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Epigenetic Modulation Mechanisms in Psychiatric Disorders: Gene and Trigger and Erase and Re-write Hypothesis

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ABSTRACT

Epigenetic modifications are investigated routinely and are one of the most rapidly growing components of molecular biology. Epigenetics has also been implicated in brain and behavior. Psychiatric disorders with complex etiologies have recently been attributed to specific epigenetic alterations in gene expression patterns leading up to behavioral maladaptations. This field has also provided a new angle to the age-old nature-nurture debate by providing a new perspective as to the role of surroundings in behavioral adaptation of an organism. Understanding the epigenetic basis in maladaptive conditions and then correlating it to development of plasticity would provide valuable insight into understanding environment-mediated effects on organisms and its evolution.

Keywords: epigenetics, psychiatric disorders, disease etiology, behavior, epigenetic modifications and plasticity.

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INTRODUCTION

"Epigenetics" a term coined with great insight in the year 1942 by Conrad Hal Waddington; originally to explain the differential expression of the genes in different tissues of an organism though more distinguished from Aristotle's "Theory of Epigenesis"(1). We are not sure if he would have known how imperative was his choice of words, which in time had indeed opened up a new horizon for science. Although now, "Epigenetics" refers to the changes in gene expression that can persist across mitotic cell division resulting in an altered phenotype; without any change in the genetic sequence of the organism. (2, 3)

The genes that you inherit define you; but do they make you for who you are? Environment; a very powerful contributor for the development of an organism, adapting and learning as and when required (4). A complex mechanism that presents itself as genotype translates to the phenotype of the organism.

Epigenetic Mechanisms:

Epigenetic regulation manifests itself either based on covalent conformational changes associated with the chromatin; thereby altering the availability of the DNA sequences to the transcriptional machinery. Epigenetics is also known to chemically altering sequences to regulate gene expression. Structurally, chromatin exists in two configurations; heterochromatin when DNA is not accessible due to tight binding of chromatin on to the nucleosome. On the other hand euchromatin marks DNA sequence availability to transcriptional machinery thereby termed active. Histone proteins part of the nucleosome undergoes covalent addition resulting in structural modification. The chromatin is wrapped 146 bp around a histone octamer 1.67bp per turn and structural modification results in opening up on the turn makes the DNA accessible to the transcription machinery. (5)

Whereas sequence modification is commonly at the CpG islands at varying regions of any gene in question in turn manipulating binding of transcription factors to influence the process of transcription.

Table I: Summarizes the types of epigenetic modifications enzymes involved and effect on the gene expression

Epigenetic modification type	nzyme Responsible and amino acid /DNA residue target	Consequence of gene expression
Histone Associated Modifications		`
Acetylation/Deacetylation	HAT (Histone Acetyl Transferase) / HDAC (Histone Deacetylase) of lysine residues	Increase/Decrease
Phosphorylation/De-phosphorylation	PK (Protein Kinases) /Protein Phosphatases on Serine or threonine residues(26)	Increase/Decrease
	HMT(Histone methyl transferase)	

Methylation	/Histone demethylase at lysine or arginine residues position dependent(3, 27) (H3K4) methylation at 4th residue of lysine (H3K9) methylation at 9th residue of lysine (H3K27) methylation at 27th residue of lysine	 Increase Repress Repress
ADP Ribosylation induce nucleosomal sliding	SWI/SNF chromatin remodelling complex at glutamate residues causes nucleosome sliding. Removed by DP-ribosylhydrolases (ARHs)(28, 29)	Increase
Ubiquitination/De-Ubiquitination	Mono-ubiquitination by Ubiquitin Ligase/Ubiquitin protease at lysine residues(30)	Increase
SUMO-lyation	Ubl activating enzyme (E1), a Ubl conjugating enzyme (E2), and typically a Ubl protein ligase (E3) at lysine residue(31)	Repress
DNA associated modifications		
Methylation/De-methylation	DNMT(DNA methyl transferases)/DMT(DNA Demethylases) at C5 Cytosine residues in pyrimidine ring mainly at CpG islands(32)	Repress

Table I in this paper concentrates on the types of epigenetic modification on histone proteins as well as on the cytosine residues at CpG islands.

Psychiatric Disorders:

DSM IV agrees, "The concept of mental disorder lacks a consistent operational definition that covers all situations". Hence, a proposed set of guidelines to classify condition as a mental disorder. Within the set of five points the one that we believe defines a psychiatric disorder should fbe "a manifestation of a behavioral, psychological, or biological dysfunction in the individual". Peculiar interest in the above mentioned point can be attributed to a common background of genetic predisposition and contribution from environmental factors relating to it.(3)

The Nature-Nurture Debate: The new angle

Here, much of the debate has happened among greats, yet a sole winner is out of sight. The opinion we favor is that the genetic composition at birth answers to the question of

immediate survival but environmental cues contribute to the adaptability and prolonged survival. Epigenetic regulation of gene expression comes into the picture right here. According to Recanzone (6) present day cortical plasticity studies in adult and developing mammals has revealed that the nervous system modifies itself in terms of functional organization due to the changes in activity patterns across sensory receptor arrays. .To correlate the translation of neural changes into behavioral changes requires further probing.

In this paper we discuss, environment mediated behavioral change; for doing so we develop necessary perspective from similar situations as that of psychiatric disorders and plasticity developed in an organism. Some of the questions that we look forward to answer in this paper are as follows:

How does epigenetic regulation contribute towards the etiology of psychiatric disorders and what inference can be drawn from the same? How does epigenetics influence neuronal plasticity and how environment mediated changes shape behavior? Finally, is it possible that epigenetics is the mediator; which induces phenotypical alteration in response to the environmental cue if so how strong and long lasting is the behavioral change? Is the change in question heritable and how does evolution explain this?

Psychiatric Disorders and environmental etiology mediated by epigenetic mechanisms:

Scientists have been in the long search for one magic molecule responsible for behavioral change in an organism in response to environmental adaptation, but there has been little success in that direction. With current available data about such molecules (e.g.: ΔFOSB) (7) causing behavioral change of last only for a few weeks after the removal of stimulus which is contradictory to the behavioral response as observed in cases of psychiatric disorders lasting a life time.

Firstly, the question arises why an effort to bring in epigenetic mechanisms to explain psychiatric disorders and their etiology?

Two cues here to fathom from psychiatric disorders are:

1. As to the long lasting behavioral maladaptation; rather than a pure molecular basis a genetic cause fits in better, but putting in this thought would re-establish the multifactorial etiology of the condition than doing any good to the discussion.

2. But combining it with the second cue, which we believe has to be the severity associated with the psychiatric disorders .It can be very clearly noted that even within a family prone to psychiatric illness the intellectual ability and the severity of deterioration differs considerably, hence directing us towards environment as a factor of vital importance. (8)

Based on the above arguments, genetic predisposition can be attributed to SNP (Single Nucleotide Polymorphism) or other kinds of mutations in the genes under concern. But, how

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the disorder manifests phenotypically is dependent on the subject's perception of the environment around. And again environmental insult during gestation has been seen to contribute towards development of the condition as well. Here, it is absolutely, logical to attribute the role of epigenetics as it can account for the alteration of cellular trait without modification of the DNA sequence.

It can be very clearly noted that genetic predisposition, contribution of environmental factors and a long or life lasting behavioral maladaptation being the common foundation on which most of the psychiatric disorders are found to be established(9-11). Even when thinking on the lines of treatment; psychiatric medications are unique in their requirement about the time frame of administration so as to derive its complete effect (3)

Table II: Summarizes the candidate genes that suggest epigenetic involvement in explaining etiology of various psychiatric disorders

	Psychiatric Disorder	Genes involved	Epigenetic involvement	Reference
1.	Major Depressive Disorder	BDNF (Brain derived neutrotrophic factor)and	In animal model of depression; chronic defeat stress in mice the BDNF gene promoter in hippocampus undergoes repressive H3-27K demethylation modification to generate down regulated transcripts.	(3, 33-37)
		GR (Glucocorticoid Receptor) genes in hippocampus	Similar animal model evaluated on the basis of after birth nursing availability and non-availability as a cause of early age stress depicted GR. Pups with no nursing showcased increased anxiety levels and methylation at the promoter sequence of GR gene ;thereby preventing binding of transcriptional enhancer NGF-1A and altering the transcriptional regulation	(38-41)
2.	Addiction/ Substance dependence	c-Fos and Fos B in striatum, prefrontal cortex and amygdala coupled with BDNF and Cdk5 (Cyclin dependent kinase).	Acute cocaine administration induces H3 phosphorylation at c-Fos gene promoter. FosB is induced in both acute and chronic cases of cocaine abuse but acute exposure produces H3 acetylation whereas H4 acetylation in case of chronic abuse. ΔFosB: a truncated alternate splice form of FosB gene is known to show increased mRNA level accumulation at nucleus accumbens and dorsal striatum (brain areas part of reward system) .	(7, 42-47)

3.	Rett's syndrome	MeCP2 gene in CNS	MeCP2 gene mutation leads to Retts syndrome characterized by seizures stereotyped motor movements, cognitive decline and autistic like behavior. The gene products result in MBD (Methyl binding proteins).These bind to the methylated sequence of DNA and accumulate proteins leading to context dependent silencing or activation of specific genes. The MeCP2 knockout mice hippocampal cultures showcased Low frequency of spontaneous excitatory post-synaptic potentials. Increased short term synaptic depression	(48-54)
4.	Schizophrenia	RELN a gene found to be expressed chiefly in the postnatal cerebellum GAD 1 gene glutamate dehydrogenase dysregulation in hippocampus Dnmt 1 (DNA methyl Transferase)	RELN gene product reelin is a glycoprotein necessary for neural cell positioning during development and expressed in adult GABA containing neurons. Post-mortem evaluation of schizophrenic brains has shown significant down-regulation of reelin expression. The hypothesis proposed as of now suggests hypermethylation of the CpG islands at the promoter sequence of the RELN gene thereby compromising GABA mediated neuronal circuitry. The enzyme encoded by GAD 1 gene is responsible for catalyzing the production of gamma-amino butyric acid from L-glutamic acid .In post mortem brains of schizophrenia patients downregulation of the gene transcripts was noticed in hippocampal and cortical region. Methylation of the promoter sequence leads to decrease in GABA mediated neuronal synchronization. Increased expression of Dnmt gene seen in the cortex of schizophrenic patients (postmortem analysis). This in turn results in methylation of promoter region of specific genes like GAD1 and RELN in the GABAnergic neurons.Even though the reason or mechanism for Dnmt 1 expression increase is yet unknown.	(27, 55-64)

5.	Autism Spectrum Disorders	GABA receptor cluster encoding genes (GABRB3)	GABA an inhibitory neurotransmitter which is a key regulator of excitability in Central nervous system of mammals. Imprinting of chromosome 15 has been associated with Autistic behavior and the region to be named Autistic susceptibility locus. Gene GABARB3 present in 15 q region has been implicated as one of the potential candidate due to the linkage disequilibrium of the same with the 15 q autism susceptibility locus.	(27, 48, 65-67)
		UBE3A gene(Ubiquitin3 ligase E3A) known to show maternal allelic expression in brain	Post mortem analysis of autistic brains has revealed abnormalities in methylation pattern at 5' CpG island of UBE3A gene leading to decreased expression of E6-AP protein.	(54, 68-71)
6.	Bipolar disorder	5HTR1A subtype of 5HT receptor for serotonin widely expressed in cortico-limbic region receiving seritoninergic input from raphe nucleus.	An Epigenome wide association study between patients and controls revealed increased methylation levels at CpG promoter sequence of the 5HTR1 gene thereby causing decreased levels of mRNA transcripts of the same gene.	(72, 73)

The table (II) summarizes the genes involved in epigenetic regulation under psychiatric disorders and the mechanisms through which the directive is met. Now, the next objective here would be to visualize the role of environment in maladaptive phenotype. The predisposition handed out by the above genes earn them the name of susceptibility genes called so "because

it is neither necessary nor sufficient for the development" (of the mental disorder) defined by Ming and colleagues(12).We would be required to account for factors other than predisposition .From a 'nature-nurture' perspective predisposition (genetic risk) and environmental risk both together trigger the initiation of the psychiatric disorder. Acceptance of environmental factors contributing to etiologies is scarce. And could be because as compared to the known risks as for the likes of eating and obesity, toxin mediated trans-generational inheritance the direct cause and effect relationship is hard to comprehend. Nonetheless, we would need much more extensive epidemiological study in case of mental disorders as well.

Proved by Kendler and colleagues by an experiment evaluating major depression disorder in twins concordant with genetic predisposition by evaluating the coupled environmental factor; being traumatic stressful incidents and risk of onset of the disorder. The risk tended to be higher in children with genetic predisposition compared to the children who had no cases of depression in their families. (12)

Here, the requirement arises to elucidate a pathway that translates the environment into meaningful genetic expression patterns in the organism. As suggested by Meaney and Smith "the challenge for neuroscientists is to come up with causal pathways linking environmental effects, epigenetic marks, genomic structure, and, ultimately, the downstream transcriptional and translational changes that cause long-term changes in behavior". (13)

"Gene & Trigger Hypothesis"

To bring in clarity to the situation we bring in "Gene & Trigger" hypothesis [Fig I]. The proposed hypothesis suggests genetic predisposition would only make the subject vulnerable to a particular psychiatric problem; however initiation of behavioral maladaptation and severity of psychosis would be based on environment. Deriving inference from Kendler's work traumatic incidents acted as an initiation factor to major depression (MD) for children considered to have a genetic predisposition to the same. On the other hand, similar incidents had no effect in inducing MD in children under the lower genetic risk cohort(12).The "Gene & Trigger Hypothesis" supports the multifactorial etiologies of psychiatric disorders and stresses on the vital role of environment in these conditions. The phenotypic variances observed in psychiatric disorders leading to classification into subtypes or severity shows variation.(14, 15) Here, the hypothesis advocates the viewpoint that this kind of variation would be dependent on the kind of environmental trigger responsible for kicking in the role of genetic factors. Though this is an empirical model, we believe that it would be beginning to provoke thoughts relating the pathways for translation of information from the environment to phenotype.

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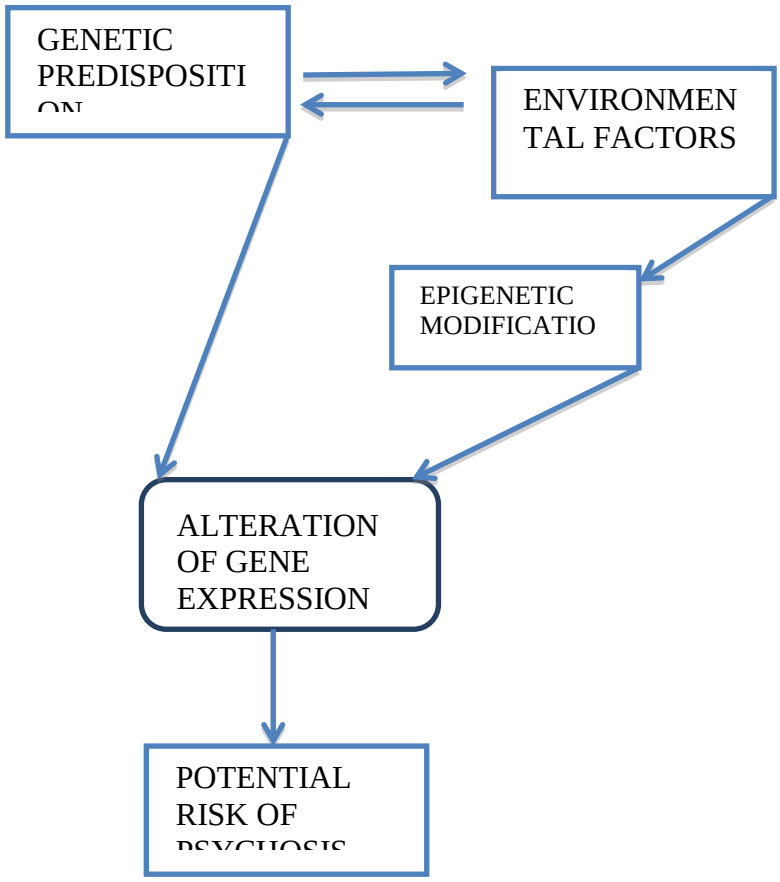

Fig I: Gene and Trigger Hypothesis flowchart

Plasticity and epigenetics:

"Plasticity is defined as the ability of the genotype to produce varied phenotypes in response to different environment through self or maternal cues"(16). In here we try to draw inference to establish a point of view with regard to the plasticity and the role of epigenetic mechanism in establishing the same. First of all how do we understand that environment mediates epigenetic signatures? To answer this question, a study by Fraga and colleagues is taken into account, which compared the methylation and histone acetylation patterns among monozygotic twins (MZ). It's well known that MZ twins are genetically identical and it was noted that in early ages they are even indistinguishable epigenetically but with age there was a significant shift in epigenetic signatures suggesting that social interactions, diet and environmental factors account for the variation in genetically identical clones(17).

Maternal care and mother-infant interaction at early postnatal weeks has been a critical find in terms of environmental contribution towards long lasting behavioral change. Path breaking discovery by Michael Meaney and colleagues on Glucocorticoid receptor gene methylation pattern depending on pups belonging to attentive or discarding mother type the role of environment was clearly substantiated (18). One more vital find of this experiment was altered of the methylation pattern of the GR gene based on the availability of maternal care. It

is vital because the finding refuted the age old concept of stability of methylation signatures. As in case of cross fostering studies it was seen the methylation pattern was subjective to postnatal care rather than the birth mother type. So, it becomes evident that, mother –infant interaction can be implicated towards psychopathology of the offspring in the future. This was also well established in an influential study conducted by Harlow and associates in depicting the role of maternal deprivation as a cause of complex social behavior and emotional disturbance. .Further proof was obtained when in another study human subjects were analyzed on the parameter of childhood abuse and implications of the same in social deficit and suicidal tendency. Post mortem examination suggested methylation at promoter of Exon 1F of the NR3C1 gene which is similar to that of rat exon I7 of GR gene, revealing the maternal effect of cytosine methylation in humans as well. (19). Now, let's shift the focus to learning induced plasticity; Altered gene expression brought about to account for learning induced neuronal activity resulting in latent responsivity described as "metaplasticity". So when we put together the implication of maternal care and appreciably high expression levels of de Novo DNMT in post-mitotic neurons it is evident that DNA methylation is an effective measure through which learning induced changes are brought about in the brain. (20)

Heritability and epigenetics:

The basic query to begin with would be "Does the plasticity conferred by an environmental stimulus transferred from one generation to the other if yes then how?" Two kinds of epigenetic modifications one referred to as the context depended epigenetic modification, which limits itself to somatic cells and is restricted to the organism under exposure (21). However, the longevity of effect of exposure varies with the kind of stimulus; for instance in maternal–infant interaction the effect can last throughout life time on the other hand toxin intervened change could be reversed. It provides a sneak peak on the dynamic nature of epigenetic modification. Conversely the other kind trans-generational epigenetic modification germ line dependent and continues to bear impacts even without current environmental stimulus. It is well exemplified by Vinclozolin an endocrine disrupter exposure during embryonic development (E8-E14) the period of sex determination resulted in re programming of male germ line leading to low spermatogenic count and adult onset of several diseases. Transcriptome analysis revealed altered expression of a substantial number of genes in amygdala and hippocampus .The effect was seen to last till F3 generation proving the trans-generational outcome of the drug exposure(22).

"Erase and Re-write Hypothesis"[Fig II]

Now, the hypothesis that I would like to bring into the picture is that, we know that

1. Methylation signatures are environment mediated. (18, 19, 23)
2. These signatures undergo resetting before gametogenesis and implantation. (24, 25)

The reset switch enables the developing organism to develop the expression patterns according to the requirement and environment around. I.e. An organism develops to sexual

maturity, undergoes the process of reproduction as a result of which an embryo is formed; the methylation pattern within the genome undergoes reprogramming. Drawing inference from the above observations a plausible interpretation can be brought to the table. The acquired epigenetic modifications influenced by individual genetic and environmental setting undergo reprogramming. Thereby, qualifying the embryo to develop epigenetic signatures characteristic to the environment and nurture in store for the embryo throughout the lifespan.

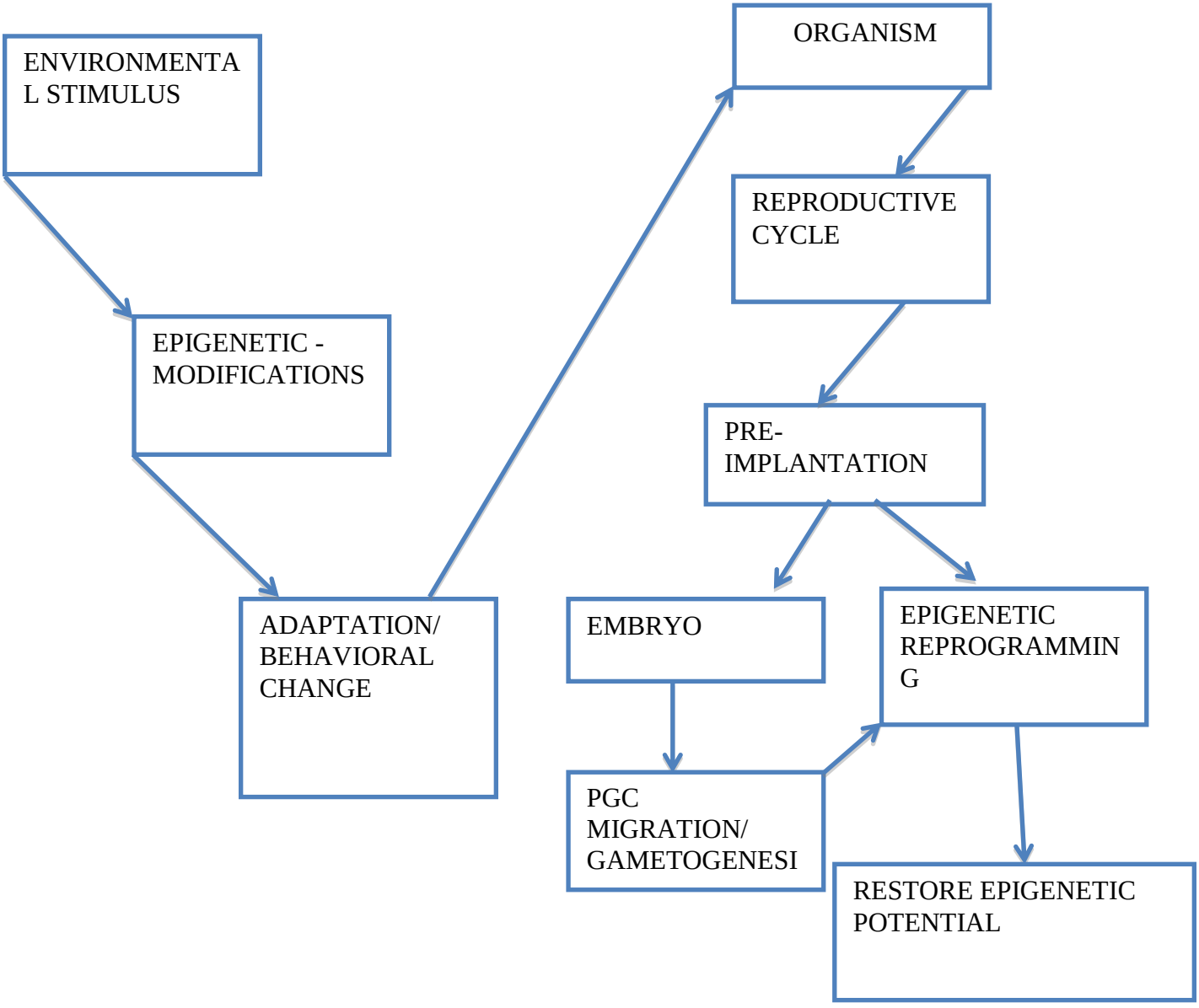

Fig II: Erase and rewrite Hypothesis flowchart

Evolution behavior and epigenetics:

Evolutionary theory would be half-finished if not for the famous Darwin's finches from the Galapagos Islands. We are beginning to wonder if the spontaneous phenotypic changes

observed in these birds in response to the environment were a very early proof of existence of epigenetics in interplay with surroundings preceding the genetic adaptation. Learning and adapting have been pillars that have guided evolutionary theory. Sir Patrick Bateson suggested epigenetics to be an intricate part of the evolution of the organism. The thought that environment cues prompt an alteration of gene expression resulting in a phenotypical adaptation which if epigenetic would be the learned changes that would eventually pave way to genetic accommodation is quietly compelling(2). Here, based upon the time and energy developing costs of the behavioral pattern evolution favors plasticity or spontaneous genomic alteration. Conversely, a question that persists, in the case of trans-generational epigenetic change which would last for generations with appreciable efficiency; wouldn't it be better at adopting an epigenetic mode of behavioral adaptation to confer flexibility of switching between adaptations?

CONCLUSION

The elaborate understanding of epigenetics in the brain is yet to be achieved. But the inference gathered above suggests that there exists immense scope for studies to be performed within this area. Gene and trigger hypothesis proposes a possible explanation for complex etiology of psychiatric disorders. But, at the same time also raises questions about how the molecular machinery translates the model? We can also see that major transcription factors (BDNF, cFos) in the brain have also been down regulated in psychosis. Generally, these observations could be relevant to identify effective strategies as well as suggesting possible pharmacological targets for the prevention of mood disorders. The second perspective is the suggestive impact of epigenetics in behavioral adaptation. The Erase and Rewrite hypothesis provides an insight on the relevance of epigenetic modifications stabilizing the behavior on the course of evolution. Even though these propositions stand well as for the available data currently further experimental proof is mandatory to validate the theory. Finally, an analogy that made sense to us, in a poker game you might hold face cards but the game shapes up according to the cards on the table. Similarly, you might carry a set of genes but the expression pattern shapes up according to the cards environment presents during the lifetime of the organism.

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Declaration of Interest:

The Authors declare that there is no conflict of interest

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