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EPIGENETIC EPIDEMIOLOGY IN PSYCHIATRY: A TRANSLATIONAL NEUROSCIENCE PERSPECTIVE

Abstract

Accumulating evidence from the field of neuroscience indicates a crucial role for epigenetic regulation of gene expression in development and aging of nervous system and suggests that aberrations in the epigenetic machinery are involved in the etiology of psychiatric disorders. Epidemiologic evidence on epigenetics in psychiatry, however, is currently very sparsely available, but is consistent with a mediating role for epigenetic mechanisms in bringing together inherited and acquired risk factors into a neurodevelopmental etiological model of psychiatric disorders. Here, we review evidence from the epidemiological and neuroscience literature, and aim to converge the evidence into an etiological model of psychiatric disorders that encompasses environmental, genetic and epigenetic contributions. Given the dynamic nature of the epigenetic machinery and the potential reversibility of epigenetic modifications, future well-designed interdisciplinary and translational studies will be of key importance in order to identify new targets for prevention and therapeutic strategies.

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Keywords

• Epidemiology • Epigenetics • Psychiatric disorders • Translational neuroscience

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Introduction

Various environmental and genetic factors interact in complex manners throughout an individual's life to contribute to psychiatric disorders. Studies on the environmental and genetic epidemiology of psychiatric diseases have taken important steps forward in estimating heritability rates and identifying associations between a range of environmental and genetic factors in psychiatric phenotypes. Recent exciting developments in the field of epigenetics and neuroscience suggest that epigenetic mechanisms may mediate sustainable effects of environmental exposures and have profound roles in neurodevelopment and aging of the brain. These ideas have generated great interest within many research disciplines, including psychiatric epidemiology. The "seductive allure of behavioral epigenetics" [1] has prompted psychiatric epidemiologists to focus on direct and indirect evidence for epigenetic involvement in mental health

and normal behavior as well as in abnormal behavior and complex psychiatric disorders, in an attempt to elucidate the role of epigenetic mechanisms and possibly identify new strategies for prevention and treatment of psychiatric disorders [2]. Without attempting to provide a complete overview, this review addresses the current status of the literature on evidence indicative of involvement of epigenetic mechanisms in psychiatric disorders. The current article starts with a summary of the evidence from the field of molecular and cellular neuroscience for a role of epigenetic mechanisms in development and aging of the brain and its functional abilities. Next, we exemplify that aberrant epigenetic mechanisms are linked to neuropsychiatric phenotypes by briefly describing psychiatric consequences of classical syndromes of genetic imprinting in humans. Thereafter, we summarize general epidemiologic findings that are indicative of epigenetic involvement in psychiatric disorders and review the

more direct epidemiologic evidence (i.e. differential epigenetic profiles) for epigenetic involvement in the most prevalent and severe psychiatric illnesses. We will end the article by discussing current research challenges in epigenetic epidemiology and neuroscience, and we propose that more studies combining epidemiological and neuroscience approaches in studying epigenetics are needed to improve our understanding of the role of the epigenetic machinery in the etiologies of psychiatric disorders.

Epigenetic mechanisms

DNA methylation

DNA methylation involves addition of a methyl group from S-adenosyl methionine (SAM) to CpG units, i.e. regions of DNA where a cytosine (C) nucleotide occurs next to a guanine (G) nucleotide in the linear sequence of bases. The methylation of CpG sites, overrepresented in CpG islands in the promoter regulatory

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regions of many genes, disrupts the binding of transcription factors and attracts proteins known as methyl-CpG-binding domain proteins that initiate chromatin compaction and gene silencing [3].

Histone modifications

Histones are the basic proteins around which DNA is packaged and ordered to form nucleosomes. Posttranscriptional modifications of histones comprise the other major type of epigenetic mechanism related to gene expression. A number of covalent histone modifications, occurring at specific residues, have been described (eg, acetylation, methylation, phosphorylation, SUMOylation, and ubiquitylation), which together constitute a complex “histone code” modulating gene expression via alterations in chromatin structure [4]. Histone acetylation is linked with transcriptional activation, while deacetylation is related to transcriptional repression [4].

Non-coding RNAs and Genetic imprinting

MicroRNAs (miRNAs) are small regulatory RNAs that individually regulate up to several hundred genes, and collectively may regulate as much as two-thirds of the transcriptome [5]. Another relevant epigenetic mechanism is genomic imprinting, the phenomenon by which certain genes are expressed in a parent-of-origin-specific manner, independently of classical Mendelian inheritance. Imprinted genes are expressed only from the allele inherited from one of the two parents.

Epigenetics and development of the brain

Pioneering work in the last decade has uncovered epigenetic regulation of gene transcription as fundamental for normal development and functioning of the organism, especially in relation to appropriate responses to stimuli [6]. The various epigenetic mechanisms encompass DNA methylation, histone modifications, genetic imprinting, X-inactivation, and non-coding RNAs which give rise to tissue- and cell-type specific profiles of gene expression and epigenetic

marks throughout the course of life. DNA methyltransferase (Dnmt) enzymes (Dnmt1, Dnmt3a and Dnmt3b) catalyze the transfer of methyl groups to DNA. Deletion of Dnmt1 or treatment with Dnmt inhibitors has been reported to lead to global DNA hypomethylation, chromosomal instability, and compromised cell-cycle progression, thereby hindering self-renewal of tissue-specific stem cells and ultimately leading to embryonic lethality. Although Dnmt3a-null mice appear to be grossly normal at birth [7,8], mice lacking Dnmt3a do acquire developmental defects in postnatal life and die prematurely [7].

Besides robust changes in reprogramming of genomic methylation patterns in germline cells as well as in pre-implantation embryos [9], it has become clear that dynamic changes occur in the patterns of DNA methylation, histone alterations and expression of microRNA's throughout life and especially during development. Brain development involves cellular processes such as cellular proliferation, cellular differentiation, and maturation [10], but also myelination [11], and synaptic plasticity, and accumulating evidence indicates that these processes depend on appropriate epigenetic regulation [12]. Recent experimental animal studies have, for example, established that the functional abilities of memory formation, learning, motivation and reward are all linked to epigenetic regulation of gene expression [13-15]. Genetic manipulation of Dnmt1 and Dnmt3a in mice has shown that long-term plasticity (which underlies learning and memory) in the mouse hippocampus depends critically on these major DNA methyltransferase enzymes [16]. Experience-driven developmental changes are furthermore known to impact at different biological levels, such as membrane depolarization, calcium influx, and induction of transcription factors [17], and recent studies have discovered that sustainable effects of developmental exposures and experiences are mediated (and reflected) by epigenetic alterations [18], as discussed in more detail below. Evidence that humans with mutations in gene encoding methyl CpG-binding protein 2 (Mecp2) frequently show markedly decreased cognitive performances is furthermore in line with this notion.

Epigenetics and aging

Epigenetic changes are proposed to have crucial impact on early life programming and thereby on neurodevelopmental disorders [19], but also affect age-related changes in the brain. Recent work reports that epigenetic markings are subject to change with advancing age [20,21]. While earlier work suggested that aging was associated with a global loss of DNA methylation, more recent work indicates that age-related changes are also CpG-island dependent [20-22]. By investigating human tissues at 1,413 autosomal CpG loci associated with 773 genes, Christensen et al. observed highly significant CpG island-dependent correlations between age and methylation; loci in CpG islands gained methylation with age, loci not in CpG islands lost methylation with age [22]. Another large scale study using human brain tissue identified CpG loci, primarily CpG islands, with consistent positive correlation between DNA methylation, and chronological age [23]. In addition, recent findings on an aging mouse cohort kept under controlled environmental conditions throughout live showed that the level of the major de novo methylation enzyme Dnmt3a increased with age in the hippocampus [24], and correlated with age-related increase in levels of 5-methyl cytidine (5-mC). The same study showed that caloric restriction, which increases lifespan and prevents age-related alterations and pathology in various animal species [25-28], was able to prevent these age-related changes in hippocampal levels of Dnmt3a [24] and 5-mC (Prevention of age-related changes in hippocampal levels of 5-methylcytidine by caloric restriction [29]. The speculation of a causal involvement of epigenetic mechanisms in age-related decline of functional abilities of the brain [30] is in line with i) findings that age-related memory disturbances in mice are associated with altered chromatin plasticity (in particular with dysregulation of H4k12ac) in the hippocampus [31], and ii) the link between sirtuins, i.e. molecules which deacetylate H4K16ac in a Nicotinamide adenine dinucleotide -dependent manner, and life span [32]. Thus, epigenetic mechanisms appear to be fundamentally involved in

the neurobiological processes that govern development [19] and aging of the brain [21], and gives credibility to the speculation that epigenetic mechanisms are involved in the formation of an individuals' functional abilities and personality characteristics, as well as in neurodevelopmental and neurodegenerative trajectories of psychopathology [1,32,33].

Genetic imprinting and psychiatry

The crucial role of genetic imprinting in brain function is exemplified by the clinical pictures of two syndromes that are caused by aberrations in genetic imprinting: Angelman syndrome and Prader-Willi syndrome [34]. Angelman syndrome results from loss of expression of the maternal gene *Ube3a* at chromosome 15, by either deletion or other genetic abnormalities [35]. The maternal gene is normally expressed while the paternal gene is normally silenced. The characteristic clinical picture of Angelman syndrome comprises neurodevelopmental disabilities, motor abnormalities, seizures and speech deficits, resembling the clinical picture in patients with deficiencies in 5,10-methylenetetrahydrofolate reductase (*Mthfr*) or in patients with mutations in *Mecp2* [36]. Prader-Willi syndrome results from the loss of paternal expression of genes (on the same region on chromosome 15 as Angelman syndrome) [34]. Prader-Willi syndrome is clinically characterized by the psychopathological features of mental retardation, obsessive-compulsive symptoms, eating problems, hypersomnia and neurodevelopmental delay of motor skills [37]. Thus, aberrations of genetic imprinting in the same region on chromosome 15 can cause two syndromes with overt neuropsychiatric illness phenotypes.

Epigenetics and twin discordance in psychiatric disorders

Although members of monozygotic twin pairs are generally considered to be identical in genetic sequence, they exhibit different patterns of gene expression. Proband-wise concordance rates for psychiatric disorders in classical twin studies have frequently been used to estimate heritability, and such studies

generally show a wide range of concordance, in the order of 20-80%, while many psychiatric disorders also have clear links to aberrant neurodevelopment, e.g. autism spectrum disorders, ADHD, and schizophrenia. The standard assumptions that greater disease concordance rates in monozygotic (MZ) versus dizygotic (DZ) twins indicates genetic contribution, and concordance rates well below 100% in MZ twins indicates an environmental component, has been challenged by evidence indicating that i) gene-environment interactions may contribute to both the 'genetic' and 'environmental' components [38], and iii) possible effects of stochastic factors exist on biological processes such as regulation of gene expression throughout life [2,39].

While most MZ twins show phenotypic similarity and MZ twin pairs are expected to be concordant for congenital malformations, chromosomal abnormalities, and Mendelian disorders, phenotypic discordance in MZ twins does occur frequently and may arise from various sources such as i) chromosomal and monogenetic variations, ii) differences in environmental exposures in the intrauterine (differential timing of the twinning process, a differential number of cells allocated to each twin, and differential placental vascularization), perinatal (such as hypoxia) and postnatal environment, as well as iii) epigenetic differences [40]. An indication of epigenetic mediation of environmental exposures during life is provided by whole-genome and locus-specific methylation analyses of DNA from lymphocytes of MZ twins (15 male twin pairs and 25 female twin pairs) showing that approximately one-third of these MZ twins harbored significant epigenetic differences in DNA methylation and histone modification that were more distinct in MZ twins who were older, had different lifestyles, and had spent more of their lives apart [41].

Recent methylation microarray analyses of DNA in lymphocytes and buccal mucosa of 114 monozygotic twins and 80 dizygotic (DZ) twins confirmed the presence of substantial differences in DNA methylation profiles in MZ twins, while also showing epigenetic metastability of 6,000 unique genomic regions in MZ twins, and greater epigenetic similarity

in MZ co-twins than in DZ co-twins [42]. Differences in methylation profiles in buccal mucosa of MZ twins have furthermore been reported for CpG sites in a number of specific candidate genes for psychiatric disorders such as the dopamine D2 receptor (*Drd2*) gene [38] and the catechol-O-methyltransferase (*Comt*) gene [43]. In addition, differential DNA methylation profiles in buccal mucosa have been observed in MZ twins discordant for bipolar disorder [44] and the behavioural phenotype of risk-taking behavior [45]. A recent methylation microarray analysis of MZ twins discordant for bipolar disorder observed increased methylation in the affected twins upstream of the spermine synthase gene (*Sms*) and lower methylation upstream of the peptidylprolyl isomerase E-like gene (*Ppiel*) [44]. Another recent study that interrogated the methylation profile of the whole genome of DNA extracted from whole blood samples of MZ twins pairs discordant for schizophrenia and bipolar disorder, showed distinct genetic loci with differential methylation profiles in affected twins [46], thus providing further evidence suggesting a role for an aberrant epigenetic machinery in schizophrenia. However, very detailed analyses on MZ twin pairs discordant for multiple sclerosis [47] indicated that the puzzle of explaining MZ twin discordance is far from being solved. Analyses of the genome sequences of a MZ twin pair discordant for multiple sclerosis, and messenger RNA transcriptome and epigenome sequences of lymphocytes from 3 MZ twin pairs discordant for multiple sclerosis failed to detect reproducible differences in approximately 3.6 million single nucleotide polymorphisms and approximately 0.2 million insertion- deletion polymorphisms between the co-twins [47]. Although the detailed analyses did detect 2 to 176 differences in the methylation of approximately 2 million CpG dinucleotides between siblings of the 3 twin pairs, it is unlikely that these methylation differences can fully explain disease discordance [47].

Thus, preliminary evidence indicates epigenetic involvement in MZ twin discordance, although the complete puzzle of explaining MZ twin discordance in the various (neuro) psychiatric disorders is far

from being solved. Future twin research will be of crucial relevance for the formulation and testing of new etiological models of complex psychiatric traits and disorders integrating the contributions of genetic components, environmental exposures, gene-environment interactions, stochastic factors and epigenetics [2,48-50].

Epigenetics and sex differences in psychiatric disorders

The onset, course and phenomenology of psychiatric disorders often show sexual differentiation [51,52]. Female sex has consistently been associated with increased risk of depressive disorders [53] and anxiety disorders such as panic disorder, post-traumatic stress disorder and social phobia [54], while male sex is associated with ADHD [55], autism spectrum disorders [55-57], and substance abuse disorders [58]. Sexual differentiation is furthermore apparent in age of onset, phenomenology and developmental trajectories towards psychopathology [59,60]. Various epigenetic mechanisms have been proposed to underlie sexual differentiation in psychiatry. Besides differential exposures to environmental risk factors with sustainable effects on the individual's phenotype, sexual differentiation in many features of psychiatric disorders may be the result of sex hormone-induced differences in the epigenetic status of key genes impacting during sensitive time periods during development [61]. For example, methylation of the promoter of the estrogen receptor- α gene has been reported to increase during development [62].

Another epigenetic mechanism giving rise to sexual differentiation is X-chromosome inactivation. X-inactivation is the irreversible epigenetic process that involves silencing of one of the two X-chromosomes in female individuals during early development [63]. X-inactivation is estimated to take place just before the morula stage when the human embryo contains less than 16 cells [64,65]. Previous studies have shown that the timing of X-inactivation is associated with the timing of chorionic twinning [64]: dichorionic

monozygotic (DC-MZ) twinning is estimated to take place at, or before the morula stage (so, just at or before X-inactivation) and the monochorionic monozygotic (MC-MZ) twinning event occurs after the morula stage (and consequently after X-inactivation) [64]. Consistent with the notion that individuals who are members of DC-MZ twins are separately subject to X-inactivation, patterns of X-inactivation are more identical in MC-MZ twins than in DC-MZ twins [64,66]. Thus, chorionicity may be used as a proxy-measure of X-inactivation. While it has been proposed that X-inactivation may affect functional abilities and risk of psychiatric disorders particularly in females [67], only a very limited number of studies in psychiatry have directly measured variations in X-inactivation, although various epidemiological studies have used proxy-measures of X-inactivation. For example dichorionicity in twins and female sex have been considered as a proxy measure of X-inactivation. In contrast to previous twin studies using sex and chorion type in isolation as proxy-measures for X-inactivation [67], a recent study by Peerbooms et al. combined information on sex and chorion type in an improved proxy measure and found no association between this proxy measure for X inactivation and variations in intelligence and behavioral problems in children with a mean age of 10 years, thus indicating no major role for X-inactivation in variations of these traits at this age [68]. However, a recent study by Rosa et al. using more direct measures of X-inactivation by comparing methylation at CpG islands of X-linked housekeeping genes on the active and inactive X-chromosomes in blood and buccal epithelial cells (as an index of X-chromosome inactivation) found evidence that was suggestive for a role of X-inactivation in bipolar disorder. The index of X-inactivation showed a borderline statistically significant difference for discordant bipolar disorder twin pairs as compared to controls [69]. Nevertheless, the role of X-inactivation in behavioral traits and psychiatric disorders has only received very little research interest thus far and urgently requires further exploration.

Transgenerational inheritance in epigenetics and psychiatric disorders

Epigenetic marks can be transmitted across generations [70] and the fact that the environment itself can alter the epigenetic regulation of gene expression, the boundary between 'environmental' and 'heritable' risks for diseases is likely to be far less clear-cut than previously recognized.

Parent-of-origin effects reflect a differential proportion of paternal or maternal disease-causing transmission to offspring. Thus, the risk-increasing effects of alleles for certain complex diseases may depend on their parent-of-origin. It has been proposed that parent of origin effects are either based on mutagenesis, causing de novo spontaneous mutations which would then propagate and accumulate in successive generations of sperm-producing cells, or on genomic imprinting [71]. Parent of origin effects have, for example, been described in autism, psychosis, and late onset cases of Alzheimer's disease [72-77]. It has furthermore been described that paternal and maternal ages (at the time point of conception) are risk factors for various psychiatric disorders with neurodevelopmental origins such as schizophrenia and autism. Paternal age effects have been proposed to be mediated by epigenetic mechanisms [78]. In autism, a 10-year increase in paternal age (independent of maternal age) was associated with a 22% increased risk for autism (independent of paternal age) while a 10-year increase in maternal age has been associated with a 38% increased risk for developing the disorder [78,79], which is in line with other findings reporting associations between parental ages and autism [80-82]. A recent meta-analysis on the association between paternal age and schizophrenia reported that both advanced paternal age (≥ 30) and younger paternal age (< 25) may increase the risk of schizophrenia, with further analyses indicating that younger paternal age may be associated with particularly an increased risk in male but not female offspring [83]. Given these effects of paternal (and maternal age) on risk of several psychiatric disorders, one could speculate that

paternal and maternal age influence general functional abilities of the offspring's brain rather than inducing abnormalities specific for a certain disorder. An interesting recent study on 33,437 children drawn from the US Collaborative Perinatal Project reported that offspring of older fathers were impaired in tests of neurocognitive ability (at an age of 7 years) while advanced maternal age was associated with better neurocognitive abilities [84]. The pattern of childhood behavioral problems in the same population was also differentially affected by advanced paternal age as compared with advanced maternal age: while advanced paternal age was associated with externalizing behaviors in the offspring but not with internalizing behavioral outcomes, advanced maternal age was significantly protective against externalizing behavioral outcomes, but associated with an increased risk of internalizing behavioral problems [85]. Evidence that, at least for some disorders, both high and low paternal or maternal age were associated with increased risk of psychopathology, e.g. in autism [80] and schizophrenia [83], is in line with the concept of the existence of an optimal (epigenetic-regulated) window of paternal and maternal ages at conception. Thus, parent of origin effects and effects of paternal (and possibly also maternal age) on risk of psychopathology in offspring point to a possible role for genomic imprinting in the etiology of psychiatric disorders.

Environmental epigenetic in psychiatric disorders

A wealth of epidemiologic evidence indicates that environmental exposures influence susceptibility to disease in later life [19,49]. A consistent line of evidence has connected exposures to nutritional factors, childhood trauma, minority group position, drugs of abuse, and pre- and perinatal complications to an increased risk of psychiatric disorders such as depression and schizophrenia later in life, especially in genetically vulnerable people [38,48,60,86,87]. It has been argued previously that the contributions of genetic and environmental factors are unlikely to be independent and that models involving gene-

environmental interactions may be much more plausible [88-90]. Epigenetic mechanisms have been proposed as a prime candidate for mediating some of these environmental effects, primarily on the basis of indirect evidence and findings in experimental animal studies [48,49]. Direct evidence in humans remains however very sparse. Based upon the currently available evidence from both animal and human research, we focus here on some examples of environmental factors associated with psychiatric disorders, for which evidence suggests epigenetic involvement.

Pregnancy and perinatal complications

Population-based studies have suggested associations between psychiatric disorders and a wide variety of prenatal exposures, including maternal stress [91-93], maternal nutritional deficiency [94,95], maternal serum homocysteine levels [96], rhesus incompatibility [97], low and high neonatal vitamin D [98], prenatal toxoplasmosis [99,100] specific viral infections [101], bacterial infections [102], maternal pyelonephritis [103], maternal hypertension [104] and maternal use of analgesics [105] and diuretics [104] during pregnancy. As many of these exposures have been found to associate (or induce) epigenetic alterations in cell culture or animal studies, epigenetic mechanisms have been proposed to mediate at least some of these effects [48,106-109].

There are, however, few true replications on the associations with corresponding trimester timing and exposure definition, or credible non-replications on the associations between pregnancy and birth complications and psychiatric disorders [110-115]. It is therefore very difficult to draw any definitive conclusions about association (nor mediation) at this stage. Nevertheless, it is attractive to hypothesise that the wide variety of exposures may reflect a single underlying epigenetic mechanism associated with subtle developmental perturbations that increase risk for psychotic outcomes in interaction with genetic risk variants [103]. A recent study provided evidence that individuals from the Dutch Hunger winter who were exposed to famine prenatally showed hypomethylation at the imprinted IGF2 gene

when compared to their unexposed same-sex siblings 6 decades after the period of severe famine [116]; an association that was specific for peri-conceptional exposure to famine, thus suggesting crucial relevance of epigenetic mechanisms in very early mammalian development [116]. Several nutritional factors such as deficiencies of vitamin A or D, protein content, essential fatty acids, and folate have furthermore been proposed to mediate the increased risk of psychiatric disorders in offspring subjected to famine during fetal development [117]. A large birth cohort study with data on schizophrenia in adulthood indicated that elevated homocysteine levels in the third trimester of pregnancy were associated with an increased risk of schizophrenia in the offspring [96]. A study in which birth interval was used as a proxy of folate levels during pregnancy (as postpartum restoration to normal maternal folate values may take up to 1 year after pregnancy) further suggested an association between folate and schizophrenia [108].

Rearing environment and childhood abuse

Adoption studies provide evidence for an association between rearing environment, childhood stress and an increased risk of psychopathology at a later age. For example, adoptees with a family history for psychosis who had been brought up in dysfunctional adoptive family environments displayed an increased risk of psychiatric disorders [118-121]. On the other hand, a positive rearing environment may decrease the risk of psychotic disorder later in life, and it has been shown that high-risk children with positive parental relationships have a lower risk for developing schizophrenia [122]. Studies on the effects of an adverse early psychosocial environment on later psychiatric disorder have been bolstered by recent prospective epidemiological findings showing that victims of bullying have a 2-fold risk of psychotic symptoms with an even more elevated risk when victimization is chronic or severe [123], while recent population studies indicate that childhood adversities may account for approximately 30% of all psychiatric

disorders [124,125], and are associated with onset of psychiatric disorders as well as with persistence and severity of disorders [125-127]. No prospective studies have yet examined the link between childhood stress, epigenetic changes, and the onset of psychiatric disorders in humans. Recent experimental animal research, however, has suggested that the psychosocial environment and stress can mediate changes in gene expression during key developmental periods through epigenetic mechanism with long lasting effects on behavior. Meaney and colleagues observed that postnatal maternal care in rats was apparently associated with epigenetic modification of a transcription factor binding site in the promoter region of the glucocorticoid receptor gene (Nr3c1) which in turn directly altered gene expression and behavioral phenotypes in the offspring which persisted into adult life although experiments lacked proper reproducibility studies with updated techniques [128]. In subsequent experiments, methyl supplementation during the same early postnatal period seemed to reverse the epigenetic modification induced by maternal care, with related gene expression changes and behavioral phenotypes in adult offspring [129]. Interestingly, subsequent transcriptomic studies by the same group identified over 900 genes in the rodent hippocampus that were stably regulated by maternal care [130]. A recent study in humans suggested epigenetic differences in a homologous Nr3c1 promoter region, comparing DNA methylation in postmortem hippocampus samples obtained from suicide victims with a history of childhood abuse to that seen in samples from either suicide victims with no childhood abuse or controls. Thus, in line with the animal findings, abused suicide victims showed increased methylation of the Nr3c1 promoter with concomitant changes in mRNA [131].

Drugs of abuse

Evidence from epidemiological studies and meta-analyses has established that cannabis and other drugs of abuse can be considered risk factors for later psychotic symptoms or psychotic disorders [132-134]. The age (or

developmental stage) at which individuals start using cannabis influences this association [135]. Further evidence suggests that gene-environment interactions are likely implicated in the association between cannabis and psychosis [133,136-139]. For example, the psychotomimetic effect of cannabis is much greater in siblings of patients with a psychotic disorder, who are at increased genetic risk to develop psychotic disorder than in controls [140]. Cannabis use increased the risk for developing psychotic symptoms and schizophreniform disorder only in carriers with the valine158 allele in the Comt gene [136], while the risk-increasing effects of cannabis on psychosis expression were moderated by genetic variation in Akt1 in another study [138]. The primary psychoactive component of cannabis is Δ^9 -tetrahydrocannabinol (THC), which is thought to exert its effects through cannabis-1 receptor-mediated signaling [141]. Administration of THC or cannabis elicits long term molecular and cellular changes in the brains of mice and humans [142-145] as well as on electrophysiological and biochemical measures of neuronal signaling in brain structures such as nucleus accumbens and hippocampus [146] with differential effects by duration of exposure and timing during development [146-149]. The abuse of psychostimulants, such as cocaine and amphetamine, has also consistently been associated with major psychotic disorders and substance use disorders. Many drugs of abuse may act via the common mechanism of sensitization addiction and psychosis. In humans and animals, repeated exposure to psychostimulants induces a sensitized state [150]. Sensitized animals share a number of neurobiological changes such as long term alterations of mesolimbic and prefrontal dopaminergic neurotransmission while also expressing behavioral abnormalities [150]. In addition, acute exposure to drugs of abuse provokes transient increases in cFos and other members of the Fos family of transcription factors in the striatum [151]. The majority of these Fos factors become desensitized during chronic abuse, with the exception of Δ FOSB, which itself stimulates the expression of other genes, such as Cdk5 [152,153] Δ FOSB

accumulates in the nucleus accumbens and dorsal striatum and remains detectable for several weeks after cessation of drug administration, suggesting a role in the onset of addiction [153]. In mouse models of cocaine response, the upregulation of cFos and Δ FOSB upon acute administration is accompanied by transient H4 hyperacetylation at the cFos and FosB gene promoters [154]. Chronic exposure, however, does not result in H4 hyperacetylation but is associated with H3 hyperacetylation of the FosB promoter, without an effect on the cFos promoter. H3 hyperacetylation of cdk5 and Bdnf associated with chronic, but not acute, drug use was also detected after chronic cocaine administration, and persisted even one week after administration ceased [154]. These findings implicate epigenetic mechanisms in the development of addiction, and particularly in the immediate and sustained behavioral effects of cocaine use [154]. Human studies also showed enduring changes in gene expression in subjects exposed to psychostimulants. For example, prolonged exposure to amphetamine is associated with long-term reductions of dopamine transporter density in the brain as measured by in vivo imaging studies [155]. Exposure to cannabis, cocaine and phencyclidine have long lasting effects on intracerebral gene expression, and recent evidence suggests that in fact these drugs may all affect common neurobiological pathways. In a recent post-mortem study using human brain tissue samples, exposures to cannabis, cocaine and phencyclidine were associated with many transcriptional changes in the brain [156]. Hierarchical clustering of these transcripts indicated that genes from the calmodulin signaling cluster were predominantly affected in the brains of abusers, which may be of particular importance given that enhanced dopamine release due to sensitization depends on calmodulin signaling [157,158]. Thus, chronic exposure to drugs may induce a sensitized state with enduring intracerebral changes in gene expression (particularly in dopaminergic neurotransmission), with evidence - at least from animal studies- suggesting a crucial, mediating role for the epigenetic machinery.

Minority group position & social defeat

Meta-analytic work shows consistency for the association between psychotic syndrome and minority group position across a wide range of approaches, endpoints, settings and cultural group definitions [159,160], and after adjustment for a range of confounders. The association with minority group position is observed in both first and second generation migrants [159,160], as well as in minority groups without recent migration [161], indicating that pre-migration factors or migration itself are unlikely to mediate effects. Studies in four different countries have shown that the effect of minority ethnic group on psychotic syndrome depends on the ethnic density of the area the person is living in: the greater the proportion of the own ethnic group in the area, the lower the risk for psychotic disorder [162,163]. These findings suggest that it is not ethnic group per se that increases risk, but rather the degree to which one occupies a minority position, or stands out in relation to the social environment. Additional research suggests that effects associated with minority group position may be mediated by chronic social adversity and discrimination [164], resulting in social marginalisation or a state of social defeat (chronic experience of an inferior position or social exclusion [165]). Although epigenetic consequences of chronic social defeat hasn't been shown in humans yet, animal research has shown that chronic social defeat stress (by daily experience of defeat by a bigger and more aggressive mouse for 10 consecutive days) induces gene expression changes, particularly of *Bdnf*, via a range of epigenetic mechanisms including histone tail modifications and DNA methylation. For example, chronic exposure to social defeat stress in mice significantly downregulated mRNA levels of histone deacetylase-5 in the nucleus accumbens [166]. Chronic defeat stress in mice also induced enduring downregulation of *Bdnf* transcripts and increased histone methylation [167]. Interestingly, chronic treatment with the antidepressant imipramine can reverse downregulation of *Bdnf* transcripts while increasing histone acetylation at the

corresponding promoters [167]. Thus, animal research suggests that social stress may be an epigenetically mediated, environmental factor that underlies proxy risk factors such as ethnicity and migration in psychiatric disorders.

Synergism in environmental exposures

It has been proposed that psychiatric disorders arise slowly from subclinical symptoms that become abnormally persistent when synergistically combined with various environmental exposures during development that may impact on behavioral and neurotransmitter sensitization [86,168,169]. Although various experimental animal studies have indicated synergistic effects of environmental exposures [170-172], data from epidemiologic studies is very limited. For example, heritable risk for depression and the combined effects of several environmental exposures (over the course of development measured as lower birth weight for gestational age, childhood adversity and negative life events in adulthood) have recently been reported to have a synergistic impact on the psychiatric phenotype of stress-sensitivity [173]. While it remains to be established whether epigenetic alterations mediate these effects, future prospective epidemiologic studies with (epi) genetically sensitive designs may further focus on synergistic effects of environmental exposures during development with inherited sensitivity and epigenetic profiles.

Variation in epigenetic-relevant genes and psychiatric disorders

Dnmts

Genetic variations in genes that are crucially involved in epigenetic machinery may increase the risk for psychiatric disorders and neurodevelopmental process. Heritable mutations in *Dnmt1*, and *Dnmt3b* are observed in patients with ICF syndrome (Immunodeficiency Centromeric instability and Facial anomalies) [174], characterized by mental retardation, and hereditary sensory neuropathy with dementia and hearing loss [175].

Mthfr

The gene encoding 5,10-methylenetetrahydrofolate reductase (*Mthfr*) is an epigenetically relevant gene as it encodes a crucial enzyme involved in the folate-mediated one-carbon metabolism, which is essential for purine and thymidylate biosynthesis, methylation of DNA and amino acids, and necessary for reactions forming neurotransmitters [176]. Dysfunction of the one-carbon metabolism has been linked to a range of disorders including neural tube defects [177,178], autism [179], leukemia [180,181], dementia [182-184], colorectal cancer [183,185], cardiovascular disease [186] and congenital abnormalities [187,188]. Genetic studies on associations between genetic variants in *Mthfr* and various major psychiatric disorders such as schizophrenia, bipolar disorder and unipolar depressive disorder, have yielded largely inconclusive and often mixed results [189-195]. Given the essential role of *Mthfr* in brain function and neurodevelopment [196,197], and the fact that family and twin studies have established considerable shared genetic variance between psychiatric disorders [198-200], a recent meta-analysis (on a total of more than 29,000 subjects) tested whether genetic variation in *Mthfr* contributes to the shared genetic vulnerability of schizophrenia, bipolar disorder and unipolar depressive disorder [201]. This meta-analysis showed that *Mthfr* C677T was significantly associated with the combined group of schizophrenia, bipolar disorder and unipolar depressive disorder (odds ratio = 1.26 for TT versus CC genotype carriers; confidence interval 1.09 – 1.46) without evidence of modifying effects of psychiatric diagnosis, sex, ethnic group, or year of publication, thus providing evidence for shared genetic vulnerability for schizophrenia, bipolar disorder and unipolar depressive disorder mediated by *Mthfr* 677TT genotype [201].

Mecp2

The gene encoding for *Mecp2* is another gene crucially involved in epigenetics. *Mecp2* protein selectively binds CpG dinucleotides in the genome and mediates transcriptional repression through interaction with histone

deacetylase [202]. Besides being the major cause of Rett syndrome (a rare but fulminant neurodevelopmental disorder in young girls) [203], mutations in this X-linked gene have been found to be associated with a broad array of other neurodevelopmental disorders in males and females, including X-linked mental retardation [204,205], severe neonatal encephalopathy, Angelman's syndrome, and autism [202]. Thus, these findings show that variants in the key epigenetic regulator gene Mecp2 acting impact crucially on brain development and thereby on risk of psychiatric disorders.

Histone modification genes

A recent large meta-analysis suggested that common variants located at chromosome 6p22.1 in a cluster of the histone genes Hist1h2bj, Hist1h2ag, Histh2bk, Hist1h4i and Hist1h2ah, are associated with an increased risk of schizophrenia [206]. Although the observed associations may be linked haplotypes that include susceptibility alleles in many genes, the strongest association was observed for a region in and near a cluster of histone protein genes, making variants in histone coding genes prime candidates for further analysis, at least in schizophrenia.

Epigenetic epidemiology in psychiatric disorders

Depression, PTSD and suicide

Methylation microarray analyses of whole blood- derived, bisulfite-converted DNA indicated differential methylation profiles in 33 individuals who reported a lifetime history of depression, as compared to 67 non-depressed adults, suggested patterns of increased methylation in genes relevant for brain development and tryptophan metabolism and patterns of decreased methylation in other biological processes [207]. In post-traumatic stress disorder (PTSD), a similar microarray approach indicated differential methylation profiles in 23 PTSD-affected as compared to 77 PTSD- non-affected individuals; genes implicated in immune function were uniquely unmethylated in the affected individuals [208]. In post-mortem obtained brain tissue,

H3k27me differed in the Trkb promoter locus in suicide completers (n=20) as compared to control subjects (n=10) in the orbital frontal cortex but not in cerebellum [61].

Schizophrenia and bipolar disorder

Early studies primarily focused on differential epigenetic marks in specific candidate genes in post-mortem brain tissue. Such studies reported DNA methylation differences associated with schizophrenia in Comt [209] and reelin (Reln) using methylation-specific PCR [210], although studies using full quantitative methylation profiling methods did not confirm these findings [211-213]. Post-mortem analyses of cortical GABA-ergic neurons in schizophrenia have shown increased levels of Dnmt1 that was associated with altered expression of reelin or Gad67 [210,214]. As discussed earlier, MZ twins discordant for bipolar disorder had differential DNA methylation profiles in regions upstream of the spermine synthase gene (Sms) and upstream of the peptidylprolyl isomerase E-like gene (Ppiel) [215]. Methylation microarray analysis of frontal cortex tissue from patients with schizophrenia and bipolar disorder revealed DNA methylation differences of numerous loci, including several involved in biological processes such as glutamatergic and GABA-ergic neurotransmission, brain development, and other processes functionally linked to disease etiology [212].

Alzheimer's disease

Decreased global levels of DNA methylation were observed in the entorhinal cortex of Alzheimer's disease patients using immunohistochemical analyses [216]. Several human post mortem brain studies analyzing the methylation status of promoter regions of candidate genes of Alzheimer's disease have yielded mixed and inconsistent findings. Analysis of the App promoter from temporal cortex failed to show a difference in methylation status of the promoter region between control and Alzheimer's disease patients [217]. DNA methylation was decreased in the promoter region of the tau protein gene in the parietal cortex but its transcription was downregulated [218]. In a postmortem analysis of the frontal cortex and hippocampus, no

significant differences between Alzheimer's disease patients and aged-matched controls were found in the methylation patterns of the promoters of Mapt, Psen1, and App [219]. Another study demonstrated increased methylation within the promoter regions of ApoE and Mthfr in Alzheimer's disease patients when compared to controls, in both post mortem prefrontal cortex tissue and peripheral lymphocytes [220]. The methylation status telomerase reverse transcriptase (Htert) in DNA of blood lymphocytes, however, differed between Alzheimer patients and age-matched controls [221]. Epigenetic analyses in post-mortem brain samples furthermore showed that the epigenetic distance from the norm (the median methylation of the control individuals) increased with age, and was higher in people with Alzheimer's disease than in healthy controls [222]. Thus, clear and consistent evidence for epigenetic involvement in AD is currently lacking while adequately powered epigenetic analyses are warranted.

Summary and perspectives

It is easy to speculate about the role of epigenetic processes in mediating susceptibility to psychiatric disorders, but investigating these modifications at the combined epidemiological and molecular level is far from a simple task. The first generation studies on epigenetic differences in psychiatric disorders are characterized by a cross-sectional design investigating DNA methylation differences of candidate genes in small numbers of patients (n = 1 to 50) and age- and sex-matched "super- controls" (i.e. healthy controls without any psychopathology). DNA was derived from a range of tissue types (whole blood, blood lymphocytes, or homogenates of various brain regions) and processed with variable laboratory procedures. As these studies harbor various limitations, such as risk of false-positive findings, lack of prospective investigations, selection bias, treatment effects, disease effects, lack of primary tissue of interest (the brain), and lack of replication, results from these first generation studies should be interpreted with caution [223]. Nonetheless, the findings do suggest possible differential epigenetic profiles in psychiatric

disorders and generate hypotheses for future studies.

Difficulties in establishing etiological classifications of psychiatric disorders and phenotypes have spurred for the establishment of intermediate phenotypes, dimensions of psychopathology or sub-classes of conventional disease categories, which may be more proximal to the actual neurobiological causal factors, and thus more suitable for epigenetic epidemiologic research.

Analyses of DSM-IV classifications of diagnoses in the WHO mental health surveys have established that the temporary presence of distinct psychiatric disorders predicts subsequent onset of other psychiatric disorders, and that, therefore, 'comorbidity' of psychiatric disorders is the rule rather than the exception [224]. As many psychiatric syndromes/disorders share common risk and protective factors, it is not surprising that common genetic factors, such as polymorphisms in *Mthfr* [201] and *Npas3* [225], as well as various environmental exposures such as childhood adversity [124] have substantial effects that transcend traditional clinical diagnostic boundaries. Such data suggest that shared genetic, epigenetic and environmental factors contributed to neurodevelopmental alterations resulting in broad dimensions of mental ill-health [226]. While integrative investigations on genetic data, epigenetic data, and environmental data thus seem pertinent, analyzing these effects

in integrative statistical models remains a tremendous challenge [227,228].

The first epigenetic studies in psychiatric disorders have furthermore increased awareness of numerous challenges at the technical level, such as for example limited accessibility to high-quality human brain tissue from well-phenotyped patients, and the cell-type-specific and temporal-specific nature of the epigenetic machinery. Interestingly, evidence from human and experimental animal studies accumulates that many epimutations are not limited to the affected tissue or cell type, but can also be detected in other tissues. There is also a great need for studies establishing the epigenomic profile in different tissue types, and correlating of epigenetic profiles across tissue types of the same individuals, and across age ranges. Translational studies that combine findings from a) carefully conducted epidemiologic studies including longitudinal twin studies [229], b) molecular biology studies on prospectively collected, easily accessible human tissue (such as blood lymphocytes, buccal mucosa or germline cells) as well as post-mortem brain tissue [230], and c) experimental neuroscience animal studies on the neurobiological effects of environmental exposures during development [60,231] will allow for further exploration on the role of epigenetics in human development, neurophysiology and pathophysiology. Figure 1 illustrates a neurodevelopmental view on the role of epigenetics in the aetiology of psychiatric

disorders. The current phase of research can take advantage of recent developments in genome-wide analyses of genetic variations, gene expression and epigenetic marks that allow for explorative, hypothesis-free investigations. The exploration of epigenetic mediation of environmental exposures may also benefit from testing for gene-environment interactions by investigating genetic variants in epigenome-relevant genes for their interaction with environmental exposures in large, well characterized samples of subjects with psychiatric disorders [38]. Furthermore, Mendelian randomization designs [232], longitudinal studies including patients with 'at risk' mental states for psychiatric disorders (such as in psychosis [233] and dementia [234]), and the use of twin studies discordant for psychiatric phenotypes and/or environmental exposures [229] may yield important insights in the role of epigenetic alterations in the onset and/or course of psychiatric disorders. However, these studies should be performed in parallel to experimental and observational neuroscience studies in humans and animals in order to identify the underlying molecular and cellular mechanisms in the brain, to establish the reversibility of epigenetic changes, and to develop novel intervention strategies. As both genetic and environmental factors can be (relatively) well controlled and brain tissue easily obtained, animal studies will continue to be very informative in elucidating the role of epigenetics in brain function and dysfunction.

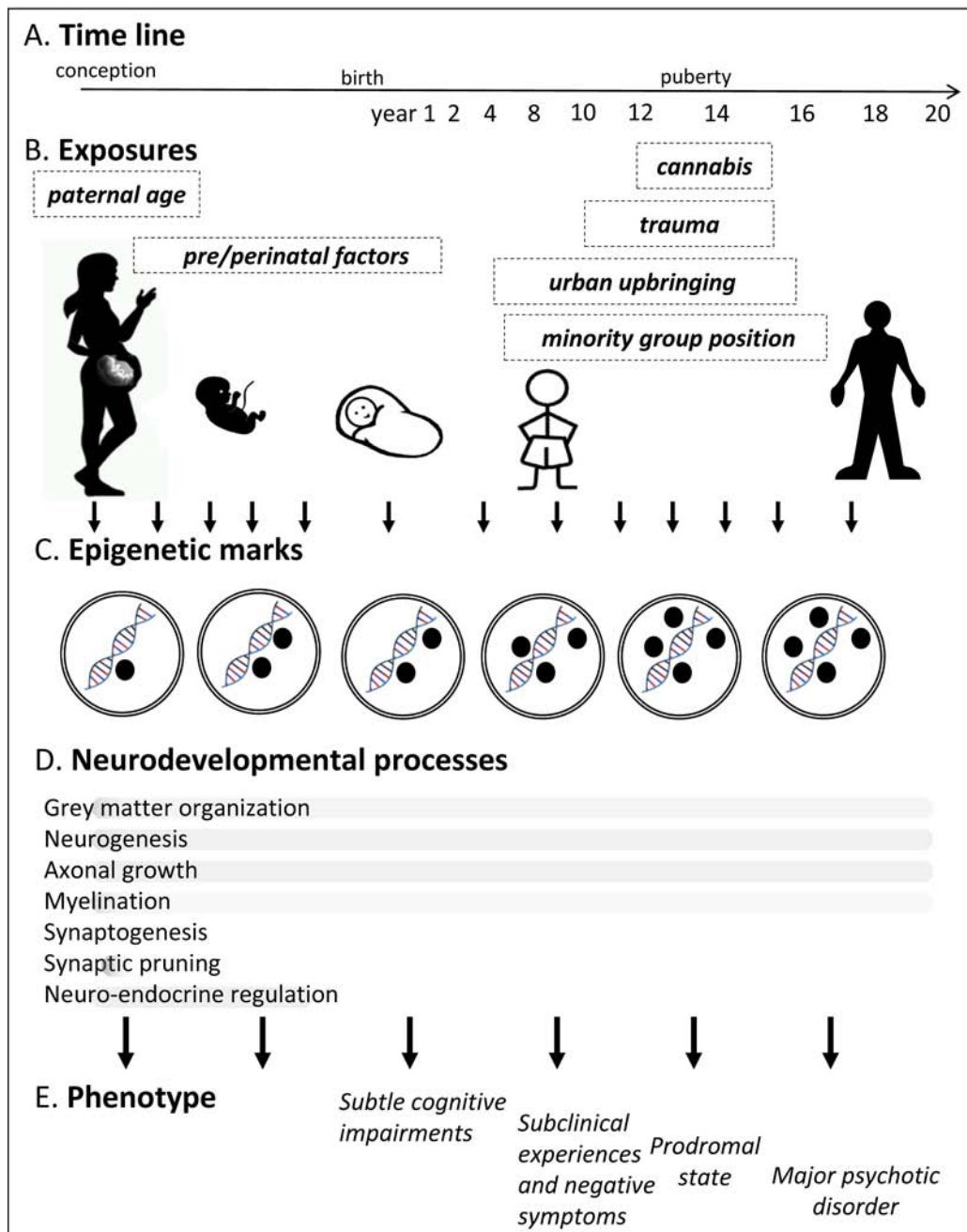


Figure 1. Neurodevelopmental model of epigenetic involvement in the aetiology of psychiatric disorders.

A scheme on a neurodevelopmental model of the aetiology of psychiatric disorders, with major psychotic disorder as an example of a psychiatric disorder, illustrating an individual's age (Fig. 1A), the approximate timing of risk-increasing exposures (Fig. 1B), epigenetic marks that can be inherited or acquired over life, as a possible consequences of exposures (Fig 1C.), timing of neurodevelopmental processes (Fig. 1D), and the temporal sequence of the expression of psychiatric phenotypes (Fig. 1E). Exposures depicted in 1B may thus induce epigenetic alterations on the molecular level that may impact on crucial neurobiological processes during sensitive periods of neurodevelopment, and may synergistically give rise to aberrations in mental health, phenotypically expressed by quantitative (and/or qualitative) alterations in psychological functions that in interaction with the individual's social world may result into psychiatric disorder. Black circles in 1C represent epigenetic modifications to DNA (e.g. methylated cytosines or histone modifications). The row represents a nucleus of a post-mitotic cells with dynamic changes to DNA modifications which may accumulate within the individual throughout development as a consequence of the synergistically combination of multiple exposures. These dynamic changes in DNA methylation may be associated with aberrations in neurodevelopmental processes such as for example myelination (Fig 1D), and the appearance of subclinical psychotic symptoms (Fig.1E) that can become abnormally persistent and ultimately lead to the onset of a major psychotic disorder (Fig 1E). Whilst this figure illustrates that development of major psychotic disorders is associated with accumulation of DNA modifications of a gene, other scenarios where removal of epigenetic modifications at a specific gene is associated with disorder, are equally possible.

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