Reviewing the Epigenetics of Schizophrenia

Cromby, John (1)

Chung, Emma (2)

Papadopoulos, Dimitris (1)

Talbot, Chris (3)

(1) ULSM, University of Leicester

(2) Dept. of Cardiovascular Sciences, University of Leicester

(3) Dept. of Genetics, University of Leicester

Abstract

Background:

Epigenetic research in mental health has grown exponentially during the last decade and holds what some claim are 'revolutionary' potentials for the development of new interdisciplinary models of mental ill health. Schizophrenia is the most appropriate diagnosis against which to assess progress in this regard.

Method:

Papers on epigenetics and schizophrenia identified in a systematic literature search are subject to a conceptually-driven narrative review that assesses the relations between schizophrenia and epigenetics; considers some issues associated with empirical studies; and thereby identifies key assumptions guiding this research.

Findings:

The revolutionary potentials of epigenetics are thus far not being realised due to various influences including a preponderance of hypotheses that begin from a primarily biological question; the 'flattening' of environmental influences and their effective reduction to their molecular consequences; and a frequent reliance upon animal studies that effectively preclude some important influences already established as relevant to this diagnosis.

Conclusion:

Epigenetic research in schizophrenia (and mental health generally) could benefit from being more thoroughly interdisciplinary, from testing hypotheses that foreground social as well as biological influences, and from reconsidering its reliance upon psychiatric diagnoses.

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Introduction

Epigenetics explores how gene expression is regulated by environmental influences. These influences potentially include life experiences, as well as changes within the intra-cellular environment surrounding the DNA. Epigenetics was initially proposed in the 1940's to explain how different tissue types develop from the same genome (because different genes get expressed in different parts of the body). Subsequently, recent epigenetic studies have sometimes been more concerned with how environmental influences might be inherited by

subsequent generations. Key to this are processes such as methylation: the addition to a gene sequence of a methyl group, which has the effect of 'silencing' that gene when the DNA replicates. Whilst our understanding of these processes is still very much developing, it is accepted that they are environmentally driven, and thought that these environmentally produced changes can be passed on to offspring. For example, Yehuda et al (2015) claim to have found evidence for increased methylation, amongst both Holocaust survivors and their children, at gene sites associated with stress reactivity. Nevertheless, in other recent studies this trans-generational focus is itself de-emphasised, and epigenetics is predominantly conceived as a way of studying the effects of the dynamic material and social environment through their molecular impacts upon the informational codes of cellular reproduction. In short, there are slightly different practical definitions of epigenetics within this newly emerging field, which therefore constitutes a somewhat disparate field of research wherein the relations between basic processes and elements are yet to be settled.

In the immediate future epigenetics is likely to impact hugely upon biology and medicine (H. Rose & Rose, 2012), including psychiatry, as well as upon medical sociology, health psychology and consanguineous disciplines. Indeed, some are already describing its influence as 'revolutionary' (e.g. Carey, 2012). In relation to mental health the considerable potential of epigenetics to undo troublesome oppositions between 'nature' and 'nurture' and negate biological reductionism has been noted (John Read, Bentall, & Fosse, 2009). Simultaneously, others have cautioned against its 'premature' application (Juengst, Fishman, McGowan, & Settersten Jr, 2014) and warned that much more work is still needed (Nestler, 2013).

Although most epigenetic research so far has focused on cancer, research into mental health - particularly schizophrenia - constitutes a notable and growing proportion of recent studies. These studies investigate how epigenetic processes including methylation, acetylation, phosphorisation and RNA interference are sensitive to environmental influences and can regulate the activation and deactivation of specific genes, by effectively either silencing or amplifying them. So whereas methylation has the effect of muting or preventing the influence of gene sequences, acetylation - the environmentally-driven addition of acetyl

molecules – has the converse quality of amplifying the effects of those DNA sequences where it occurs. Dramatically illustrating the integrative potentials of epigenetic research, McGowan et al. (2009) found increased methylation of glucocorticoid receptors in the hippocampi of suicide completers who had been abused as children, by comparison to levels of methylation in the brains of controls who had not been abused. This and other studies suggest intimate links between environmental adversities, biological capacities and behavioural outcomes, operating at interconnected levels from the social to the molecular, and behaviourally mediated by changes such as modified HPA axis reactivity.

Schizophrenia is an appropriate focus for an analysis of epigenetic research in mental health for a number of reasons. First, as we demonstrate, it is the diagnosis that has attracted most interest from epigenetic researchers. Second, the experiences associated with this diagnosis are typically distressing and disabling and schizophrenia indexes significant personal and societal costs (economic, occupational and relational). Third, as with the other functional psychiatric diagnoses, no consistent, necessary or sufficient biomarkers or biological pathways for schizophrenia have been identified and a range of competing biological hypotheses currently exist. Fourth, and relatedly, the reliability and validity of this diagnosis – and, indeed of the functional psychiatric diagnoses more generally – are still being questioned. Fifth, in recent years studies have linked psychosis to childhood adversities (Varese et al., 2012) and abuse (J. Read, van Os, Morrison, & Ross, 2005), suggesting the possible relevance of developmental (and hence epigenetic) processes to schizophrenia and related diagnoses. And sixth, schizophrenia has considerable cultural and societal significance because of its frequent portrayals in news, novels and fiction, TV and cinema. Epigenetic explanations for schizophrenia may therefore reverberate beyond their immediate sphere of scientific and practitioner relevance, helping constitute what Meloni & Testa (2014) call an emergent 'epigenetic imaginary' wherein distinctly new arrangements of responsibilities for health and illness may appear, and which could potentially give rise to a range of innovative research questions, treatments and intervention strategies.

In short, epigenetics in mental health potentially supplies a vision of a new unifying empirical paradigm that will integrate biological and environmental research by delineating

the biochemical pathways and processes whereby these disparate elements come together to forge characteristics of individuals. In its 'ideal' form epigenetics represents a thoroughly interdisciplinary endeavour that could unite biological, psychological and social scientific researchers in a common research program that thoroughly addresses and remedies the disputes and shortcomings associated with previous research that has attempted to move across these different yet mutually constituting fields. But whatever the eventual fate of this grand vision it is already clear, as a consequence of the significant levels of investment and infrastructure committed, that epigenetic research will impact significantly upon mental health and its relations to social, ecological and biological influences: funding bodies in Europe and the USA have launched epigenomic projects, new journals have been inaugurated, and many new journal papers and textbooks published (Landecker & Panofsky, 2013). The eventual consequences of all this for contemporary understandings of mental ill health, of which we can take schizophrenia as paradigmatic, whilst likely to be significant are as yet unknown. In this paper we therefore review the epigenetics literature on schizophrenia, in order to identify how concepts and evidence from within each of these fields are being brought together to constitute the emergent network of assumptions guiding this research.

Method

As part of a larger project we conducted a PubMed search using terms including "epigenetic*", "psychiat*" and a series of psychiatric diagnostic categories including schizophrenia and bipolar disorder. The search identified papers published between 1958 and 11th May 2012 and covered all languages. Both human and animal studies were included, and the papers retrieved consisted of review articles, letters, comments, editorials, hypotheses, theoretical proposals and models, as well as empirical studies. Our search retrieved 969 papers in total; 275 of these contained the stem "schizop*" in the title: this subset of 275 papers were selected for this review. The abstracts of these papers were read by the first author. Extended and repeated discussions within the authorial team and readings of subsets of abstracts and of whole papers by the first and other authors then took place, enabling us to jointly formulate an appropriate conceptual frame around which to organise our narrative review.

Below we first present a brief quantitative overview of general features of the literature on epigenetics and schizophrenia. We then present a conceptually-driven narrative review of this literature, organised with respect to four relevant questions: (1) how is schizophrenia positioned and understood with respect to epigenetics?; (2) how is epigenetics positioned and understood with respect to schizophrenia?; and what issues are associated with or raised by current empirical epigenetic research with (3) humans and (4) animals? Since the aim of our review is to identify the emergent network of assumptions currently constituting epigenetic research in schizophrenia, we pay due heed to empirical studies by devoting two sections to their analysis. Simultaneously, we also consider claims published in reviews, hypotheses and editorials since these are equally constitutive of the 'epigenetic imaginary' of schizophrenia research. We conclude by identifying some possible implications for epigenetic research in relation to mental health generally, and by making some constructive suggestions regarding future research.

General Features of the Literature on Schizophrenia and Epigenetics

Our initial search revealed 969 papers and demonstrated that interest in psychiatric epigenetics has increased exponentially since 2000 and shows no sign of having reached a plateau (see figure 1).

[FIGURE 1 NEAR HERE]

[TABLE 1 NEAR HERE]

275 of the 969 papers identified in our initial search referred to schizophrenia in the title, making this by far the most the most studied diagnosis; next was depression (205 papers), with numbers then falling off rapidly so that anorexia, the least studied diagnosis, returned just 12 papers. These 275 papers were examined in order to ascertain their primary character and focus; Table 1 summarises their key features. The majority of published papers are reviews of some kind (including book chapters and historical surveys, but no systematic literature reviews). There were 100 empirical papers, reporting 74 studies with human participants and 27 with non-human animals, primarily mice (one empirical paper reported two studies, one with humans and one with mice).

Positioning Schizophrenia in Epigenetics

For the majority of epigenetics researchers, there is seemingly little doubt that schizophrenia is a brain disease with a substantial genetic component. These statements exemplify the tone of much of the research and commentary:

> "Schizophrenia is a debilitating mental disorder with a global prevalence of 1% and a presumed neurodevelopmental origin. The disease is incurable.." (Boison, Singer, Shen, Feldon, & Yee 2012, p.1527)

> "Schizophrenia is a severe psychiatric illness with symptoms such as hallucination, delusion, and disorganized thought. Twin, family, and adoption studies demonstrated the involvement of genetic factors in its pathogenesis." (Iwamoto et al. 2006, p.477)

> "Etiology is now known .. Schizophrenia, a mainly cortical disease, is distinguished by sub-optimality: excessive CNS regressive events before birth, in infancy and at puberty." (Saugstad 2008, p.111-112)

Despite the predominance of such claims, however, the literature also acknowledges both continuing uncertainty about the nature and status of schizophrenia and the well-documented contribution of environmental influences to the experiences associated with this diagnosis. A sizeable minority of papers contain claims such as:

> "Pathophysiological studies in schizophrenia have focused on disturbances of the dopaminergic neurotransmission for decades without convincing results and antipsychotic antidopaminergic drugs still show unsatisfactory therapeutic effects. New concepts in the biological research of schizophrenia are required" (Muller & Dursun 2011, p.713).

> "Accumulating evidence from recent studies suggests that environmental exposures may play a more significant role in the etiopathogenesis of [schizophrenia] than previously thought." (Brown 2011, p.23).

> "While the list of copy number variations, microdeletions and polymorphisms associated with genetic risk for schizophrenia is steadily increasing, straightforward genetic causes are still lacking for a large majority of affected individuals" (Akbarian 2010, p.103)

> "The current construct of schizophrenia as a unitary disease is far from satisfactory, and is in need of reconceptualization." (Keshavan, Nasrallah, & Tandon 2011, p.3)

Hence there are acknowledgements that current biological accounts of schizophrenia are problematic or incomplete, that treatments are not always optimal, that the concept of schizophrenia is problematic, and that more emphasis upon environmental influences is appropriate. Simultaneously, there seems to be little overt acknowledgement that no consistent biomarkers for schizophrenia have been identified, and so – taken as a whole - the epigenetic literature largely promotes an illness, disease or pathology model of schizophrenia within which epigenetic processes are therefore seen to produce a medically-diseased or impaired brain. Despite the potential of epigenetics to include environmental influences equally alongside biological ones, a fundamentally biomedical perspective predominates within which scholars typically investigate one or other biologically dysfunctional aspect of this putative disease. For example, Dong et al., (2005) used a mouse model of schizophrenia to investigate the effects of reelin and glutamic acid decarboxylase67 promoter remodelling. Although their discussion acknowledges that this approach "is an incomplete model of SZ morbidity" (p.12581) this acknowledgement is less prominent than their opening claim that "Schizophrenia (SZ) pathophysiology is characterized by a down-regulation of several GABAergic neuronal markers including GAD67 and reelin mRNAs and proteins" (p.12578).

On the basis of papers such as this it would be easy to conclude that schizophrenia is well established as a brain disease associated with a specific biological pathway or aberrant process, even though it is widely accepted that no such resolution has been reached (Charney et al., 2002; Chou & Chouard, 2008; Mathalon & Ford, 2012). Consequently, epigenetic research in schizophrenia is tending to mirror and reproduce wider patterns of uncertainty and presumption regarding the status and character of schizophrenia as a presumed brain disease. This tendency somewhat undercuts the potential of epigenetics to be truly interdisciplinary, since influential social scientific and psychological accounts of schizophrenia do not necessarily begin from such a presumption (e.g. Bentall, 2003). Epigenetic research nevertheless has considerable potential to introduce more complex, nuanced understandings of the aetiology of schizophrenia that give equal weight to social and environmental factors alongside the biological: in what follows we explore to what extent this potential is being realised.

Positioning Epigenetics in Schizophrenia

Rather than assess how epigenetic research understands schizophrenia, here we consider how schizophrenia research understands the contribution of epigenetics. We identify two primary and interconnected issues: the relation between genetics and epigenetics, and the conceptualisation of the environment.

With respect to the first issue, there is an occasional tendency to use epigenetics to invigorate traditionally genetic accounts of schizophrenia. Some papers invoke epigenetic research in conjunction with claims of strong genetic influence in schizophrenia in ways that blur the distinctions between them. Strong claims for heritability are reiterated, and the emerging consensus from GWAS and other molecular genetic studies that there are no major genes associated with this diagnosis (Bentall, 2009) gets more-or-less subtly glossed:

> "Schizophrenia is a complex genetic disorder, the inheritance pattern of which is likely complicated by epigenetic factors yet to be elucidated." (Pun et al. 2011,p.557)

> "Despite consistent evidence from family, twin, and adoption studies of a strong genetic contribution to schizophrenia, the genes investigated so far have been found to have a small effect .. One explanation for the lack of strong candidate genes is that epigenetic mechanisms such as methylation are more important." (S. J. Lewis, Zammit, Gunnell, & Smith 2005,p.3)

The second issue relates to how the environment is conceptualised. Epigenetic research into schizophrenia works primarily with biological mechanisms, processes or features that might be aberrant in schizophrenia, and - despite its characterisation as epigenetic - typically says relatively little about the environmental impacts that might modify them. There are some exceptions, notably diet (Singh, Murphy, & O'Reilly, 2003), smoking (Hillemacher et al., 2008), famine (Lumey, Stein, & Susser, 2011), and trauma (Dennison, McKernan, Cryan, & Dinan, 2012). For the most part, however, the research focuses upon biological, epigenetic pathways and does not specify, or does not quantify, the environmental and social influences that might have modified them.

This raises two related concerns. First, research typically involves working backwards from a primarily biological hypothesis where the general form of the research question is something like "this gene/site/biological feature is (thought to be) unusual in schizophrenia: what epigenetic processes might regulate it?" For example, Gardiner et al. (2011) studied the hypothesis that epigenetic or genetic changes in micro-RNA in the cortex might be associated with schizophrenia. They compared micro-RNA expression in the blood of patients with blood from a control sample, and found a pattern of differentially-expressed micro-RNA in the patients that "may be indicative of significant underlying genetic or epigenetic alteration associated with schizophrenia" (p.1). The concern is not that this kind of question is invalid, nor that such matters should not be studied; rather, that the predominance of questions that take this form may be producing a distorted picture that fails to realise epigenetics' potentials. There is extensive evidence that schizophrenia diagnoses are associated with environmental, relational and social influences including famine, nutrition, prenatal infections, trauma, abuse, childhood adversity, neglect, low socio-economic status and ethnicity. This evidence suggests that an alternate generic

research question could viably be posed: "this environmental factor is known to be significantly related to schizophrenia: what epigenetic processes are consistently associated with or modified by it?" However, studies pursuing such questions are to date rare in this literature.

The second concern is that there is a tendency here for the environment to get 'overdetermined' by biochemistry, so that its effects get driven down to the biomolecular level. The environmental, relational and social influences associated with schizophrenia are often ill-defined, under-specified and only superficially quantified because the emphasis is not so much upon these influences as upon the biochemical processes – such as DNA methylation, acetylation or phosphorisation, histone modification - they are said to regulate. Environments modify biological pathways: researchers therefore study these pathways, rather than the environmental influences per se. This tendency was especially apparent in empirical studies which reported little or no information about participants' experiences. Ruzicka et al. (2007) comprehensively detailed how tissue samples had been harvested, stored and prepared, but said almost nothing about the varied and complex circumstances of the people from whom they had been collected: indeed, it was only apparent that these were people who had been given a diagnosis of schizophrenia – and were therefore humans, rather than laboratory animals - from the title and framing of the paper. Whilst there is a (biomedical) logic to this approach, when combined with the tendency to start from biological hypotheses its overall effect is to render many kinds and gradations of environmental influence largely abstract, homogenous or invisible.

In this 'flattening of the environment' (Papadopoulos, 2011) the effects, variations and fluctuations of environmental influences are relevant solely to the extent that they are seen to produce measurable biological variation. Consequently, significant nuances of environmental influence - for example Boydell et al.'s (2001) finding that black people in London only have elevated rates of schizophrenia diagnoses if they live in majority white areas, or van Nierop et al.'s (2014) evidence that childhood trauma is associated more strongly with psychosis when there is a deliberate intent to harm - are effectively excluded from consideration.

Empirical research with humans

Of the 100 empirical papers identified in our literature search, 74 reported findings from studies with humans. These papers are mixed with respect to their methods, research questions and findings. Over one third (36) worked with post-mortem tissue samples, typically from the brain. 22 studies used blood samples, either collected specifically for the research or archived. A handful of studies were epidemiological (e.g. Nazarova, 1996), whilst others used methods including saliva samples (Ghadirivasfi et al., 2011), GWAS and other molecular genetic techniques (e.g DeLisi et al., 2002), cognitive testing (e.g. Quinones et al., 2009), the Minnesota Multiphasic Personality Inventory (Bolinskey et al., 2001), and comparisons of fingerprint similarity between twins (Markow & Gottesman, 1989).

The predominance of post-mortem brain tissue samples reflects the impossibility of taking regional brain tissue samples from live subjects. Studies of (say) methylation in blood or saliva samples must necessarily presume that they systematically reflect levels of methylation in relevant brain areas, but this is unproven. However, post-mortem samples raise their own challenges, such as the effects of variable post-mortem delay and storage temperature upon tissue samples (e.g. acetylation in brain tissue can be triggered by hypoxia – Ferrer, Martinez, Boluda, Parchi, & Barrachina, 2008) and the effects of possible medications and toxins (where detailed information is often difficult to obtain, incomplete, and not available to the same degree across subjects – D. A. Lewis, 2002). Sample sizes in these studies, whilst highly variable, were sometimes quite small and therefore unlikely to afford adequate investigation of the very many covariates associated with schizophrenia diagnoses. Moreover, the great majority of epigenetic research is correlational and so the identification of epigenetic changes does not of itself demonstrate epigenetic causation; caution is therefore needed when causal inferences are inferred from its findings.

With respect to research questions, some studies investigated variation associated with neurotransmitter systems including GABA, glutamate and serotonin (e.g. Benes et al., 2007; Carrard, Salzmann, Malafosse, & Karege, 2011; Ghadirivasfi et al., 2011). Others investigated brain features such as cerebellar weight and pre-frontal cortex variations, levels of

methylation in brain or blood tissues, associations between epigenetic processes and smoking, age, medication use and physical activity, studies of x-chromosome linkage, and paternal age and its association with schizophrenia diagnoses (e.g. DeLisi et al., 2000; Glatt et al., 2011; Melas et al., 2012; Naserbakht, Ahmadkhaniha, Mokri, & Smith, 2011). Sometimes the link with schizophrenia was solely by inference: Stadler et al. (2005) studied histone modification in glutamate receptors amongst people without psychiatric diagnoses, but argued that their methods might be suitable for studies of schizophrenia and associated medications. Likewise, epigenetic components were sometimes largely inferential. DeLisi et al. (2002) reported a GWAS that failed to replicate linkages with various candidate genes reported in previous studies, and so concluded that "it has to be questioned whether the genetic contribution to [schizophrenia] is detectable by these strategies and the possibility raised that it may be epigenetic" (p.803). Similarly Harlap et al. (2009) reported findings from the Jerusalem Perinatal Cohort Prospective Study of 92,408 live births of people born in Western Jerusalem between 1964 and 1976, and which had been linked to Israel's national Psychiatric Registry. Their study of associations between grandfather-of-origin locations and propensities to receive a schizophrenia diagnosis produced a mixed picture within which the few significant variations identified were attributed throughout to epigenetic processes, but without any direct test of these processes ever being conducted.

Given the variation in methods and research questions, there was also considerable variation in findings and the overall picture is correspondingly difficult to summarise. This is unsurprising given that this is an emergent field of research where standardisation is still underway, and which rests upon a prior history of biologically-oriented research that is similarly diverse. One observation was that a significant minority of studies - 14 from 75 - reported no (12) or very few (2) significances. Another was that studies sometimes elaborated previous investigatory traditions in psychiatry and pharmacology but without providing any resolution of their competing status. Biological research in schizophrenia has identified differences in multiple neurotransmitter systems, including those for dopamine, GABA and serotonin. Likewise, in this literature Melas et al. (2012) and Petronis et al. (2003) provided evidence supportive of the dopamine hypothesis of schizophrenia. At the same time, Kundakovic, Chen, Costa, & Grayson (2007) and Ruzicka et al. (2007) found evidence

associating schizophrenia with epigenetic down-regulation of GABA-ergic neuronal markers; conversely, Carrard et al. (2011) found evidence linking schizophrenia with increased DNA methylation of the serotonin receptor (5HTR1A) gene. This suggests a putative dilemma: the strategy of exploring epigenetic processes in relation to biological systems previously studied in relation to schizophrenia allows researchers to refute allegations that they are merely conducting atheoretical 'fishing trips', but at the same time may blind them to the possible new avenues of conjoint biological-environmental influence that epigenetic studies might reveal.

Another feature of this research is the extent to which schizophrenia is being studied in conjunction with other psychiatric diagnoses, including bipolar disorder, major depression, autism, drug dependency, 'schizoaffective', 'psychotic' and Alzheimer's disease. 13 studies included participants given diagnoses of bipolar disorder as well as participants given diagnoses of schizophrenia. Whilst in these studies comparisons between diagnostic groups were typically conducted, the majority also compared all patients with healthy controls. Whereas most found some differences between diagnostic groups, Sharma et al (2008) - whose study included people given diagnoses of schizophrenia, bipolar and schizoaffective disorders - found none. Likewise, Delisi et al (2000) found no significant differences between diagnostic groups in a study of people given diagnoses of schizophrenia and of schizoaffective disorder.

Animal studies

Of the 100 empirical research papers, 27 reported empirical studies with non-human animals; 20 of these were with mice. Many involved specially-bred strains of genetically modified or 'knockout' animals, where specific genes - candidate genes identified in previous research into schizophrenia - had been deliberately impaired. The construct validity of this research is therefore ultimately dependent upon the extent and quality of evidence from previous studies that demonstrate genetic influence in schizophrenia. Molecular genetic research has shown that there are no major genes of significant effect in relation to the functional psychiatric diagnoses, schizophrenia included, and this seems to be giving rise to at least two different research strategies. One proposes "that the genetic risk to

psychiatric disorders is likely to be a multifaceted problem. Complexity is now a central theme in psychiatric genetics"' (McInnis & Potash 2004, p. 243) because there is "a substantial polygenic component to the risk of schizophrenia involving thousands of common alleles of very small effect" (International Schizophrenia Consortium 2009, p.748). The other strategy involves searching for common disease factors proposed to underlie clusters of related diagnoses; for example a study by the Cross Disorder Group of the Psychiatric Genetics Consortium (2013) which claims to have identified some common genetic mechanisms underlying autism spectrum disorder, ADHD, bipolar disorder, major depression and schizophrenia. Additionally, these strategies are not wholly independent of each other: the International Schizophrenia Consortium (2009) claimed that the polygenetic component in schizophrenia also contributes to risk of bipolar disorder.

In this context, research with animals provides reassuringly rigorous levels of experimental control and measurement and is often seen as providing the clearest proof of hypotheses. However, whilst animal models are well-established in mental health their general limitations are also widely acknowledged, including that (primates excepted) animals mostly lack the higher cognitive capacities and related neuroanatomical structures of humans, and that (with the possible exception of primates) there is no evidence that they experience identifiable disorders.

With respect to schizophrenia, Marcotte, Pearson, & Srivastava (2001) note that these issues are compounded by the difficulty of reproducing a (presumed) cognitive disorder in animals that lack developed cognitive abilities, and by the great heterogeneity of causes, symptoms, course and outcome in humans. In relation to causes we have noted the evidence linking schizophrenia to factors including socio-economic status, ethnic difference and racial discrimination, migration, urban living, childhood adversity and trauma: influences which are all difficult, if not impossible, to model in animals. In relation to symptoms animal models necessarily rely upon behavioural indicators rather than subjective self-reports, but this can be problematic. Tremolizzo et al. (2002) propose an epigenetic model of vulnerability to schizophrenia using heterozygous 'reeler' mice (mice with one impaired reelin gene), in part because these mice display impaired 'prepulse inhibition of startle'

(impaired PPI): they show a larger response to an alarming stimulus such as a loud noise, even when primed to expect it, than do mice without this genetic profile. Impaired PPI has been implicated in schizophrenia (e.g. Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000), although like other putative biological markers it is neither necessary nor sufficient, and its applicability to human populations has been questioned (Csomor, Vollenweider, Feldon, & Yee, 2005). Moreover, impaired PPI is also associated with anxiety disorders (Pynoos, Steinberg, & Piacentini, 1999), obsessive-compulsive disorder (Hoenig, Hochrein, Quednow, Maier, & Wagner, 2005), schizotypal personality disorder (Cadenhead, Geyer, & Braff, 1993) and post-traumatic stress disorder (Grillon, Morgan, Southwick, Davis, & Charney, 1996). Thus, there are three concerns here: the prepulse inhibition paradigm might not transfer readily from animals to humans; the index behaviour described as symptomatic of schizophrenia is not specific to this diagnosis; and, phenomenologically, this response seems more closely associated with affect system activity than with the cognitive impairments hypothesised in schizophrenia. Whilst there are claims that impaired PPI is well established as a feature of schizophrenia (e.g. Martinez-Gras et al., 2009) it is not ubiquitous and the procedure is not routinely deployed in diagnosis. It is therefore unclear whether this behavioural indicator is sufficiently closely associated with schizophrenia, as conventionally diagnosed in psychiatry, such that this procedure can effectively be treated as equivalent to the structured clinical interview used with humans.

These problems with interpretation of evidence from animal studies gain further weight because in the epigenetics literature there are occasional tendencies to overstate what can be concluded on the basis of this kind of research. These tendencies typically arise when scholars work with the 'headline' claim of previous papers and pay less heed to cautionary or moderating statements contained within them. For example, Tremelizzo et al (2002) say:

> "In closing we stress that *these results do not elucidate the etiopathogenic processes that may bring about an altered pattern of methylation .. in schizophrenia patients*, but do offer a mouse model to study the pharmacology of reelin and GAD67 promoters." (p17100, emphasis added)

Regardless of this unambiguous cautionary statement, other papers made stronger claims, supported in part by reference to this paper, which go considerably beyond the kind of restricted pharmacological modelling that Tremolizzo et al propose:

> "There is accumulating evidence that dynamic chromatin conformation provides the link between external environment and gene expression and activity .. This holds not only for chemical or biological environmental pathogens .. but also for psychosocial exposures" (Maric & Svrakic 2012, p.3)

> "..the methylation of the reelin promoter region may play a key role in the onset of schizophrenia" (Toyokawa, Uddin, Koenen, & Galea 2012, p.69).

> "There is mounting evidence that epigenetic mechanisms are involved in the pathogenesis of schizophrenia "(Tsankova, Renthal, Kumar, & Nestler 2007, p.364)

Conclusion

In relation to schizophrenia, so far there is limited empirical evidence for firm associations between specific environmental conditions and epigenetic pathways. Current epigenetic research is producing evidence wherein presumed biological/genetic causes predominate and social/environmental causes are largely relegated to the status of subsidiary, modifying or mediating influences. The 'revolutionary' promise that epigenetics might forge new bio-social explanations of schizophrenia therefore remains to be realised. Nevertheless, epigenetics research in schizophrenia (and mental health generally) does potentially open a new field wherein more sophisticated questions about the co-action of biology and the environment can now legitimately be posed. Consequently, we conclude with some brief recommendations for how these potentials might be realised.

First, and most fundamentally, research that realises the full potentials of epigenetics will necessarily be genuinely inter-, trans- or multi-disciplinary, and so can usefully be informed by the extensive (albeit disparate) literature enumerating the obstacles facing such research and suggesting how these might be addressed. Obstacles arise because certain paradigms

come to dominate academic disciplines and to create dominant research cultures (languages, frames of reference, methods and objectives); because rather than enabling communication these cultures maintain boundaries between the disciplines that, in turn, locate them within hierarchies of influence and status; because these boundaries inform the judgements of risk-averse funders, discipline-centric journal editors and target-driven REF managers; because interdisciplinary working can therefore adversely influence career trajectories (Brewer, 1999; Rhoten & Parker, 2004); and, finally, because this prevents genuinely cross-disciplinary paradigms in the involved disciplines (social science, bioscience, medicine, psychiatry, psychology etc.) from gaining influence and shaping future research.

These obstacles might be addressed by means including seed and directed strategic funding of research (Metzger & Zare, 1999); changes to research training (Hall et al., 2006); and by ongoing debate and dialogue between researchers, activities themselves facilitated by factors such as geographical and institutional co-location, shared conceptions of the scale and character of the research problem, and the formation of small teams with common value orientations. In relation to empirical epigenetic research the profound differences between the dominant mainstream traditions in the social and biological sciences mean that dialogue should begin long before studies are designed and planned, so that precepts from both fields can equally and mutually inform hypothesis development, study design, sampling and operationalization.

Second, there is increasing recognition amongst mental health researchers generally that psychiatric diagnostic categories are not sufficiently reliable and valid as the basis for research, and this is already leading to the development of new strategies. In 2013 the American National Institute of Mental Health committed to developing their own research taxonomy, and other extant or emergent strategies include studying possible underlying biological characteristics (endophenotypes) not entirely dependent upon diagnosis, identifying possible biomarkers for unimpaired function, identifying systemic neural deficits, combining schizophrenia with other diagnoses, researching relatively homogenous experiences such as 'hearing voices' or 'paranoia', and re-conceptualising neural differences as injuries (caused by abuse and adversity) rather than illness processes (Author, in press).

Empirical taxonomy using factor analysis, or by investigating patterns of comorbidity, challenges the notion that schizophrenia constitutes a 'natural kind' and suggests instead that a focus on empirically derived symptom dimensions might be more fruitful (Bentall, 2003). In the epigenetics literature there are some investigations into endophenotypes and numerous studies combining schizophrenia with other diagnoses; however, researchers might also consider applying other strategies to manage diagnostic shortcomings.

Third, even where epigenetic studies begin from a primarily biological hypothesis (for example, potential modifications of the dopamine system) studies might routinely recruit and/or stratify samples with respect to major social and environmental influences known to be significant in schizophrenia, particularly those where biological pathways are multiple or unclear e.g. socio-economic-status, migration, racial discrimination.

Fourth, in addition to extant epigenetic work, researchers might also pursue questions of the general form 'this environmental influence is significant in schizophrenia: what epigenetic processes are associated with it?' Studies might for example recruit matched samples with and without specific prior experiences (e.g. early adversity, migration) and with/without psychiatric problems, then look for evidence of epigenetic modifications by which the effects of such experiences might precipitate biological vulnerabilities to mental ill health. More broadly, in order to do full justice to the promising radical potentials of epigenetic research, future studies need to include both social/environmental and genetic/biochemical variables in genuinely non-reductionist ways. This means that there cannot be truly valid epigenetic research in relation to schizophrenia that does not explicitly engage with the many and varied experiences *and* their associated influences that are typically associated with this diagnosis.

Applying recommendations such as these could help forge an integrative bio-social approach to epigenetic research in mental health, one that is truly capable of realising the considerable potentials held out by this promising new field.

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Literature review	143
Empirical: human	74
Empirical: non-human	27
Hypothesis/model/theory	18
Editorial/comment/letter	12
Methodological discussion	2
Total	275

Table 1

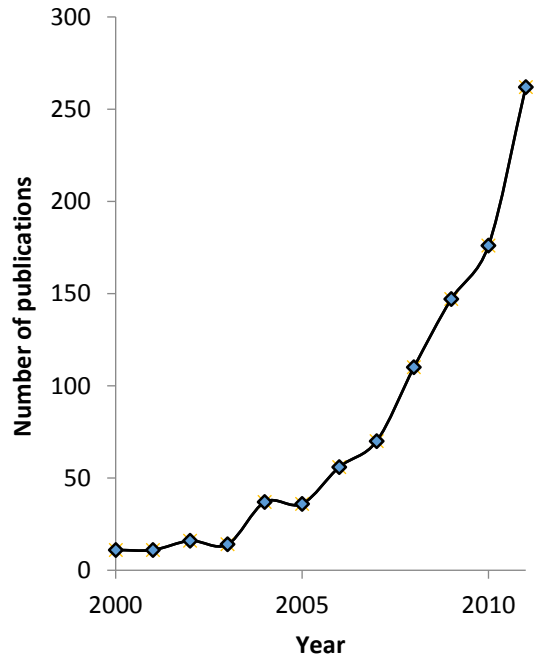

Figure 1