From epigenetic associations to biological and psychosocial explanations in mental health – the need of a multi-disciplinary approach

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Summary

Abstract

The development of mental disorders constitutes a complex phenomenon driven by unique social, psychological and biological factors such as genetics and epigenetics, throughout an individual's life course. Both environmental and genetic factors have an impact on mental health phenotypes and act simultaneously to induce changes in brain and behaviour. Here, we describe and critically evaluate the current literature on gene-environment interactions and epigenetics on mental health by highlighting recent human and animal studies. We furthermore review some of the main ethical and social implications concerning gene-environment interactions and epigenetics and provide explanations and suggestions on how to move from statistical and epigenetic associations to biological and psychological explanations within a multi-disciplinary and integrative approach of understanding mental health.

Keywords: mental health; epigenetics; neuronal epigenesis; genetics; gene-environment interactions; mental disorders; environment; epidemiology; brain development.

1. Introduction

A major challenge of current research in the field of mental health is to understand how different factors related to the social environment; psychological characteristics, genetic make-up, transcription of genes (epigenetics) and cerebral architecture are involved in wellbeing and in the development of mental disorders in an individual. In order to be more effective, treatment and prevention need to be adjusted to individual differences related to all these factors.

There is abundant evidence in social epidemiological research regarding social determinants of mental illness during one individual's life course, e.g. unemployment, financial strain, living on social welfare, work environment with lack of decision latitude, job strain and bullying[1-3]. Social and psychological programs are available to help population groups and affected individuals cope with stressful conditions, e.g. community-based interventions for parents (parenting support). However, the effect of these interventions and programs may also depend on biological parameters that are unique for each individual. Some of these interventions and programs may at least work better for some individuals than others, possibly due to differences in their biological make-up.

Inter-disciplinary studies of the nature of these relationships and their effects on mental health conducted from genetic, neuroscientific and social perspectives are key to deepening our understanding of mental disorders.

There is growing evidence of associations between non-genetic variables and gene expression in regard to nutrition, maternal care/behaviour, psychosocial stress, adversity and neglect in early life indicating that the environment plays an important role in the evolving neuronal networks of the brain and in shaping the proteome and the metabolome[4,5]. Molecular epigenetic mechanisms in the cell may explain how the exposure to environmental factors influences the phenotypic outcome and variability both between individuals and within an individual at different points in time. As an example, the organisational complexity of the brain is not only a result of gene expression patterns but is also affected by the strength, selection and stabilization of synapses in a critical reciprocal interaction between the brain and its physical, psychosocial and cultural environment. Similarly, the homeostasis and the complex interplays of proteins' expression and metabolic pathways can be modified by these factors. Notably, the plasticity of gene expression, brain maturation, and metabolic signatures

in response to postnatal and adult social life events, both with increasing evidence of trans-generational effects, suggest the evolutionary significance of these mechanisms in enabling organisms to adapt to changing environmental conditions. In this sense, the subjective experience, or even the experiences of ancestors, may model the equilibria of human systems.

An interesting feature of epigenetics as well as of neuronal epigenesis is the putative reversibility of epigenetic changes, e.g. due to demethylation or synaptic plasticity, opening new avenues for prevention. The reversible nature of epigenetic pathways illustrates the potential of developing and bringing epigenetic drugs into therapeutics[6,7], accompanied by the possibility of developing approaches focusing on the understanding and improvement of psychosocial, cultural and political environments for the purpose of reversing unfavourable processes towards being epigenetically proactive[8,9].

2. Mental health – still awaiting a multi-disciplinary approach

Mental health involves emotional, psychological and social well-being. It affects directly how individuals manage challenges in everyday life. The World Health Organisation (WHO) reports from systematic reviews in some European countries indicate that as much as 27% of the adult population (aged 18-65) has experienced at least one of a series of mental disorders in the past year, including problems arising from substance use, psychoses, depression, anxiety, and eating disorders. Figures like these represent an enormous human toll of ill health. Yet, as WHO acknowledges, even these figures are likely to underestimate the scale of the problem, as only a limited number of disorders were included and it did not collect data on those aged over 65, a group that is at particular risk[10]. In addition, there is also data suggesting increasing prevalence of anxiety disorders in young children, with some even given medication in pre-school[11,12]. Mental disorders are by far the largest contributor to chronic conditions afflicting the population of Europe. They rank as the first cause of years lived with disability (YLD) in Europe, accounting for 36.1% of those attributable to all causes[13]. WHO estimates that 3 out of 4 patients with major depression in Europe, do not receive adequate treatment[14]. The treatment gap extends to other disorders like schizophrenia (32.2%), bipolar disorder (50.2%) and panic disorder (55.9%), where individuals remain untreated despite the availability of effective treatments[15].

Therefore, it is no surprise that since the last century, research has devoted particular attention in establishing the determinants of mental health and mental disorders. However,

deterministic models ranging from theories of biochemical imbalance to genetic approaches are not sufficient in explaining the phenotypic variability in the mental illness severity and in the response of individuals to treatment [16].

Some studies indicate that the simple use of medication is not sufficient to obtain a stable remission for disorders like psychosis, and that minimal or time limited use of antipsychotic medication seems to be associated with better long-term outcomes[17-19]. Similarly, although genetic loci have been identified which confer risk to mental disorders, the absolute risk conferred by individual loci is small, similar to other complex traits. Genetic association studies have demonstrated the importance of large cohorts, rigorous statistical analyses and independent replication in order to avoid confounding [20].

Diagnosis based solely on signs and symptoms like the diagnostic and statistical manual (DSM) do not reflect the nature of mental phenotypes which cut across the traditional diagnostic boundaries. This may lead to a number of fallacies including misdiagnosis but also categorization of conditions and as such overlooking valuable information. After all, depression, bipolar disorder, and PTSD may share common underlying mechanisms than what was originally expected. It has also been observed that the possibility to adapt to a changing environment is linked to mental health (see e.g.[21]). Evolutionary approaches have suggested that some behavioural syndromes or mental conditions which are classically considered mental disorders actually represent normal evolutionary attempts to overcome challenging situations and increase fitness to the environment (e.g.[22-25]).

In an attempt to provide a broader approach to health, the biopsychosocial model[26,27] had the merit to re-propose a holistic view of the individual as part of a complex network of factors where circularity rather than causality prevails[28]. Yet, it has been argued that this model has some limitations as research framework to investigate the etiology, diagnosis and treatment of mental disorders such as depression[29,30] and in implementing effective preventative policies[31]. It has been suggested that the biopsychosocial model needs to be revisited in light of the systems theory[30], in order to bridge better integrate biological, psychological, and social components of mental disorders.

For example, an individual that has experienced a highly stressful situation may go through a phase of depression characterized by the predominance of a) unpleasant emotions such as sadness, despair, anxiety; b) thoughts related to sense of uselessness, hopelessness, self-pity, self-blaming, unworthiness; c) lack of sleep, chronic fatigue, difficulties focusing, and reduction of pleasant activities. In some cases, the person may enter into a circuit where these emotions, thoughts, and behaviours constitute the premises to confirm the negative image that

the individual has of himself, associated with deeper negative emotions and with the adoption of behaviours that tend self-perpetuate and constantly reinforce the feeling of being depressed[32,33].

Garcia-Toro and Aguirre[30] identified and selected ten relevant empirical findings about depression from different research domains: 1) genetic predisposition; 2) predisposition due to early cerebral damage; 3) precipitating biological factors (such as somatic illnesses or drugs); 4) structural and functional neuroimaging changes; 5) effective biological treatment (such as the use of certain pharmaceutical drugs or of brain stimulation techniques); 6) predisposing early psychological stress; 7) predisposing personality traits (such as neuroticism); 8) predisposition due to social maladjustment (such as low socio-economic level and lack of social support); 9) precipitating psychological stress; and 10) effective psychosocial treatments (such as interpersonal therapy and cognitive-behavioural therapy). Further, they propose possible interactions between these evidences in the attempt to provide a more integrated non-causal view of the possible generative mechanisms related to depression. For instance, a parallel could be draw between reinforce of hyperactive neurons and atrophy of hypoactive neurons at the biological level and reinforce of the most used (depressive) cognitive-emotional schemas and segregation of the others (pleasure). This, in turn, calls for the implementation of early interventions, which could intervene before these schemas become rigid.

Network medicine, a newly emerging field, is based on the use of large data from different contributing aspects to a better understanding of disease development[34-37]. The integrative network approach bridges findings from the clinic (signs and symptoms), biological findings in the laboratory (metabolomics and genomics), increasing the understanding of mental disorders, even in the context of comorbidity between disorders of the brain like depression and medical conditions like inflammation. It has been argued that network-based models have been more successful in the diagnosis of non-mental diseases characterized by less ‘complexity’ and more straightforward distinctive symptomatic relations. Nevertheless, it is important to note that this observation could be attributed to nosological complexities or the lack of information concerning the fundamental etiology of mental disorders such as depression or schizophrenia compared to diseases such as lung cancer, and not due to “fuzzy symptom networks” in mental disorders. In principle, mental disorders like depression constitute a complex dynamic network of symptoms constantly creating a reinforcing loop of the disorder itself.

While the network approach allows the clinicians a closer approach to personalized medicine, several fundamental concepts of psychiatry are being overlooked and hence improvements in diagnosis and treatment using this approach are being stalled. For instance, network methods have reinstalled division between the two co-existing school of thoughts- biological and psychological- instead of complementing one another to improve diagnosis and treatment. Therefore, how can we rely on studies based on the network approach using tools unqualified to make accurate conclusions? To truly benefit from the network theory, replication studies for transparency and reproducibility, and longitudinal data for statements on temporal and causal relationships are needed. This comes hand-in-hand with increasing population size and heterogeneity, and relying on a combination of criteria and fundamental functional domains, like the Research Domain Criteria (RDoC).[38]

3. Environmental influences on mental health phenotypes

Associations between a range of environmental exposures and mental health phenotypes have been well-established[39-44]. One should keep in mind that the nature of these associations may act through a variety of pathways, which may contribute differently depending on the period of life, the tissues analysed or on the type of phenotype considered. The classical perspective is that genetic variants may modulate how an individual respond to environmental stressors, and so represent intrinsic susceptibilities to mental health or disease. An alternative perspective is that genetic variants impact on behavioural patterns that shape or select the surrounding environment and thereby modulate the likelihood of being exposed to adversity, stress or protective environments[45]. Another framework is represented by structural effects such that population groups with certain genetic profiles are exposed to e.g., poorer living conditions or welfare policies as well as to racial discrimination or refugee status. In addition, of course, personal or familiar experiences may trigger chains of events that represent risk or protective factors[43,46]. In the first phases of development, the family represents the main environment to which a child is exposed. Since it represents one of the pivotal vectors through which the influence of the surrounding environment is exerted, it is important to take this perspective into account as it may give important insights. An important challenge is to understand how environmental stressors or life events may have pervasive effects such that they alter mental health in the long term. Environmental factors have been shown to affect brain development[47-49], neuroendocrine functioning[50], the immune system[51], and possibly

disease progression[52]. In turn, patterns of cognitive and affective processing which result from the complex interplay between different body systems may affect the selection of environments by the individual as well as how the information from the environment or from interactions with other individuals is conceptualized and mentally represented.

In this vein, a series of studies by the group of Helen Neville reported that in pre-school children low socio-economic status was associated to a delay in selective attentional patterns[53-55]. Furthermore, the genotype of the serotonin transporter linked polymorphic region (5-HTTLPR) was also linked to a difference in the effects of selective attention on neural processing in this population of children. Interestingly, a family based training involving pre-school children and their parents was shown to reverse the effects of the socio-economic status and of the genotype on children' selective attention[56].

Importantly, whatever the perspective assumed, it is crucial to consider that these associations may not represent causal mechanisms. Particular caution should be taken in distinguishing between risk indicators (e.g., parental divorce) and risk mediators (e.g., family discord and conflict which often precede or accompany parental divorce), and between distal risks (e.g., poverty or parental loss) and proximal risks (impaired parenting often experienced in poor economic conditions or in the absence of one parent)[46]. Erroneous assumptions on causality or risk type may partially arise from the use of single frameworks or level of analysis that may be overcome by adopting a multi-level, complex approach. Complex approaches increase the likelihood of including simultaneously risk indicators and risk mediators as well as proximal and distal risks.

An important factor to be considered is that studies often assumed that environmental influences would be active in extreme conditions (e.g., parental loss) while they may well operate with a gradient of effect across the distribution (e.g., parenting difficulties). Another assumption concerns the period of plasticity for such influences. It is often supposed that the prenatal and early post-natal period is a unique window of opportunity. However, one should keep in mind that different environmental factors might have a variable degree of influence depending on the developmental stage, and that the period of plasticity for the influence of some environmental factors may be wider than expected ranging from prenatally to adulthood. Furthermore, individual characteristics or prior experiences may concur in determining greater vulnerability or protection from environmental risks.

4. Genetic influences on mental health

The relative importance of genetic and environmental influences on mental health has for long been studied in twin cohorts[57]. Comparisons of similarity between genetically identical (monozygotic, MZ) pairs and fraternal (dizygotic, DZ) pairs have been made for many decades in order to establish genetic contributions to normal human variation and the risk of clinically significant outcomes. The average heritability across different phenotypes is estimated to 49%[58]. Twin study designs have also been able to demonstrate causal interrelationships between brain structure and neuropsychological performance[59,60]. Comparing MZ with DZ pairs with shared environmental exposures will give information on the relative contribution of genetic and shared environmental effects. Of particular interest is to identify gene-environment interactions, such as the findings of Hicks et al.[61] that the genetic contribution to mental disorders expressing externalizing behaviours (e.g. attention-deficit/hyperactivity disorder, alcohol- and substance-related disorders) was especially pertinent in those individuals that had experienced high environmental adversity, and as described for psychotic disorders[62,63].

There is abundant evidence in terms of association between genotypes and mental disorders and health, e.g. genetic overlaps with schizophrenia and gender differences[64], genomic predictors of combat stress vulnerability and resilience[65] and posttraumatic stress[66]. In order to determine the causal influence of environmental factors such as early stressful life events and trauma, family relationships, socio-economic factors or school factors on neuropsychological development and mental health, one needs to assess genetic influence and gene-environment interactions as well as features that are correlated both with the environment, the brain and gene expression[67].

5. Effects of environmental exposures on behaviour and mental health mediated via epigenetic mechanisms

There is growing evidence of the impact of non-genetic variables on gene expression, e.g. nutrition, maternal care/behaviour, psychosocial stress, adversity and neglect in early life, hormones and drugs[68,69 70]. For instance, the Developmental Origins of Health and Disease (DOHaD[71,72]) paradigm states that environmental exposures in critical developmental periods may contribute to long-term modifications, programming our functioning at the biological

level. For instance, deprived environments early in life were associated with changes in the stress response system and with changes in brain architecture[73,74].

Molecular epigenetic mechanisms (DNA methylation and hydroxymethylation, histone modifications, non-coding RNAs and the three-dimensional organisation of chromatin within the nucleus[75]) may explain how the exposure of environmental factors influence the phenotypic outcome and variability both between individuals and within an individual at different times[63,68,76-78]. The possibility of maternal behaviour to influence epigenetic programming has been demonstrated in rat models. For example, increased pup licking and grooming by rat mothers altered the offspring epigenome, and was associated with differences in stress reactivity across generations[79]. These effects were reversed through cross fostering, indicating reversibility in programming through changes in behaviour. Moreover, Murgatroyd and Spengler recently demonstrated that adversity in early life might shape the experience-dependent maturation of stress-regulating pathways underlying emotional functions[80]. Similar social experience-dependent memory has been suggested to have an epigenetic basis, induced by the social and/or physical environment, via intracellular pathways[81]. It has therefore been hypothesised that exposures to adversities during early life may substantially affect stress sensitivity and immunity trajectories later in life by modifying DNA methylation during critical periods earlier in life.

Since the mid-twentieth century, several studies have also analysed the regulatory stress response in both children and adults as one of the most important mediating mechanisms for the influence of poverty on cognitive, emotional, and social functioning[82]. For example, threats, negative events, exposure to environmental hazards, family and community violence, changes in the dynamics of family life, job loss, instability and economic deprivation –which are most likely to occur under poverty conditions[83], are all phenomena that activate differently the systems of stress regulation[84,85]. The physiological responses to stress can also be manifested in different ways: vagal tone, allostatic load and neuroendocrine activity. In rodent models, stress has been observed to result in intergenerational transmission of phenotypes. For instance, repeated unpredictable separations of pups from the dam results in depressive-like behaviours and altered methylation profiles up to the third generation with a complex gender-dependent profile[86]. Family history of stress is associated also with altered miRNA expression and behavioural and metabolic signatures in the progeny, such as altered sensory-motor development, with some evidence for the strongest impact on the third

generation[86,87]. A growing body of literature indicates that traumatic prenatal experiences in the mother, such as wars, invasions or bereavement may be linked to a higher likelihood of experiencing mental ill-health in the offspring[88,89]. At a less extreme level, maternal stress or depression during pregnancy (a condition that is more likely to co-exist with low socio-economic status) was found to have an effect on diurnal cortisol pattern and to be transmitted to the offspring through biological mechanisms such as "diurnal cortisol coupling"[90,91].

Importantly, the psycho-social environment does not only exert negative influences on development. Positive early experiences and enriched environments can have a protective or mitigating effect on stress pathways[52,92,93] via epigenetic mechanisms. For instance, the results of the follow up of the Bucharest Early Intervention Project indicate that positive caregiving can reduce the effects of early life institutionalization on the stress pathway[93]. Furthermore, even in later phases of life, individuals can use (brain) plasticity to mitigate the negative effects of traumatic experiences[94].

Interestingly, Van Der Bergh[39] proposed to extend the DOHaD into the "Developmental Origins of Behaviour, Health, and Disease" (DOBHaD) hypothesis, in order to integrate also aspects of the behavioural development and to adopt a preventive approach to diseases and disorders. Starting from the evidence that many disorders have specific architectural or electric signatures before the individual shows clinical symptoms[53,95], he argues that more research is needed in order to increase our comprehension of the complex interplay between genes, gene expression, brain and behaviour and the biological mechanisms involved.

6. Effects of environmental exposures on brain networks: the neuronal epigenesis

The environment plays an important role also in the evolving neuronal network of the brain. The organisational complexity of the brain is not only a result of gene expression but affected by the selection and stabilization of synapses in a critical reciprocal interaction between the brain and its physical, social and cultural environment. As previously described[9], the word "epigenesis" can be traced back to William Harvey (1651), who stated in contrast to contemporary preformationist views that the embryo arises by "the addition of parts budding out from one another"[96]. It was subsequently used by Conrad Waddington (1942) to specify the relationship between the genes and their environment to produce a phenotype[96]. This is also the meaning adopted in the theory of the epigenesis of neuronal networks by selective

stabilization of synapses, according to which the environment affects the organisation of connections in an evolving neuronal network through the stabilization or elimination (pruning) of labile synapses, under the control of the state of activity of the network[97]. This meaning contrast with the more recent and biochemically distinct meaning of the word *epigenetic*, as described above**,** which refers to the molecular mechanisms through which altered genomic activity states are achieved. The modulatory role of chromatin modifications in long-term memory has already been described (see e.g., [98]), but the informational content involved—which relies upon cell bodies —is expected to be in orders of magnitude smaller that of synaptic epigenesis, based upon the combinatorial power of individual synapses.

During embryonic and postnatal development, the million billion (10^{15}) synapses that form the human brain network do not assemble like the parts of a computer, that is, according to a plan that precisely defines the disposition of all the individual components. If this were the case, the slightest error in the instructions for carrying out this program could have catastrophic consequences. On the contrary, the mechanism appears to rely on the progressive setting of robust interneuronal connections through trial-and-error mechanisms that formally resemble an evolutionary process by variation selection[97,99,100]. At sensitive periods of brain development, the phenotypic variability of nerve cell distribution and position, as well as the exuberant spreading and the multiple figures of transiently-formed connections originating from the erratic wandering of growth cone behaviour, introduce a maximal diversity of synaptic connections. This variability is then reduced by the selective stabilization of some of the labile contacts and the elimination (or retraction) of others. The crucial hypothesis of the model is that the evolution of the connective state of each synaptic contact is governed globally, and within a given time window, by the overall "message" of signals experienced by the cell on which it terminates[97]. One consequence of this is that particular electrical and chemical spatiotemporal patterns of activity in developing neuronal networks are liable to be inscribed under the form of defined and stable topologies of connections within the frame of the genetic envelope. In humans, about half of all adult connections are formed after birth at a very fast rate[101]. The nesting of these multiple traces directly contributes to forming and shaping the micro- and macroscopic architecture of the wiring network of the adult human brain.

Both epigenetic regulation and neuronal epigenesis point to the importance of multidisciplinary approaches in order to understand the effects of epigenetic mechanisms and the role of psychological, social and cultural factors in shaping behaviour, susceptibility to

disease and effects of treatment interventions. Furthermore, a significant feature of epigenetic mechanisms is their reversibility. Unlike genetic mutations, if a phenotype is caused by epigenetic phenomena, such as DNA methylation and histone acetylation, they can be chemically reversed. The reversible nature of epigenetic pathways indicates a potential of developing therapeutics and social interventions, which modulate epigenetics state. However, in order to be safely applied, therapeutic drugs will need to be extremely targeted, which remains a major challenge in the field. Reversibility is also a feature related to synaptic plasticity. Both epigenetic and neuronal epigenesis mechanisms indicate the importance of the environment and the need to understand and improve psychosocial and cultural environments in order to reverse an unfavourable process.

The neuronal organisation of the adult brain develops over a twenty-five year period following birth, during which it is subject to cultural influence, both on the individual level and at the social group level[102]. Synaptic epigenesis theories of cultural and social imprinting on our brain architecture (which differ from less discriminative epigenetic modifications of nuclear chromatin)–suggest that there is an interesting possibility, namely, that one could potentially be *epigenetically proactive*[8,9,103,104] and adapt social structures, in both the short and the long term, to benefit, influence, and constructively interact with the ever-developing neuronal architecture of the brains. For example, with the aim of preventing the development of mental disorders.

7. Ethical and social implications regarding gene-brain-environment interactions and proactivity

Social practices, local cultures and family patterns of lifestyle clearly also play a role in creating a milieu for the developing conceptus or infant. That in turn can induce parental effects that may or may not involve epigenetic processes but nevertheless have clear transgenerational effects. That being said, when non-contagious diseases become "contagious" to future generations, the distinction between communicable and non-communicable diseases in the area of public health may become less relevant from an ethical point of view. Links between individual liberties and health conditions for large population groups may change over time, and may lead to arguments for strengthening the social context, especially when the health effects of strengthening the social context would be positive for both current and future generations. However, social prevention programs need to be carefully

considered from an ethical point of view. Mental illness and disorders have been connected with social stigma, and explanatory hypotheses that connects biological and psychosocial data with mental disorders and illness will most likely give rise to a number of ethical issues.

As mentioned above, the use of large data that underlies network medicine give rise to issues around privacy and integrity. Comprehensive sets of health care information can be expected to be easier to collect, handle and transfer, even though the question if epigenetic information will as sensitive as genetic information remains open. Since environmental factors may be perceived to contribute more to the phenotype than genetic factors[105], also the issue around "the right not to know" may be less controversial in epigenetics than in relation to genetic information, see, e.g., UNESCO's Universal Declaration on the Human Genome and Human Rights, article 5c,

One issue relates to distribution of responsibilities and justice. There is an inter-relationship between individual and social responsibility where the balancing point may shift due to developments in genetics and epigenetics. Arribas-Ayllon, Featherstone and Atkinson[106] placed the balance close to individuals and their families when suggesting that there is a genetic responsibility whereby "individuals and families have a right, a duty, even a compulsion, to choose in relation to managing the risks of themselves and others". Relating to the insights of how important parental behaviour may be to the health of future generations, one might argue that this is a question of intergenerational equity (Rothstein et al, 2009)

That individuals should be held responsible for their health as well as for the health of their off-spring, is controversial since genetic risks are involuntary and may rather be seen as part of an individual's identity. However, when knowledge on how the environment, e.g. traumatic events in childhood, psychological stress in a family, poor living conditions, may affect the reading of a genetic make-up, both the individual and his/her family will have at least a theoretical possibility to affect the phenotype, and *eo ipso* a greater responsibility, at least to try to manage the environmental factors. However, from a public health and social justice perspective the extent to which individuals are free to choose their lives is to a significant extent depending on how opportunities are distributed and made available to them.

Public health research makes clear that justice in relation to health does not only involve the distribution of health care. It reaches into the fabric of society as a whole. A large number of

studies show that social factors affect health, such as education, socioeconomic status, relative wealth/poverty, gender, ethnicity, and individual and group behaviour. For instance, it was shown in the so-called Black Report that life expectancy varied strictly with social class position[107-110]. Other studies have shown that the prevalence of early deaths due to smoking and unhealthy food consumption is greater among the least well off. (Bartley 2004) Inequalities in health have been studied from various aspects: socio-economic, gender, age, and ethnicity. These factors should be understood as intersecting categories[111,112].

Arguably individuals and their families may have responsibilities for that which is in their capacity to change. However, from a social justice perspective the responsibilities fall heavily also on society in order to provide equal access and e conditions and on this basis give extra support to those who are 'worst off', due either to genetic make-up or to environmental factors affecting the transcription. Justice was explicitly and extensively addressed by John Rawls[113], who also presented the idea of giving priority to the worst off. According to Rawls' theory, inequalities can be justified, but only to the extent that they exist in the alternative that leaves the worst off as well off as possible. Special concern for the worst off is now a standard feature of most theories of justice. Norman Daniels adjusted Rawls' theory to accommodate health care[114].
Amartya Sen raised the question "Equality of what?", a central theme in discussions on justice ever since. Equality in the distribution of functions, opportunities, capabilities, and primary goods are some suggestions found in research, all relevant for sorting out the ethical quandaries related to accommodating epigenetics of mental disorders in a just society[115116-119].

Some of the theoretical assumptions and suggested social implications in this field may also be ethically controversial. Mental conditions may be problematic for the individual per se - intrinsic problems – while others only arise in a social context, e.g. when the individual encounters others: relational problems. Theories about causes of mental disorders include references to diverse factors: genetic, neurobiological, social and cultural. In addition to the scientific challenge of assessing suggested possible causal factors of mental disorders there is a challenge to avoid hype, over-interpretations, unjustified generalisations and ideological bias particularly for the field of neuroepigenetics and mental health.

As stated above, epigenetic variability may also be related to variation in results from empirical analyses and in the understanding of central concepts used to define phenotypic

expressions, such as “stress”, “traumatic stress”, and “resilience”. Indeed, different conceptualisations may also rely on different theoretical underpinnings, in particular psychological or social theory. One needs also understand the effects of environmental cues related to risk, resilience at both the molecular and the synaptic levels. Reversibility is a potential feature of epigenetic and synaptic mechanisms, thus making some of these amenable to both pharmaceutical and nutritional interventions. But even so, to what extent may social changes have the same effect, such as reversing or compensating for the effects of childhood deprivation for children less than 3 years of age? Linked to this are pertinent ethical issues related to the policy implications and the need to understand how social perceptions and norms of stress, resilience and aggression affect the social context of individuals and groups. Most importantly, evidence on gene-environment interactions across the life course of individuals and families calls for stronger and better coordinated efforts in improving the environments and living conditions during sensitive periods of development accompanied by interventions that will attempt to reverse and compensate for earlier disadvantage in the current ageing populations.

8. Going from associations to explanations

As described by Frances Champagne and in the beginning of this chapter, decades of longitudinal, preclinical and clinical based studies have highlighted the relationship between the social environment and behavioural/health outcomes[120]. There are several epidemiological registry-based studies also pointing in the same direction[121-125]. Continuous similar studies are coming from the Stockholm Public Health Cohorts[126], as well as other study cohorts such as a prospective military cohorts[127]. The potential role of epigenetic mechanisms in these processes has so far been based primarily on animal models. Public health, population registries and biobanks are vital in order to apply what has been learnt from animal models to a human context. There are several examples of environmental factors, both during prenatal and childhood/adolescence developmental stages, that have been proposed to interact with genetic factors in major psychotic disorders[77]. However, as noted by Rutten and Mill[77], these factors often represent only statistical interactions, and despite the existence of several epigenetic mediators identified in animal models, there remains a lack of knowledge about the underlying etiological mechanisms in human populations. Psychotic syndromes may be understood as disorders of adaption to a social context, implying that one needs to understand

both the social context in addition to the genetic, molecular and cellular factors. A lesson from epigenetics is that heritability estimates from classical twin studies reflect both the genetic influence and the underlying gene-environment interactions[128]. As concluded by Champagne, "epigenetic mechanisms play a critical role in development and may serve both to shape development in response to social experiences and to induce variation in social behaviour"[120].

As noted in a recent review by Vinkers *et al.*[129] the seminal observations by Weaver *et al*.[79] about the influence of the environment on the significant methylation effects related to stress has resulted in fairly consistent replication. It has also triggered numerous observational studies suggesting associations between DNA methylation and environmental impact. However, as Vinkers *et al.*[129] conclude there is a need to move beyond simply collecting large volumes of observational data of associations and design research projects that may provide plausible explanations of how epigenetic variability is related to meaningful biologic and psychosocial differences. A recent review by Provencal & Binder[68] concludes that exposure to stress in early life may prime the stress related system towards future responses to environmental challenges, being silent until the appropriate challenge occurs. As such, the consequences may be beneficial or detrimental depending on the challenge. However, as Provencal and Binder conclude, a full understanding of these effects will require longitudinal studies starting before conception with repeated sampling of different tissues, outcomes and environmental exposure[68].

In order to move beyond mere associations to plausible explanations of the relation between environmental impact and gene transcription or synaptic plasticity a number of questions must be addressed. For instance, a methodological shortcoming is that most studies in the field are cross-sectional, preventing conclusions on causal relationships, when in fact longitudinal and inter-generational studies are needed. One recent example of the first upcoming wave of longitudinal studies is a genome-wide, blood-based DNA methylation profiles in relation to the development of Post-Traumatic Stress Disorder (PTSD) symptoms in two prospective military cohorts. This study comprised discovery analyses in combat-trauma exposed Dutch military soldiers and replication analyses in U.S. marines, and indicated that the emergence of PTSD symptoms over a deployment period to Afghanistan was significantly associated with alterations in DNA methylation levels at several genomic positions regions (36).

Besides, DNA-methylation may also have a protective function for the organism rather than being a detrimental causal factor. Furthermore, epigenetic marks can be the consequence of phenotypic development, instead of causal[130], and therefore longitudinal study designs and techniques aiming at understanding causality such as Mendelian randomisation[131] or additive noise models[132] are required. There is therefore a great need to specify and understand confounding factors, including biological, psychosocial and cultural aspects. One needs also to tackle the fact that despite similar environmental exposures some individuals adapt and survive with a strong sense of identity while others suffer from poor health or low self-esteem. Advanced statistical methods are needed in order to understand the relative importance of different factors. Although researchers are now able to collect a wealth of clinical and molecular information in a large number of individuals, most of the discoveries to date in mental health, originate mainly from isolated analysis using only few selected factors. This results in loss of valuable information on how disease associated factors act in synergy to cause complex phenotypes. The lack of data integration using all available information is mainly due to the high complexity of bioinformatics and statistical analysis required.

Advances in bioinformatics are beginning to provide such tools using a network perspective to integrate multi-factor analysis in the study of complex phenotypes. In network models, correlations between variables, e.g. symptoms, are no longer explained by the common latent factor, the mental disorders, but rather mental disorders are conceptualized as complex systems where psychological, biological and environmental factors have autonomous causal power to influence each other[133]. There are a range of network analysis methods available with varying complexity from simple correlation networks to undirected graphical networks, such as Gaussian graphical networks, which are created on partial correlations, to Bayesian networks, which represent directed a-cyclical graphs and thus estimates of causal relations in a probabilistic way, again exploiting conditional dependencies between the observed variables. For an early example of a Bayesian network analysis see Curiac et al. Further research into causality methods in networks within this very general framework has come from additive noise models, where the structure of the noise is used to infer causality also in high dimensional data. Some of these methods have been shown to be quite robust to violations of the original underlying assumptions, which make them practical in applications. The use of longitudinal registries on environmental exposure combined with individual studies in genetics, brain development and epigenetics may provide the multi-dimensional data of sufficiently large sample size required for these novel integrative analysis techniques.

While recent advances have suggested that mechanistic reasoning paradigms may be applied using formalized computable knowledge, much research still being warranted in this domain[134,135].

Thus, taken together, it is evident that there is a current, great need, promise and challenge in embracing multi-disciplinary research approaches in moving from epigenetic associations to biological and psychosocial explanations in mental health and illness.

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