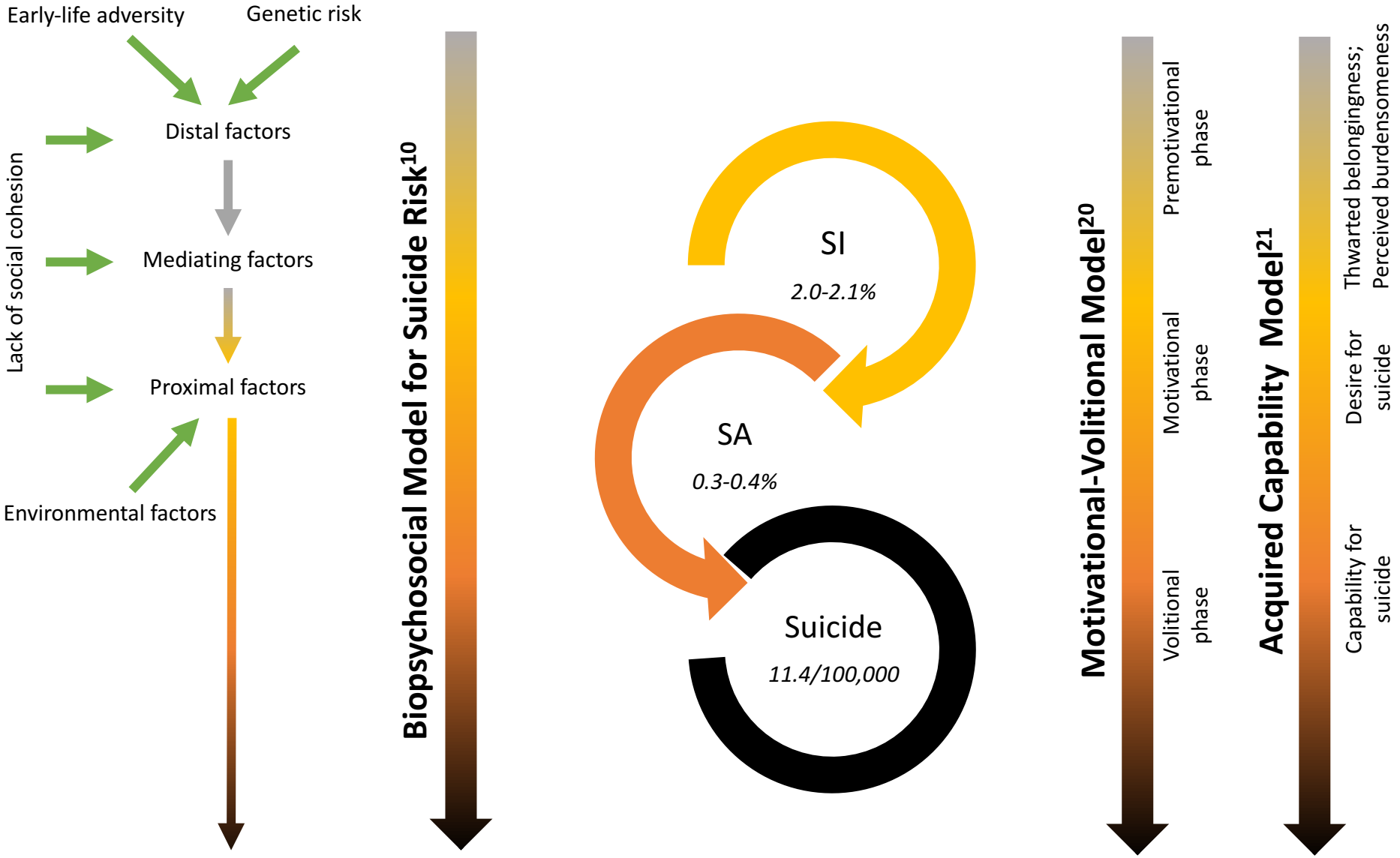
	gamma receptor signaling pathway involved in phagocytosis, positive regulation of I-kappaB kinase/NF-kappaB signaling, response to morphine, positive regulation of MAPK cascade, regulation of peptidyl-tyrosine phosphorylation, positive regulation of lipid catabolic process, release of sequestered calcium ion into cytosol, regulation of release of sequestered calcium ion into cytosol, cell division, regulation of insulin secretion involved in cellular response to glucose stimulus, positive regulation of mucus secretion, cellular response to ethanol, cellular response to prostaglandin E stimulus, cellular response to hypoxia, positive regulation of wound healing, positive regulation of receptor activity, negative regulation of sodium ion transmembrane transporter activity, positive regulation of cellular glucuronidation nucleus, cytoplasm, mitochondrion, endoplasmic reticulum, Golgi apparatus, cytosol, cytoskeleton, plasma membrane, perinuclear region of cytoplasm, cell periphery actin monomer binding, protein kinase activity, protein serine/threonine kinase activity, protein kinase C activity, calcium-independent protein kinase C activity, signal transducer activity, protein binding, ATP binding, enzyme activator activity, enzyme binding, receptor activator activity, ethanol binding, metal ion binding, 14-3-3 protein binding				
PROM1	**<u>Prominin 1</u>** retina layer formation, photoreceptor cell maintenance, retina morphogenesis in camera-type eye, camera-type eye photoreceptor cell differentiation, glomerular visceral epithelial cell differentiation, glomerular parietal epithelial cell differentiation, positive regulation of nephron tubule epithelial cell differentiation photoreceptor outer segment, extracellular space, endoplasmic reticulum, endoplasmic reticulum-Golgi intermediate compartment, plasma membrane, integral component of plasma membrane, cell surface, integral component of membrane, apical plasma membrane, microvillus membrane, vesicle, photoreceptor outer segment membrane, intracellular membrane-bounded organelle, extracellular exosome protein binding, actinin binding, cadherin binding	rs17387100[46]	No	7.98×10^{-7}	SA, Meta-Analysis of RADIANT, GSK-Munich, and BACCs
		rs17387100[42]	No	9.53×10^{-6}; RADIANT analysis	MDD; discrete trait: SA; $P=4.52\times10^{-3}$ in meta-analysis
PSME2/RNF31	**<u>PSME2: proteasome activator subunit 2</u>** Immunological Disease, inflammatory response[39] MAPK cascade, protein polyubiquitination, stimulatory C-type lectin receptor signalling pathway, antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent, regulation of cellular amino acid metabolic process, positive regulation of endopeptidase activity, anaphase-promoting complex-dependent catabolic process, tumor necrosis factor-mediated signalling pathway,NIK/NF-kappaB signalling, Fc-epsilon receptor signalling pathway, proteasome-mediated ubiquitin-dependent protein catabolic process,regulation of mRNA stability, T cell receptor signalling pathway, negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle, positive regulation of ubiquitin-protein ligase activity involved in regulation of mitotic cell cycle transition, Wnt signalling pathway, planar cell polarity pathway, regulation	rs4575[39]	No	7.49×10^{-6}	SA/Suicide vs. Non-attempter live/non-suicide postmortem

	of proteasomal protein catabolic process, negative regulation of canonical Wnt signalling pathway, positive regulation of canonical Wnt signalling pathway, regulation of G1/S transition of mitotic cell cycle proteasome complex, nucleoplasm, cytoplasm, cytosol, proteasome activator complex, membrane, extracellular exosome protein binding, identical protein binding, endopeptidase activator activity **RNF31: Ring finger protein 31** protein polyubiquitination, I-kappaB kinase/NF-kappaB signalling, regulation of tumor necrosis factor-mediated signalling pathway, CD40 signalling pathway, positive regulation of I-kappaB kinase/NF-kappaB signalling, T cell receptor signalling pathway, positive regulation of NF-kappaB transcription factor activity, protein linear polyubiquitination, positive regulation of protein targeting to mitochondrion cytosol, cytoplasmic side of plasma membrane, CD40 receptor complex, LUBAC complex ubiquitin-protein transferase activity, protein binding, zinc ion binding, ligase activity, ubiquitin protein ligase binding, ubiquitin binding, metal ion binding				
RARRES2	**Retinoic acid receptor responder 2** retinoid metabolic process, in utero embryonic development, positive regulation of protein phosphorylation, platelet degranulation, chemotaxis, inflammatory response, positive regulation of macrophage chemotaxis, positive regulation of fat cell differentiation, embryonic digestive tract development, brown fat cell differentiation, positive regulation of chemotaxis, regulation of lipid catabolic process, positive regulation of glucose import in response to insulin stimulus extracellular region, extracellular matrix, platelet dense granule lumen, extracellular exosome receptor binding, protein binding	rs17173608[46]	No	2.41×10^{-7}	SA, Meta-Analysis of RADIANT, GSK-Munich, and BACCs
SLC19A2	**Solute carrier family 19 member 2** transport, folic acid transport, thiamine transport, thiamine-containing compound metabolic process, thiamine transmembrane transport plasma membrane, integral component of plasma membrane, integral component of membrane protein binding, folic acid transporter activity, thiamine transmembrane transporter activity, thiamine uptake transmembrane transporter activity	rs2072757[48]	No	2.2×10^{-6}	SA, observed in imputed and genotyped SNPs
SLC4A4	**Solute carrier family 4 member 4** ion transport, integral component of membrane, transporter activity‡ transport, sodium ion transport, inorganic anion transport, bicarbonate transport, sodium ion transmembrane transport, regulation of intracellular pH, anion transmembrane transport plasma membrane, integral component of plasma membrane, integral component of membrane, basolateral plasma membrane, extracellular exosome inorganic anion exchanger activity, protein binding, sodium:bicarbonate	rs2602098[41] rs7655668[41]	No No	8.80×10^{-7} 4.16×10^{-6}	SA in MDD (Discovery cohort) SA in MDD (Discovery cohort)

	symporter activity				
SORBS1	**Sorbin and SH3 domain containing 1** muscle contraction, actin filament organization, cell adhesion, cell-matrix adhesion, insulin receptor signaling pathway, positive regulation of signal transduction, glucose transport, cellular response to insulin stimulus, stress fiber assembly, positive regulation of glycogen biosynthetic process, positive regulation of glucose import, positive regulation of lipid biosynthetic process, focal adhesion assembly, positive regulation of establishment of protein localization to plasma membrane stress fiber, nucleus, nucleoplasm, cytoplasm, centrosome, cytosol, plasma membrane, insulin receptor complex, cell-cell adherens junction, zonula adherens, cell-substrate adherens junction, focal adhesion, nuclear matrix, membrane raft actin binding, SH3/SH2 adaptor activity, insulin receptor binding, protein binding, cytoskeletal protein binding	rs4918918[41]	No	3.28×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
		rs7076888[41]	No	8.62×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
		rs7079293[41]	No	6.19×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
		rs7900095[41]	No	5.58×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
		rs955760[41]	No	4.87×10^{-6}	SA in all mood disorders (random-effects meta-analysis)
SPACA6*	**Sperm acrosome associated 6** fusion of sperm to egg plasma membrane integral component of membrane protein binding	rs12462673[41]	No	8.85×10^{-6}	SA in MDD (Discovery cohort)
STK3	**Serine/threonine kinase 3** Neuronal cell death[39] neural tube formation, endocardium development, protein phosphorylation, apoptotic process, signal transduction, central nervous system development, negative regulation of cell proliferation, signal transduction by protein phosphorylation, positive regulation of protein binding, hippo signaling, intracellular signal transduction, positive regulation of apoptotic process, positive regulation of fat cell differentiation, positive regulation of JNK cascade, negative regulation of organ growth, protein stabilization, positive regulation of sequence-specific DNA binding transcription factor activity, positive regulation of protein kinase B signaling, primitive hemopoiesis, cell differentiation involved in embryonic placenta development, regulation of cell differentiation involved in embryonic placenta development, positive regulation of protein serine/threonine kinase activity, negative regulation of canonical Wnt signaling pathway, hepatocyte apoptotic process, positive regulation of extrinsic apoptotic signaling pathway via death domain receptors nucleus, cytoplasm, cytosol, protein complex magnesium ion binding, protein kinase activity, protein serine/threonine kinase activity, receptor signaling protein serine/threonine kinase activity, protein binding, ATP binding, protein serine/threonine kinase activator activity, protein dimerization activity	rs3019286[39]	No	8.24×10^{-6}	SA/Suicide vs. Non-attempter live/non-suicide postmortem
TBL1XR1	**Transducin beta like 1 X-linked receptor 1** negative regulation of transcription from RNA polymerase II promoter, response to dietary excess, transcription, DNA-templated, lipid catabolic process, histone deacetylation, regulation of cAMP metabolic process, multicellular organism growth, proteasome-mediated ubiquitin-dependent protein catabolic process, cellular lipid metabolic process, positive	rs1466846[41]	No	1.98×10^{-6}	SA in BD (Discovery cohort)

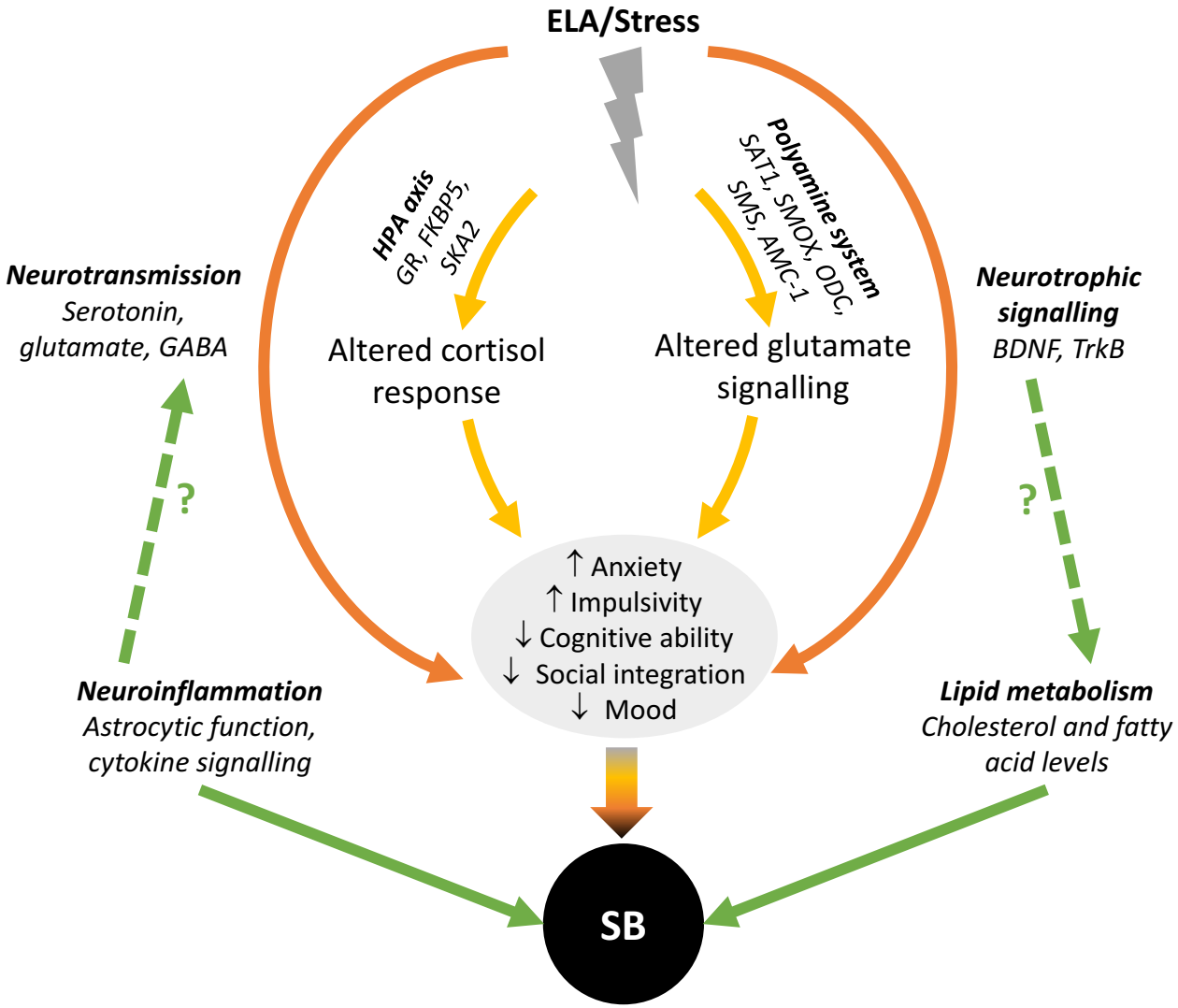
	regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, white fat cell differentiation, canonical Wnt signaling pathway, fat pad development, regulation of triglyceride metabolic process histone deacetylase complex, nucleus, nucleoplasm, spindle microtubule, integral component of membrane, transcriptional repressor complex transcription corepressor activity, protein binding, beta-catenin binding, histone binding, transcription regulatory region DNA binding, protein N-terminus binding				
TBX20	**T-box 20** Brainstem motor neuron development[39] *Cell Death and Survival*[39] negative regulation of transcription from RNA polymerase II promoter, patterning of blood vessels, endoderm formation, neuron migration, heart looping, embryonic heart tube morphogenesis, outflow tract septum morphogenesis, tricuspid valve development, aortic valve morphogenesis, pulmonary valve formation, endocardial cushion morphogenesis, cardiac chamber formation, cardiac right ventricle morphogenesis, endocardial cushion formation, cardiac septum development, pericardium morphogenesis, transcription from RNA polymerase II promoter, muscle contraction, blood circulation, cell proliferation, dorsal/ventral pattern formation, negative regulation of SMAD protein complex assembly, visceral motor neuron differentiation, foramen ovale closure, embryonic heart tube elongation, negative regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, lateral mesoderm formation, cardiac muscle tissue morphogenesis, positive regulation of cardiac muscle cell proliferation, atrial septum morphogenesis, pulmonary vein morphogenesis nucleus, cytoplasm, RNA polymerase II regulatory region sequence-specific DNA binding, RNA polymerase II core promoter proximal region sequence-specific DNA binding, transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding, RNA polymerase II transcription factor binding, RNA polymerase II activating transcription factor binding, RNA polymerase II transcription coactivator activity, transcription factor activity, sequence-specific DNA binding	rs17675131[39]	No	1.2×10^{-6}	Suicide vs. Non-suicide postmortem
		rs2109090[39]	No	2.8×10^{-6}	Suicide vs. Non-suicide postmortem
		rs2240994[39]	No	1.0×10^{-6}	Suicide vs. Non-suicide postmortem
		rs336284[39]	No	7.56×10^{-6}	SA/Suicide vs. Non-attempter live/non-suicide postmortem
		rs336284[39]	No	2.00×10^{-7}	Suicide vs. Non-suicide postmortem
		rs4723402[39]	No	2.7×10^{-6}	Suicide vs. Non-suicide postmortem
TMEM132C	**Transmembrane protein 132C** integral component of membrane	rs7296262[45]	No	1.09×10^{-6}; (combined analysis of 2 datasets)	SA; Bipolar disorder subjects; *P*-value primary dataset = 9.08×10^{-6}

*SNPs were mapped back to their corresponding genes using GWAS Central: ***http://www.gwascentral.org/markers***
‡Functional annotation from ***http://www.ebi.ac.uk/QuickGO/***
§Functional annotation from ***https://www.ncbi.nlm.nih.gov/gene/***
Note: Reference [41] included multiple tables of SNPs associated with SB that were too voluminous to be included here but can be consulted online at:
http://ajp.psychiatryonline.org/doi/suppl/10.1176/appi.ajp.2010.10040541



Lutz, Figure 1. Modelling suicide risk

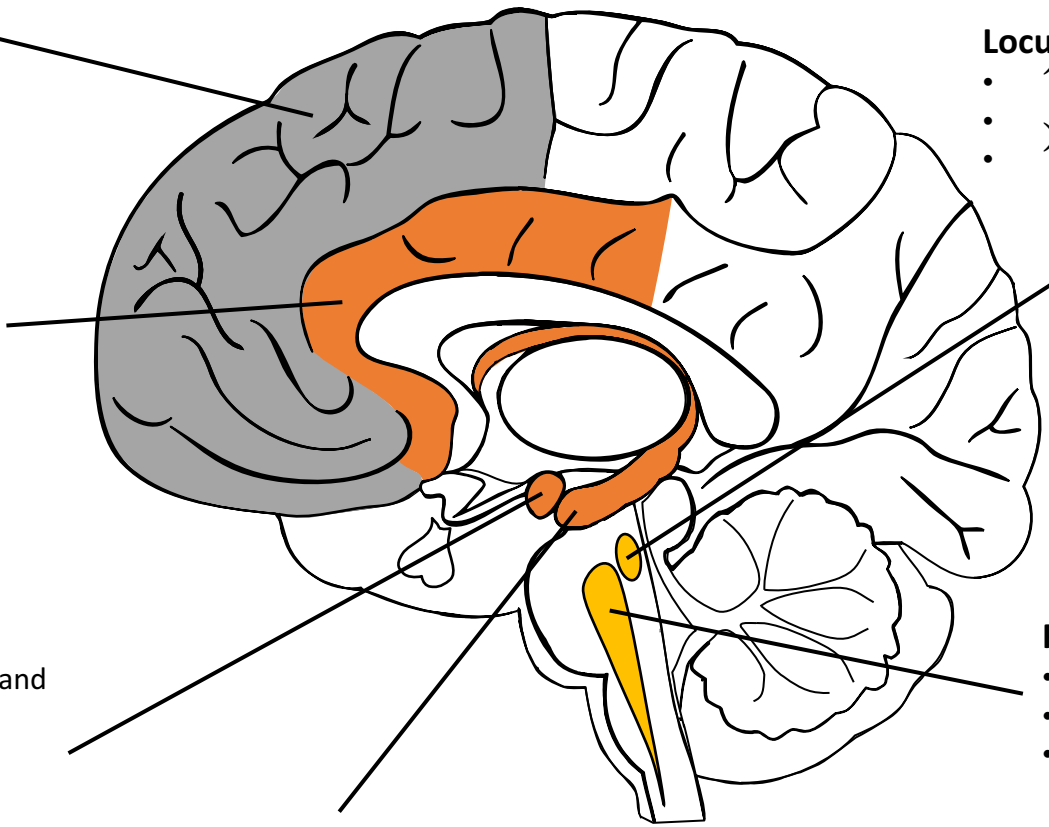
Global 12-month prevalence statistics for SI, SA and suicide; reviewed in: Turecki G, Brent DA. Suicide and suicidal behaviour. *Lancet* 2015.



Lutz, Figure 2. Biological pathways to suicidal behaviour

Prefrontal cortex
- ↓ activity
- ↓ grey matter volume
- Functional Δ in orbitofrontal cortex
- Δ cell type densities
- ↑ macrophage activity

Anterior cingulate cortex
- Δ microglial densities
- Astrocyte hypertrophy in dorsal ACC white matter
- Low level inflammation?
- Morphology Δ of layer VI pyramidal neurons



Locus coeruleus
- ↑ TH
- ↓ glutamate transporters
- ↑ NMDA receptor subunits

Amygdala
- ↑ cerebral blood flow and glucose metabolism
- Δ volume
- ↑ BLA volume
- ↓ glial densities
- Δ neuroplasticity

Raphe nuclei
- ↓ serotonin function
- ↓ 5-HT transmission
- ↑ TPH

Hippocampus
- ↓ volume
- ↓ neurogenesis in DG
- Δ granule-cell neuron maturation /survival?
- Δ CA cellular densities

Lutz, Figure 3. Brain regions implicated in depression and suicidal behaviour