EPIGENETICS IN PSYCHIATRY

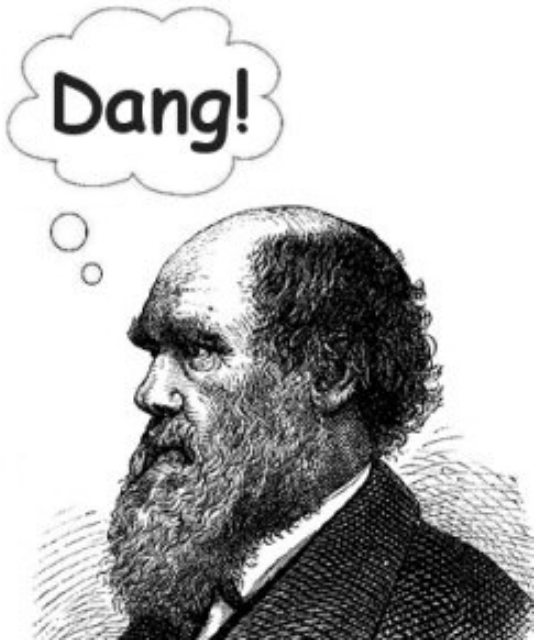
Introduction

New technology has continually advanced the practice of medicine, but more slowly in psychiatry than most other areas. Epigenetics is a new field which is revolutionizing all branches of medicine, and this time, Psychiatry is not being left behind. In fact, the impact of epigenetics may be greater in psychiatry than most other fields.

Epigenetics is difficult to define, but can be simply described. It refers to heritable changes in gene expression that are *not* caused by changes in the DNA sequence. (It also deals with changes in gene expression which are not heritable, but let's not be distracted.) It is THE WAY the environment interacts with the genome at a molecular level.

Example: for the last century, psychiatry has claimed the quality of care an individual receives in the early years of life greatly influences the personality development of that individual, and the risk of mental disorder. Further examples: psychiatry has known for the last century that psychotherapy and ECT can be effective treatments, but we have not been able to explain these responses. Epigenetics promises to explain the biological basis of these observations.

The important biological events of the 19th C were the theories of evolution (Darwin) and genetics (Mendel). The important biological events of the 20th C were the discovery of DNA (Watson and Crick) and the deciphering of the genome (lots of people). The important biological event of the 21st C will be the understanding of epigenetics. It will be THAT important!



MECHANISM

Epigenetics is about altering (increasing and decreasing) gene expression (without disturbing the DNA sequence). There are three main mechanisms.

But, first we need to understand how DNA is packaged. The DNA of a human cell is 2-3 meters in length. And it has to be fitted not simply into the cell, but into the nucleus of the cell. This is possible because the DNA winds around bunches of proteins called histones. The combination of DNA and histones is called chromatin. The basic unit (the nucleosome) is DNA making 1.65 turns around a bunch of histones (before going on to the next bunch). Nucleosomes can be packed together tightly or loosely.

When the nucleosomes/chromatin are tightly packed together, genes are inaccessible and therefore inactive, and when they are loosely packed the genes are accessible and active. Much of epigenetics is about the packing and unpacking of nucleosomes/chromatin.

There are two main mechanisms. A third epigenetic mechanism has other actions. See the beautiful illustration below which comes from the kind people at Wikipedia.(http://en.wikipedia.org/wiki/Epigenetics)

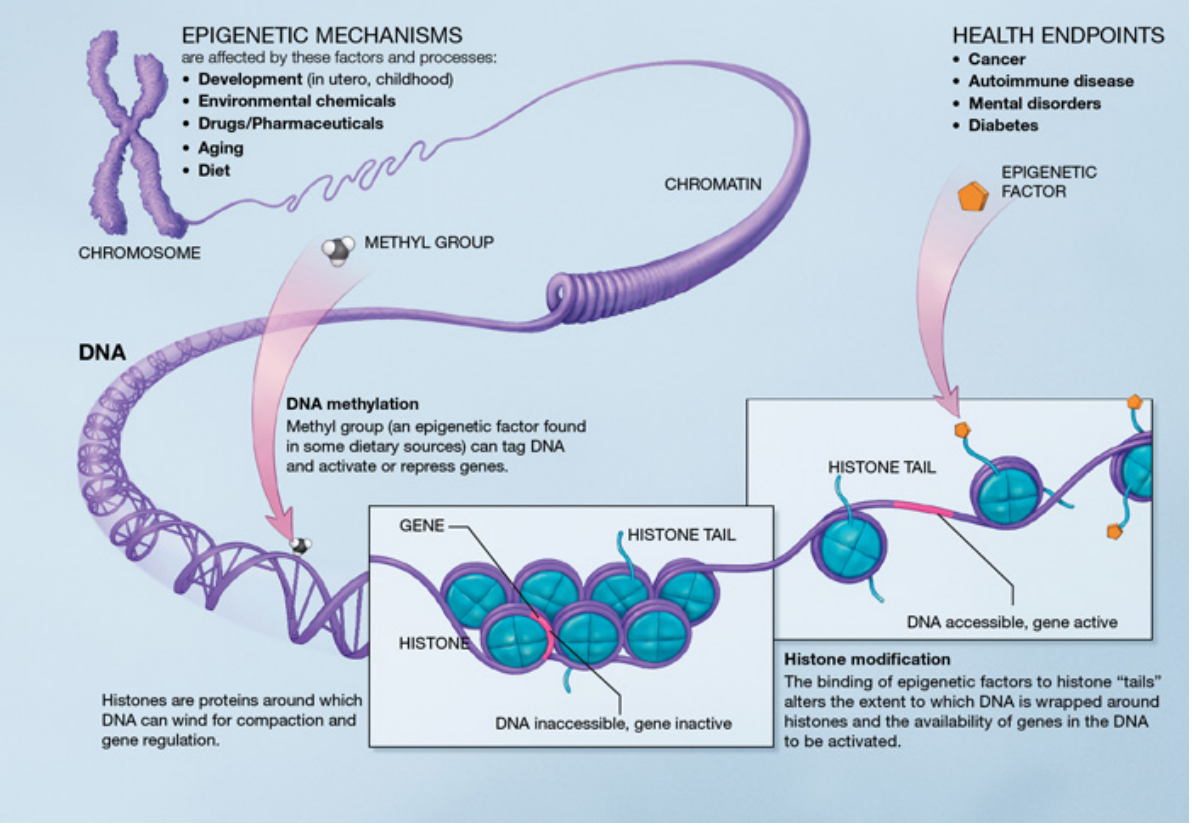


Illustration. This illustration comes from Wikipedia (http://en.wikipedia.org/wiki/Epigenetics). DNA winds around histones (forming nucleosomes) and can be tightly or loosely packed (influencing gene activity). Methylation of DNA is illustrated in the left lower and modification of histone tails is illustrated in the right lower quadrant.

1. **DNA modification**
   One modification which regulates (usually suppressing) gene expression is the addition of a methyl group to DNA. It is added to a cytosine residue where the cytosine nucleotide occurs next to a guanine nucleotide. The DNA backbone is composed of pentose sugars linked by phosphate groups. Thus, a cytosine next to a guanine nucleotide is termed a CpG sequence. The process is catalyzed by DNA methyltransferases (DNMTs).

2. **Histone modification**
   Each histone (there are 8 in each bunch) has an amino acid tail. Acetylation of tails causes the relaxation chromatin, allowing the gene to be active. The catalyst is histone acetyltransferases (HATs), and is reversed by histone deacetylases (HDACs). In contrast to acetylation, histone methylation can cause either gene activation or repression, depending on the point at which the methylated occurs. For example, methylation of histone H3 at Lys9 is associated with gene silencing (Jaenisch & Bird 2003).

3. **Non-coding RNAs**
   Non-coding (nc)RNAs occupy at least 30% of the mammalian genome, and were once denigrated as 'genomic junk'. That was a mistake; these molecules have many important actions, some of which are 'epigenetic functions'.

   The ncRNA epigenetic functions are manifold, they include DNA and histone modification, and many more, way beyond the understanding of the current author.

   Even the classification of ncRNA is complicated – this has been influenced by the order in which new varieties have been discovered. A classification based simply on length recognizes short (<200 nucleotides), long (>200 nucleotides), and micro (20-25 nucleotides).

   Recently, even the classification/division into coding and ncRNA has become less clear, with the recognition that mRNA performs some regulatory functions.

   ncRNAs influence gene expression through direct and indirect interaction with the classical epigenetic mechanism (Peschansky and Wahlestedt, 2014), including,

1) binding to histone modifying complexes and influencing the addition and removal methyl and acetyl groups to and from histone tails
2) combining with DNA methlytransferase and facilitating DNA methylation
3) the loci targeted by these by these mechanism may encode for ncRNA, thereby potentially exaggerating the epigenetic effects of the ncRNAs
4) ncRNAs may combine with a protein complex and attach to mRNA, with the result that either the mRNA is destroyed/degraded, or the translation process is blocked. In either case, gene expression is reduced.

INTRA-UTERINE ENVIRONMENT

Maternal folate levels during pregnancy impact on DNA methylation patterns (Joubert, et al, 2016).

Maternal anxiety in pregnancy is associated with a decrease in DNA methylation, which is passed on to the baby (Mansell et al, 2016). Molecular evidence of the mental health of the mother impacting on the offspring.

RAT MOTHERING

As mentioned, for the last century, psychiatry has believed the quality of care an individual receives during the early years of life greatly influences the personality development of that individual, and the risk of mental disorder. But the underpinning mechanisms have not been clear.

Rat studies have provided profound results. Two features of rat mothering can be quantified, 1) 'licking and grooming' (LG) of the pups by the mother, and 2) 'arched back nursing' (ABN) which creates better access to the nipples for the pups. Some mothers provide 'high' levels of LG and ABN, while others provide 'low levels'.

The pups of 'high' LG-ABN mothers become 'high' LG-ABN mothers (and the pubs of 'low' LG-ABN mothers become 'low' LG-ABN mothers). Cross-fostering - the removal of the pups of one type of mother at birth, and placing them in the care of the other type of mother – however, reveals that type of mothering is learned (Francis et al 1999). But, what is the molecular basis of this, 'learning'?

In a classic study Weaver et al (2004) demonstrated that the pups of 'high' LG-ABN rat mothers had increased DNA methylation of the glucocorticoid receptor (GR) gene promoter in the hippocampus. At last one molecular explanation of the effects of early life tactile experiences had been identified.

The offspring of high LG-ABN mothers manifested,
1. increased hippocampal expression of glucocorticoid receptor (GR)
2. decreased methylation of the GR gene promoter
3. enhanced glucocorticoid feedback sensitivity
4. decreased hypothalamic CRF expression

These offspring demonstrated a modest HPA responses to stress, and behaviorally, were less fearful and more adventurous. Thus, "good" mothering produced life-long molecular effects and only a modest response to stress.

"Low" LG-ABN mothers produced pups with increased methylation, decreased GR, and greater stress responses.

HUMAN EARLY PARENTING

Studies in humans have examined the molecular consequences of poor parenting (childhood abuse). McGowan et al (2009) examined post mortem hippocampal tissue from three group: 1)

suicide victims with a history of child abuse, 2) suicide victims with no history of child abuse, and 3) controls.

Predictably, among those who had experienced early life abuse, they found the reverse of the 'high' LG-ABN rat mother findings. They found, a) increased methylation of the promoter regions of the GR gene, and, b) decreased GR mRNA (indicating decreased GR population).

However, epigenetic alterations associated with child adversity are not limited to those associated with GR. Roth et al (2009) have described methylation of DNA altering the expression of 'brain derived neurotrophic factor' (BDNF) and Labonte et al, (2012) have described methylation of yet other sites.

ADVERSE EXPERIENCE IN ADULTHOOD

Holocaust survivors demonstrate an altered methylation pattern which is passed on to their children (Yehuda et al, 2015). Fascinatingly, this is a different methylation pattern than that associated with childhood adversity.

EPIGENETICS OF MENTAL DISORDERS

PTSD

Yehuda et al (2014) found that lower methylation of the promoter of the GR gene (blood sample) in combat veterans with PTSD compared to veterans without PTSD. Methylation was inversely correlated with markers and symptoms of PTSD, and may prove useful in distinguishing between veterans who have PTSD from those who do not.

Perroud et al (2014) studied the transmission of PTSD from mother to child. They studied mothers who had been pregnant (and their subsequent children) who were exposed/not exposed to the Rwandan Tutsi genocide. They found that PTSD (and depression) was transmitted from mother to offspring, and was associated with transmission of higher methylation of the promoter of the promoter of the GR gene and lower GR levels. This transgenerational effect is amazing!

Antisocial personality disorder

Here we continue to consider the trauma of childhood sex abuse, but move away from the GR.

Beach et al (2011) studied females who had experienced childhood sex abuse. They found increased methylation of the promoter region of the serotonin transporter gene (*5HTT).* (The serotonin system is central to mood and social behavior, including aggression.) In addition, they found a significant effect of this increased methylation on the presence of antisocial personality disorder. Thus, the connection between childhood sex abuse and antisocial personality disorder may be mediated by epigenetic marks placed on the promoter region of *5HTT*.

Depression

Chronic social defeat stress in mice (a model of depression) is associated with increased histone methylation at the promoter regions of BDNF gene in the hippocampus. Imipramine treatment reversed this process by histone acetylation at the promoters. Thus, histone remodeling has been implicated in the pathophysiology and treatment of depression (Tsankova et al 2006).

In human inpatients with major depressive disorder increased methylation of the insulin dependent glucose transporter 1 (GLUT1) was demonstrated (Kahl et al, 2016). After treatment, remitters (but not non-remitters) demonstrated significant lowering of GLUT1 methylation.

Drug and alcohol addiction

Findings of many epigenetic changes have been reported in association with addiction to many different agents. So far, many are from animal studies, however, Andersen et al (2015) have reviewed robust changes in DNA methylation in humans with a range of substance abuse disorders.

In laboratory animals, Maze et al, (2010) described histone methylation in the nucleus accumbens (an important pleasure center) associated with cocaine use. Sun et al (2012) described similar molecular events in response to chronic morphine administration. Sakharkar et al (2016) demonstrated that intermittent alcohol consumption in adolescent rodents decreased histone acetylation which reduced brain-derived neurotrophic factor (BDNF) and neurogenesis in the hippocampus of adults.

Vassoler et al (2013) described amazing transgenerational epigenetic effects in the offspring of male rats which have been self-administering cocaine. The male offspring (but not the females) display little interest in the self-administration of cocaine. These animals feature modification of histone acetylation and *Bdnf* promoter and increased BDNF in the medial prefrontal cortex (mPFC).

Schizophrenia

Wockner et al (2014) performed genome-wide DNA methylation analysis on post-mortem human brain tissue from patients with schizophrenia and controls. 2929 unique genes were found to be differentially methylated. Two clusters were identified, one contained 88% of people with schizophrenia and 12 % of controls, and the other contained 27% of people with schizophrenia and 73% of controls. These findings indicate that differential DNA methylation is important in the etiology of schizophrenia. Eventually it may be possible to identify aberrant DNA methylation profiles which can be translated into a diagnostic test for use with blood or saliva samples.

Montano et al (2016) studied 689 people with schizophrenia and found some overlap with the above study.

Major psychosis

In this section, schizophrenia and bipolar disorder are considered together. There is some evidence that these disorders may not be distinct (Craddock and Owen, 2005). However, to date, epigenetic studies support a distinction.

Dempster et al (2011), conducted a genome-wide study of peripheral blood of monozygotic twins discordant for schizophrenia and bipolar disorder. They found differences in DNA methylation which they believe explained the different phenotypes.

Rubin et al (2016) studied DNA methylation of the oxytocin receptor gene, and reported higher methylation in schizophrenia than bipolar disorder.

Alzheimer's disease
Alzheimer's disease is being discussed in terms of DNA modifications (Condliffe et al, 2014) and ncRNA activity (Van den Hove et al, 2014).

Other psychiatric disorders
It is probable that epigenetic modifications will be important in most psychiatric disorders. **Eating disorders** (Pjetri et al 2012), **anxiety** (Hunter & McEwen 2013), **OCD** (Nissen et al, 2016), **ADHD** (Schuch et al, 2015) and **borderline personality disorder** (Teschler et al, 2016) have all been studied or studies are in the planning stage.

SUICIDE

Suicide is not a mental disorder and is not always the result of mental disorder (Pridmore 2015). However, biological 'explanations' attract attention.

Low levels of BDNF have been reported in suicide. A postmortem study of the Wernicke area of suicide subjects found hypermethylation of the promoter of *BDNF*, which could explain the downregulation of BDNF expression in this population (Keller et al 2010).

A recent genome-wide investigation of the brains of suicide subjects, demonstrated 366 promoters that were differentially methylated in the hippocampus of suicide completers compared to controls. The effects of these changes remain to be confirmed (Labonte et al 2013).

Reviews (Lockwood et al, 2015) support a role for epigenetics in depression and suicide, but it is not clear whether identified changes are associated with depression, or suicide or both.

GRAY MATTER VOLUME
Methylation of the serotonin transporter gene is associated with hippocampal increased gray matter volume (hippocampal caudate, insula and caudate nucleus grey matter volumes). Thus, epigenetic processes can alter brain structure (Dannlowski et al, 2014).

TREATMENT

Changing epigenetic markers - a form of treatment
There is great interest in finding ways to alter epigenetic status in the hope of therapeutic outcomes.

Weaver et al (2004&5) (working with rodents) used central infusion of a histone deacetylase inhibitor to remove epigenetic marks and the effects of maternal care. Maddox et al (2013) (also working in rodents) used central infusion and also intraperitoneal administration of 'gracinol' a histone acetyltransferase inhibitor from the fruit of the Kokum tree (*Garcina indica*) to extinguish conditioned fear.

Changing epigenetic markers – a consequence of treatment

There is interest in understanding the impact of established treatments on the epigenome. These effects need to be taken into consideration when seeking to describe epigenetic patterns of particular disorders.

Perroud et al (2013) have demonstrated that in borderline personality disorder, response to psychotherapy was associated with a decrease in methylation of the promoter of the BDNF gene. De Jong et al (2014) suggest that electroconvulsive seizure in animals (a model of ECT) has a robust impact on epigenetic mechanisms, which may be useful in the development of electrical treatments.

Changes in DNA methylation changes have been demonstrated with valproic acid and quetiapine (Houtepen et al, 2016).

Mentioned above, imipramine treatment reversed histone methylation associated with depression (Tsankova et al 2006).

CONCLUSION

Epigenetics is a most exciting development in biology. It promises to provide insights and even therapies for mental disorders – students are encouraged to take an active interest.

References

Andersen A, Dogan M, Beach S, Philibert R. Current and future prospects for epigenetic biomarkers of substance use disorders. Genes (Basel) 2015; 6: 991-1022.
Beach S, Brody G, Todorov A et al. Methylation at 5-HTT mediates the impact of child sex abuse on Women's antisocial behaviour: and examination of the Iowa adoptee sample. Psychosomatic Medicine 2011; 73: 83-87.
Condiffe D, Wong A, Troakes C, et al. Cross-region reduction in 5-hydroxymethlcytosine in Alzheimer's disease brain. Neurobiology of Aging 2014; 35: 1850-1854.
Craddock N, Owen M. The beginning of the end for the Kraepelinian dichotomy. British Journal of Psychiatry 2005; 186: 365-366.
Dannlowski U, Kugel H, Redlich R, et al. Serotonin transporter gene methylation is associated with hippocampal gray matter volume. Human Brain Mapping 2014, in press.
De Jong J, Arts B, Boks M, et al. Epigenetics of electroconvulsive seizures. Journal of ECT 2014; 30: 152-158.

Dempster E, Pidsley R, Schalkwyk L, Owen S, Georgiades A, Kane F and Kalidini S. Disease-associated epigenetic changes in monozygotic twins discordant for schizophrenia and bipolar disorder. Human Molecular Genetics 2011; 20: 4786-4796.
Francis D, Diorio J, Liu D and Meaney M. Nongeneomic transmission across generations of maternal behaiveor stress responses in the rat. Science 1999; 286(5442):1155-1158.
Houtepen L, van Bergen A, et al. DNA methylation signatures of mood stabilizers and antipsychotics in bipolar disorder. Epigenomics 2016; 8: 197-208.
Hunter R and McEwen B. Stress and anxiety across the lifespan: structural plasticity and epigenetic regulation. Epigenomics 2013; 5: 177-194.
Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nature Genetics 2003; 33 Suppl: 245-254.
Joubert B, den Dekker H, et al. Maternal plasma folate impacts differential methylation in an epigenome-wide meta-analysis of newborns. Nat Commum 2016; 7: 10577.
Kahl K, Geogi K, et al. Altered DNA methylation of glucose transporter 1and glucose transporter 4 in patients with major depressive disorder. J Psychiatr Res 2016; 76: 66-73.
Keller S, Sarchiapone M, Zarrilli F, Videtic A, Ferraro A, Carli V. Sacchetti S, Lembo F and Angiolillo A. Increased BDNF promoter methylation in the Wernicke area of suicide subjects. Archives of General Psychiatry 2010; 67: 258-267.
Labonte B, Suderman M, Maussion G, et al. Genome-wide epigenetic regulation of early-life trauma. Archives of General Psychiatry 2012; 69: 722-731.
Lockwood L, Su S, Youssef N. The role of epigenetics in depression and suicide. Psychiatry Res 2015; 228: 235-242.
McGowan P, Sasaki A, D'Alessio A, Dymov S, Labonte B, Szyf M, Turecki G and Meaney M (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nature Neuroscience 2009; 12:342-348.443.
Maddox S, Watts C, Doyere V, Schafe G. A naturally-occurring histone acetyltransferase inhibitor derived from *Garcinia indica* impairs newly acquired and reactivated fear memories. PLoS One 2013; 8: e54463.
Mansell T, Novakovic B, et al. The effects of maternal anxiety during pregnancy on IGF2/H19 methylation in cord blood/ Transl Psychiatry 2016; 6: e765.
Maze I, Covington H, Dietz D, et al. Essential role of histone methlytransferase G9a in cocaine-induced plasticity. Science 2010; 327(5962): 213-216.
Montano C, Taub M, et al. Association of DNA methylation differences with schizophrenia in an epigenome-wide association study. JAMA Psychiatry 2016 [Epub ahead of print]
Nissen J, Hansen C et al. DNA methylation at the neonatal state and at the time of diagnosis etc. Front Psychiatry 2016; 7:35.
Perroud N, Salzmann A, Prada P, Nicastro R, Hoeppli M-E, Furrer S, Ardu S, Krejci I, Karange F and Malafosse A. Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. Translational Psychiatry 2013; 3:e207. doi: 10.1038/tp.2012.140.
Perroud N, et al. The Tutsi genocide and transgenerational transmission of maternal stress: epigenetics and biology of the HPA axis. World J Biol Psychiatry 2014; 15: 334-45.
Peschansky V, Wahlestedt C. Non-coding RNAs as direct and indirect modulators of epigenetic regulation. Epigenetics 2014; 9: 3-12.
Pjetri E, Schmidt U, Kas M and Campbell I. Epigenetics and eating disorders. Current Opinion in Clinical Nutritional and Metabolic Care 2012; 15: 330-335.

Pridmore S. Mental disorder and suicide: A faulty conne. Aust N Z J Psychiatry 2015; 49: 18-20.
Rubin L, Connelly J, et al. Sex and diagnosis specific associations between DNA methylation of the oxytocin receptor gene etc. Biol Psychiatry Cogn Neurosci Neuroimaging 2016; 1: 141-151.
Roth T, Lubin F, Funk A, Sweatt J. Lasting epigenetic influence of early-life adversity on the BDNF gene. Boilogical Psychiatry 2009; 65:760-769.
Sakharkar A, Vetreno R, et al. A role for histone acetylation mechanisms in adolescent alcohol exposure-induced deficits in hippocampal etc. Brain Struct Funct 2016 [Epub ahead of print]
Schuch V, Utsumia D, Costa T, et al. Attention deficit hyperactivity disorder in the light of the epigenetic paradigm. Front Psychiatry 2015 [Epub ahead of print]
Sun H, Maze I, Dietz D, et al. Morphine epigenomiclly regulates behaviour through alterations in histone H3 lysine 9 dimethylation in the nucleus accumbens. Journal of Neuroscience 2012; 32: 17454-64.
Teschler S, Gotthardt J, Dammann G, Dammann R. Abberant DNA methylation of rDNA and PRIMA 1 in borderline personality disorder. Int J Mol Sci 2016; 17. pii: E67.
Tsankova N, Berton O, Rentha W, Kumar A, Neve R and Nestler E. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nature Neuroscience 2006; 9: 519-525.
Van den Hove D, Kompotis K, Lardenoije R et al. Epigenetically regulated microRNAs in Alzheimer's disease. Neurobiology of Aging 2014; 35: 731-745.
Vassoler F, White S, Schmidt H, et al. Epigenetic inheritance of cocaine-resistance phenotype. Nature Neuroscience 2013; 16: 42-47.
Weaver I, Cervoni N, Champagne F, D'Alessio A, Sharma S, Seckl J, Dymov S, Szyf M, Meaney M. Epigenetic programming by maternal behaviour. Nature Neuroscience 2004; 7:847-854.
Weaver I, Champagne F, Brown S, Dymov S, sharma S, Meaney M, Szyf M. Reversal of maternal programming of stress response in adult offspring through methyl supplementation: altering epigenetic marking later in life. Journal Neuroscience 2005; 25: 11045-11054.
Wockner L, Nobel E, Lawford B, et al. Genome-wide DNA methylation analysis of human brain tissue from schizophrenia patients. Translational Psychiatry 2014; 4, e399.
Yehuda R, Flory J, Bierer L, et al, Lower methylation of GR gene promoter 1_F in peripheral blood of Veterans with PTSD. Biological Psychiatry 2014, in press.
Yehuda R, Daskalakis N, Bierer L, et al. Holocaust exposure induced intergenerational effects on FKBP5 methylation. Biol Psychiatry 2015 [Epub ahead of print]