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# Stress Shaping Brains: Higher Order DNA/Chromosome Mechanisms Underlying Epigenetic Programming of the Brain Transcriptome

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## 1. Introduction

*"I believe there is little reason to question the presence of innate systems that are able to restructure a genome. It is now necessary to learn of these systems and to determine why many of them are quiescent and remain so over very long periods of time only to be triggered into action by forms of stress, the consequences of which vary according to the nature of the challenge to be met". Barbara Mc Clintock, (1978), as cited in (Jorgensen, 2004).*

Attempts to link specific neurobehavioural phenotypes with causative genes, a necessary step preceding the development of highly specific neuroimaging biomarkers for these phenotypes, have been spectacularly unsuccessful, although numerous significant gene candidates emerged during the process. Various family study approaches, including twin studies, sib pairs, 'trios' and so-called 'pure multiplex pedigrees' excluding comorbid disorders have been employed in various linkage and association study designs to determine the genes and proteins underlying the relevant disorders. Some genomewide association studies surprised investigators with the information that, when initially promising genomic coding region hotspots were supersaturated with markers at increasingly closer map distances, the results showed weakening of signals in targeted exonic areas, possibly indicating an influence outside these coding areas. The importance of epigenetics (including increasingly complex regulatory region and RNA metabolism gene expression-modifying mechanisms), gradually emerged during the course of molecular genetic 'brain and behaviour' studies. "Epigenetics is defined as mitotically or meiotically stable molecular processes that regulate genome activity independent of DNA sequence. The term 'heritable' has been included in the definition, but has been omitted recently since this implies generational inheritance by definition and therefore does not include all elements of epigenetics (Skinner, 2011). The brain represents a particular area of interest with regard to epigenetics, where it has been demonstrated that epigenetic modifications are not static, but dynamically change in response to external stimuli including synaptic activity (Crepaldi & Riccio, 2009). The increasing likelihood of the role played by transgenerational epigenetic influences in neurogenetics studies now also impacts on the tracking of neuropsychiatric disorder gene candidates in families, implying a requirement for analyses of both coding as well as noncoding polymorphisms and the manner in which these interact,

as well as distinguishing between context dependent and germline dependent epigenetic changes (Crews, 2008).

The extensive comorbidity recorded in neuropsychiatric disorders and the acknowledgement of their role when devising candidate gene approaches has been a major challenge. Even though the importance of epistasis and gene pleiotropy are generally acknowledged, there is still no clear understanding of the mechanisms of comorbidity, and biomarker investigative choices thus often remain too simplistic.

The increasing application of sophisticated network dynamics analyses may provide the means to resolve these issues, and the problems posed by variable overlapping of disparate conditions in complex syndromes may soon be better understood by a 'diseasome' approach (Potkin et al., 2010; Barabási et al., 2011), as outlined below. While seemingly introducing even more variables, the aim of network medicine concepts is to actually reduce the noise arising from experiments producing vast amounts of data and organise the information existing in published and newly executed research, ranging from studies of single markers to massively parallel array sequencing experiments. Applying genetic data from genome-wide association studies in a gene network analytic approach, using brain imaging as a quantitative trait phenotype, can increase the statistical power to identify the molecular pathways in which risk genes participate (Potkin et al., 2010). These authors demonstrated the utility of a regulatory network approach by measuring correlations among transcript levels in the mouse and human postmortem tissue which allowed the derivation of an enriched gene set that identified several microRNA's that could be associated with negative symptom schizophrenia. Last but not least, there may be a belated resurgence of interest in the value of 'clinical experience' when discussing which phenotypes to analyse and how to identify the most appropriate research subjects by using experienced investigators within a specific field, rather than relying on massive amounts of data (and biospecimens) accrued by means of research questionnaires dealt with by inexperienced but willing junior research assistants.

This review deals only with the first step in the development of radioligands for imaging in neuropathology (i.e. understanding the clinical genetic context before the selection of disorder-relevant biomarkers). Once a suitable molecular biomarker candidate can be demonstrated, this needs to be followed by selection of leading compounds, radionuclide, labeled position, and synthesis methods; in vitro and in vivo evaluation including probability for imaging, selectivity, specificity, and species differences, and finally an evaluation of factors impinging on safety such as acute toxicity, mutagenicity and radiation dosimetry (Ishiwata, 2009). This does not mean that simpler biomarker identification approaches may not be effective, but it is proposed that a total understanding of the full scope of specific neurobehavioural problems and the mechanisms according to which they overlap can only be developed in this manner. An attempt will be made to integrate the fundamentals of an interface system in the brain with an evolutionary understanding of the mechanism that could give rise to a cluster of seemingly unrelated disorders. This approach may be useful as a model according to which some currently important facets regarding comorbidity can be placed in context.

## 2. Combining in vivo neuroimaging technologies with 'omics' biomarkers

Noninvasiveness of molecular imaging offers a potent advantage for monitoring endpoints of molecular medicine interventions. In particular, pharmaceutically-relevant neuroimaging endpoints based on disorder-specific biomarkers have great potential for

better definition and stratification of preclinical study groups, and for providing direct biological measures of response (Waerzeggers et al., 2010). Not all biomarker molecules are suitable for radioimaging approaches, though many potentially interesting molecular biomarkers also appear to be suitable molecular imaging agents. Activatable molecular probes are designed to elicit a detectable change in signal upon enzymatic activity or in response to specific biomolecular interactions. In many cases, these unique characteristics allow for very high signal-to-background ratios compared with conventional targeted contrast agents and they open up the possibility of imaging intracellular targets (Garcia-Campayo et al., 2009).

Molecular biology now offers system-wide insights which have to be incorporated in the derivation of appropriate imaging biomarkers: '*Omics'* is a general term for a broad discipline of science for analysing interactions of biological information. These include studies of the genome, fragilome, transcriptome, proteome, metabolome, expressome, interactome etc. The main focus in these endeavours is on mapping information objects such as genes, proteins, and ligands, finding interaction relationships among the objects and engineering the networks to understand and manipulate the regulatory mechanisms. *Systems biology* integrates information from the various 'omics' subfields, and generates a more comprehensive 'interactome'.

Combined with the disciplines of molecular imaging and molecular medicine, systems biology approaches to understanding disease complexity promises to provide predictive, preventive and personalized medicine that are expected by many to be able to transform healthcare in the future. Continued development of these technologies and applications requires collaboration transcending traditional boundaries between disciplines – e.g. for suitable biomarker consideration, clinical molecular geneticists and radiochemists have to liaise to decide on the choice and molecular characteristics of biomarkers suitable for both laboratory assays as well as being able to bind radioligands. Using disorder specific biomarkers for both laboratory assays and radioimaging allows a two-pronged approach enabling both mass screening and targeted imaging.

## 3. Epigenetics and the brain – foetal programming

The observed foetal basis of some adult onset diseases requires both epigenetic and genetic factors to be involved in regulating developmental biology outcomes, as emphasized by Skinner (2011), who cites the now classical example of insulin resistance and obesity. Developmental studies of metabolic 'programming' suggest that insulin resistance may appear during early development in individuals born small for gestational age. Insulin resistance can promote obesity, which in turn, could sustain the state of insulin resistance in later life. Skinner et al. (2011) stresses that "the current paradigm of DNA mutational events promoting evolution is accurate, but the inclusion of epigenetics allows for a much higher degree of variability in the biological system to facilitate an adaptation event and epigenetic transgenerational inheritance is a novel concept with considerable experimental support in plant and mammalian studies. This insight, therefore, does not modify the fundamental Darwinian evolutionary paradigm, but adds a neo-Lamarckian component allowing a more diverse molecular mechanism" (Skinner 2011). The role of epigenetics in controlling neuronal functions that may ultimately underlie behavioural adaptations represents a strong emerging research theme (Nelson & Monteggia, 2011).

### 3.1 Context-dependent epigenetic modifications

Context-dependent epigenetic modifications refer to transmission within a generation (within an individual's own lifetime, including the interaction of parent and young), while germline-dependent epigenetic modifications deal with transmission across generations (Crews, 2008). The best examples of context-dependent epigenetic modifications are those that either have an effect early in life, such as exposure to endocrine disrupting compounds *in utero* or smoking during childhood and adolescence (known collectively as the foetal basis of adult disease, or foetal programming also alluded to above. In the first instance the onset of disease manifests later or the deleterious effects decline with time. However, "the extent to which the modification is perpetuated is by simple persistence of the environmental factors that bring about the epigenetic modification; that is, in each generation individuals are exposed to the same conditions. Hence, the environment can induce epialleles, but this environmentally induced epigenetic state can be reversed by a different environmental factor" (Crews, 2008). An example supplied by Crews (2008) of a context-dependent epigenetic modification on behaviour is considered to be exemplified by the study of Meaney and colleagues (Meany, 2001; Meaney & Syzf, 2005; Champagne, 2008). In a series of studies in rats, this group demonstrated that the nature and amount of care a pup receives from the mother modulates its reaction to stress in later life, largely through effects on the glucocorticoid receptor (GR) in the hippocampus. This maternal effect can cross generations, but its heritability depends upon the pup's experience in the first week of life. Crews (2008) mentions in his review that Meaney's group also recently documented that being reared by a high quality mother results in the expression of the transcription factor A (NGFI-A), a nerve growth factor-inducible protein, that binds to the first exon of the GR gene, resulting in increased expression of GR. High quality maternal care during this critical period demethylates NGFI-A and the acetylation of histones. Just as cross-fostering can reverse these molecular and behavioural changes, infusion of methionine, a histone deacetylase inhibitor, into the hippocampus can also reverse these events (Weaver et al., 2006).

Selective breeding cannot stabilize these brain–behaviour differences and, the effects of high and low quality mothering disappear after five generations indicating that it is not a germline-dependent epigenetic modification but a context-dependent epigenetic modification. The implications of the work are, however, still regarded as important: in humans it has been reported that rearing environment can overcome the influence of a polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A in the aetiology of violent behaviour (Caspi et al., 2003).

### 3.2 Germline-dependent epigenetic modifications

Germline-dependent epigenetic modifications "are fundamentally different from context-dependent epigenetic modification in that the epigenetic imprint has become independent of the original causative agent" (Crews, 2008). Here the epigenetic modification is transferred to subsequent generations because the change in the epigenome has been incorporated into the germline. Thus, the effect is manifest each generation without the need for re-exposure. The inheritance of environmentally induced phenotypes is the origin of the concept of epigenetics as conceptualized by Conrad Waddington in 1934. (Costa et al., 2004; Morange, 2009). In such instances the DNA methylation imprints of heritable epialleles are passed through to subsequent generations rather than being erased as occurs normally during gametogenesis and shortly after fertilization. Germline-dependent epigenetic modifications tend to be associated with one sex, an important aspect as many behaviours

and affective disorders show sex differences (Crews, 2008). A comprehensive review of over 100 cases of transgenerational epigenetic inheritance have now reported the phenomena in a wide range of organisms including prokaryotes, plants, and animals (Jablonka et al., 2009). It appears that RNA plays a major role in germline dependent epigenetic modifications (Ashe & Whitelaw, 2007), an aspect which is relevant to links suggested to exist between chromosomal rearrangement at fragile regions, transgenerational transmission of certain behaviours and neurodevelopment.

### 3.3 Caveats of twin studies in disorders where epigenetics are important

Twin research findings clearly indicate how an appreciation of epigenetics is missing from an understanding of how different phenotypes can originate from the same genotype. Although epigenetically indistinguishable during the early years of life, monozygotic twins exhibit remarkable differences later in life in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, affecting their gene-expression profiles (Fraga et al., 2005). Epigenetic changes can result in a normal genotype suddenly being associated with a disease phenotype and genotypes associated with susceptibility to certain disorders may have reduced penetrance and subsequently develop as a normal phenocopy (Singh et al., 2004). Due to the indirect relationship between phenotype and genotype in epigenetics, finding a distinct set of genes that will be consistently linked with a particular neurobehavioural disorder phenotype on a worldwide basis may prove to be more difficult than originally envisaged.

## 4. The brain genome - environment interface: – stress as an evolutionary driver

Following Waddington's early epigenetic concept, biological stress could be stated to represent a dyshomeostatic influence which produces a diversifying biological response following which a novel variant may have a survival advantage, making it an essential driver of evolution. Evolutionary processes are strongly influenced by the competition for available energy, with the required physical or mental skills being passed to offspring of the most able competitors. Diversity is clearly an asset in this process. A broader repertoire of cognitively linked, novelty stress-based learning associated with a complex range of emotions and increased cognitive integration through higher interneuronal density in humans is suggested to have diversified novelty information management. Stress hormones participate in modulation of memory consolidation processes in both the amygdala and the hippocampus (Guterman et al., 2006).

It increasingly appears possible that stress management systems operating within non-pathological parameters are utilised to deal with 'novelty'. The physiological activity of stress hormones has been shown to play an important role in modulation of memory consolidation processes in both the amygdala and the hippocampus (Turner et al., 2008). Severe psychosocial stress in early life crossing the proposed physiological stress management system boundaries, can adversely impact brain development itself, and the literature on stress suggests that these changes also occur largely through the hypothalamic pituitary adrenocortical (HPA) axis (Loman and Gunnar, 2010). Steroid receptors function by binding to specific structural elements in the regulatory regions of target genes by recruitment of cofactors that modify histones and chromatin structure (Trapman & Dubbink, 2007). Global changes in epigenetic markers in response to fear conditioning have been demonstrated

(Lubin & Sweatt, 2007), and RNA-mediated chromatin-level silencing is increasingly implicated in development, stress responses, and natural epigenetic variation that may promote phenotypic diversity, physiological plasticity, and evolutionary change (Madlung & Comai, 2004). Epigenetic markers on the promoter regions of the Bdnf gene have been the most extensively studied, including alterations in histone acetylation, phosphorylation, methylation, and DNA methylation associated with memory behaviour (Gupta et al., 2010), as well as activity-dependent changes in DNA methylation (Nelson et al., 2008).

### 4.1 How it all comes together: A flexible networking "interface system"

The ability to alter development, physiology, growth, and behaviour in response to different environmental conditions represent critical assessments of both external and internal factors as a function of energy balance and environmental stress as well as physiological, developmental, and behavioural responses to these determinations (Crespi & Denver, 2005). What may have made humans unique, is an enormously increased feedback capability for constructive interaction between internal structures and extra-biological factors, self reflective evaluation and an improved ability to shape the environment, to such an extent that there is now an unprecedented information continuum between information captured in biological processes and the environment itself. In support of more holistic modelling, integrative biological concepts have also arisen, for instance the concept of a "neuro-immuno-endocrine system". It is additionally proposed here that the flexible disparate stress response mechanisms responsible for the storage of novel information should be considered as a combinatorially regulated "interface system". It can be expected that an evolutionary strategy would exploit the effect of integrating the different systems for the transmission of genetic information with systems relating to the external adaptation of the organism (Bengtsson, 2004). An interface can be defined as a point at which independent systems or diverse groups interact. Although such a proposed environmental interface system presumably consists of many more components than mentioned here, an example will be provided of a nonlinear brain system with flexible internal structural responses to environmentally induced perturbation i.e. the brain chromosomal 'fragilome' which appears to underly certain aspects of neuroplasticity and memory storage and which appears to be closely linked with the stress hormonal system and immunoglobulin DNA strand break and genomic rearranging phenomena. The essential important characteristic of the brain fragilome is that of genetic breakage and recombination offering a structural basis for genetic/neuronal diversification and storage of memories (Gericke, 2010).

Chromosomal fragile sites represent large heritable chromosomal regions that preferentially exhibit gaps or breaks after DNA synthesis is partially perturbed by stressors affecting the replication process (Arlt et al., 2006) and are classified as 'rare' or 'common', depending on their induction method and frequency within the population. Common fragile sites (CFS) are found in all individuals, are variable, extend over large regions and are associated with transcriptional activity (Sbrana et al., 1998).

Several of the currently known human CFS regions span large genes that extend from 700 kb to over 1.5 Mb of genomic sequence. Many of these genes have been functionally linked with neurological development. Chromosomal fragile sites (*in toto* represented by the fragilome), represent *in vitro* observed genomic regions with particular structural characteristics related to epigenetic plasticity, resulting in the creation of diversity through a process of controlled double strand breaks and imperfect mismatch repair shielded from and/or below an apoptotic risk threshold under physiological circumstances. This modular

assembly process has been adapted from the immune paradigm at the expense of a risk for instability and/or malignant transformation when associated control mechanisms are not in place (such as tumour suppressor genes). It is suggested that the abilities for diverse recognition of externally derived information, a dynamic response of somatic hypermutation followed by genome rearrangement creating a template for memory formation, and entry into a terminally differentiated state are features common to both the brain and immune system. Chromosome breaks and the various resulting structural rearrangements (genetic instability) have mostly been viewed in a pathological context by researchers, but controlled chromosomal breakage and rearrangement leading to altered gene expression without adverse effects may have been necessary for the evolutionary and neurodevelopmental flexibility required by the human brain (Gericke, 2010).

Such chromosomal breakage relates to alterations in DNA higher order structures and studies of fragile sites at the level of chromosome organization reveal an unusual chromatin structure associated with fragile sites influencing formation of nucleosomes and the formation of nucleosome arrays (Wang, 2006). The study of epigenetics focuses on the relationship between chromatin structure and gene transcription. DNA is commonly packaged into nucleosomes and wrapped tightly around a core of histone (H) proteins. Modifications that regulate chromatin structure influence transcriptional activity, in part, through effects on transcription factor binding. the environmental regulation of histone methylation states. Chromatin remodeling and gene transcription are linked in that transcriptional activation associates with chromatin states that enhance the probability of subsequent transcriptional activity, providing a feed-forward loop. (Cordero et al., 2006, Murr, 2010; Hayashi et al., 2011). Recent observations reveal that histones are removed and replaced to enable or restrict, respectively, access of the transcription machinery to regulate transcription. The ultimate goal of some epigenetic modifications might well turn out to be the regulation of histone occupancy on the DNA (Williams et al., 2008). CFS-associated duplication and deletion altering AT tract length and DNA flexibility have been linked with variation in nucleosomal architecture (Cosgrove & Walberger, 2005). AT-rich repeats mediate recombination events in non-homologous chromosomes during meiosis (Jackson et al., 2003) and due to a modification of binding factor characteristics, CFS have been proposed to contribute to epigenetic sensitive phenotypes (Woynarowski, 2004), a phenomenon which has been suggested to include neurobehavioral effects (Garofalo et al.,1993; Gericke et al., 1995, Gericke 1998, 2006, 2010; Simonic & Gericke 1996; Simonic & Ott, 1996; Savelyeva et al., 2006).

### 4.2 Developmental cytogenetic instability in the mammalian brain

"As many of the examples of epigenetic inheritance are mediated by position effects, the possibility exists that chromosome rearrangements may be one of the driving forces behind evolutionary change by exerting position effect alterations in gene activity, an idea first articulated by Richard Goldschmidt in 1940 in his book "The Material Basis of Evolution"(Reprinted in 1982).

The emerging evidence suggests that Goldschmidt's controversial hypothesis deserves a serious reevaluation" (Varmuza, 2003). Recent findings of rearranged and aneuploid chromosomes in brain cells suggest an unexpected link between developmental chromosomal instability and brain genome diversity (Yurov et al., 2007), (Yang et al., 2003). In humans, previously unrecognized large-scale double-stranded DNA breaks are now known to occur under normal circumstances in early postmitotic and differentiating

neurons (Gilmore et al., 2000). In general, accumulation of DNA breaks in differentiating cells cannot be attributed to a decrease in the DNA repair efficiency. Poly(ADP)ribose synthesis often follows the DNA breakage in differentiating cells. It has been hypothesized that DNA fragmentation is an epigenetic tool for regulating the differentiation process (Sjakste & Sjakste, 2007). Genomes of developing and adult neurons can be different at the level of whole chromosomes (Rehen et al., 2005). Not only breakage and rearrangement and associated structural sequelae, but also large scale chromosomal ploidy alterations seem to have been recruited as a diversifying process, similar to processes involved in genetic diversification in plants. Metaphase chromosome spreads from whole brains of the teleost *Apteronotus leptorhynchus* revealed an euploid complement of 22 chromosomes in only 22% of the cells examined. Together with the recent discovery of aneuploidy in the adult mammalian brain, investigations suggest that the loss or gain of chromosomes might provide a mechanism to regulate gene expression during development of new cells in the adult vertebrate brain (Rajendran et al., 2007),(Yurov et al., 2005). Both neurons and non-neuronal cells can be aneuploid as a normal feature of the human brain (Rehen et al., 2005).

One possible consequence of nervous system aneuploidy is altered gene expression through loss of heterozygosity (Kaushal et al., 2003). Aneuploid neurons were found to be functionally active and demonstrate that functioning neurons with aneuploid genomes form genetically mosaic neural circuitries as part of the normal organization of the mammalian brain (Kingsbury et al., 2005). The average aneuploidy frequency has been found to be 1.25-1.45% per chromosome, with the overall percentage of aneuploidy tending to approach 30-35%. Furthermore, such mosaic aneuploidy appears to be exclusively *confined to the brain* (Yurov et al., 2007) and it is probably crucial to contain the extensive rearrangement processes in brain cells in order to prevent this extent of breakage and ploidy alterations from creating havoc in other mitotically active cells. This appears to be different from altered chromosomal breakage which can be demonstrated in peripheral blood and may reflect more widespread gene expression changes.

### 4.3 Protocadherin genetic rearrangement in the brain

Both the immune system and the brain evolved from a cell adhesion system. Evidence of the importance of DNA rearrangement in essential neurogenic processes also highlighted recent discoveries of genes encoding neuronal adhesion protocadherins which display structural similarity to immunoglobulins. Cadherin-related neuronal receptor/protocadherin transcript variance has also been linked with chromosomal variations in the nucleus of differentiated neurons (Yagi, 2003). Together with cytoskeletal proteins, such as tubulin, microtubule-associated proteins, and intermediate filament proteins, the neural adhesive protocadherins with immunoglobulin-like functional features and extracellular matrix glycoproteins are associated with dynamic structural remodelling in the nervous system (Miyate & Hatton, 2002; Chun 1999). Some brain protocadherins are specific to the hominoid lineage (Durand et al, 2006) and single nucleotide polymorphisms in the protocadherin-alpha and –beta genes are possible contributors to variation in human brain function (Pedrosa et al., 2008). Furthermore, different codons in the mammalian protocadherin ectodomains are under diversifying selection. These diversified residues likely play an important role in combinatorial interactions, which could provide the staggering diversity required for neuronal connections in the brain (Miki et al., 2005).

While lymphocytes express a single receptor molecule specifically directed against an outside stimulus, in contrast, each neuron has three specific recognition sites, each

expressing a different protocadherin. In this way, 4,950 different neurons arising from one stem cell form a neuronal network in which homophilic contacts can be formed in 52 layers, permitting an enormous number of different connections between neurons (Wu, 2005). At the single-cell level, protocadherin-alpha mRNAs are regulated monoallelically, supporting the idea that diversified protocadherin molecules contribute to neural circuit development and provide individual cells with their specific identity (Hilschmann et al., 2001). The neocortical genomic response to stress is relayed via hormones and reactive oxygen/nitrogen species signaling, thereby implicating the mitochondrial genome and bioenergetic metabolism (Wallace, 2010), which is suggested to represent an extension of dynamic genomic changes in parallel to the immune recombination and neural rearrangement (protocadherin) histories and fragile site events (Gericke, 2006) of a particular individual.

## 5. Stress memory and immune-like rearrangement in the human brain

Doubts have more recently been raised whether gene transcription activated by dendritic calcium signals is sufficient to consolidate long-term functional alterations associated with memory consolidation. An alternative genomic hypothesis of memory suggests that acquired information is persistently stored within individual neurons through modifications of DNA, and that these modifications serve as the carriers of elementary memory traces. The emerging idea is therefore that lifelong behavioural memory storage may involve lasting changes in the physical, three-dimensional structure of DNA itself and chromatin alterations are emerging as a key epigenetic mechanism in the process in conjunction with use-dependent synaptic plasticity (Levenson & Sweatt, 2006; Delcuve et al., 2009). The expression of immune recombination activating genes in key stress-induced memory regions in the brain suggests the adoption by the brain of this ancient pattern recognition and memory system to establish a structural basis for long-term memory through controlled chromosomal breakage at highly specific genomic regions. Fundamentally unstable processes with narrow safety margins (controlled chromosomal breakage) thus appear to underlie pattern recognition and memory consolidation in both the immune system and brain.

Unusual genetic mechanisms for diversifying recognition proteins may be a widespread characteristic of animal immunity and may have paved the way for adaptation for management of neural sensory information (Litman et al., 2005). Stress reactions form part of neuroendocrine influences that also modulate immune function. The appearance of a lymphocyte-based recombinatorial system of anticipatory immunity in vertebrates approximately 500 mya facilitated developmental and morphological plasticity in addition to the advantage conferred by the ability to recognize a larger portion of the antigenic world (Pancer & Cooper, 2006). A prototypic example of epigenetic-facilitation in memory retention pertains to memory T-cells of the mammalian immune system (reviewed in Nakayama & Yamashita (2008)). Numerous epigenetic mechanisms such as histone modifications and DNA methylation modulate gene expression and thus play a role in T-cell survival and maintenance of T-cell function in various differentiated states. These processes underlie the formation of persistent immunological memory cells in response to transient environmental stimuli (reviewed in Nakayama & Yamashita (2008). Thus, like immune T-cells, it is plausible that epigenetic mechanisms such as methylation of the cytosine base are changeable and occur in post-mitotic neurons to mediate neuronal function. However,

unlike epigenetic mechanisms in the immune system, chromatin modifications in the CNS are greatly understudied. Lymphoid cells purposely introduce DNA double strand breaks into their genome to maximize the diversity and effector functions of their antigen receptor genes (Rooney & Chaudhuri, 2004). Recombinase activation gene RAG-1 directed V(D)J recombination affecting only specific recognition sequences allows the immune system to encode memories of a vast array of antigens. Research findings provide a formal demonstration that certain CFS can function as signals for RAG complex targets (Raghavan et al., 2001). Conversely, CFS were found to be enriched for genes associated with the immune response (Re et al., 2006). RAG proteins have been proposed to contribute to chromosomal translocations in general (Chatterji et al., 2004), suggesting that these may be involved in immune-like stress induced rearrangement processes following breakage at CFS. Rag1 positive-cells mainly appear in the amygdalae, hypothalamus, thalamus and hippocampus at developmental stage (Sun et al., 2007). The RAG-1 gene is also localized to neurons in the hippocampal formation and related limbic regions that are involved in spatial learning and memory as well as other parameters of neurobehavioural performance (Cushman et al., 2003). While the role of RAG-1 in learning and memory in humans still has to be determined, it remains attractive to propose that their localization in relevant anatomical areas in the brain, the importance of epigenetics changes and the postulated role of chromosomal rearrangement make this an interesting area for future studies.

### 5.1 CFS, RAG genes and transposable elements (TE's)

It has been motivated that the recombination system that carries out rearrangements may be a significant evolutionary force, perhaps not limited to rearrangements only at antigen-receptor loci (Roth 2000) (Chuzhanova et al., 2009). Genomic changes in V-gene structure, created by RAG recombinase acting on germline recombination signal sequences, led variously to the generation of fixed receptor specificities, pseudogene templates for gene conversion, and ultimately to Ig sequences that evolved away from Ig function (Hsu et al., 2006). RAG1 and RAG2, like the adaptive immune system itself, are found exclusively in jawed vertebrates, and are thought to have entered the vertebrate genome by horizontal transmission as components of a transposable element (Schatz, 2004). Such dynamicity allows extensive genome repatterning during transient stress phases (including oxidative stress signaling), during which some epigenetic features, such as DNA methylation, are relaxed, thus allowing transposable element (TE) amplification. Analysis of genomic rearrangement breakpoint regions has revealed specific TE repeat density patterns, suggesting that TEs may have played a significant role in chromosome evolution and genome plasticity. Hairpin DNA structures formed in palindromes (such as associated with CFS) are intermediates in V(D)J recombination and are formed by a chemical mechanism very similar to the early steps of transpositional recombination and retroviral integration. RAG proteins are able to capture exogenous target DNA molecules and carry out authentic transposition of signal ends into these targets.

Genomic instability has been indicated to involve epigenetic activation of mobile elements dispersed throughout the human genome (Stribinskis & Ramos, 2006). Barbara McClintock originally proposed that mobile elements restructure host genomes as an adaptive response to environmental challenge (McClintock, 1987; Dai et al., 2007). Retrotransposons are mobile genetic elements that can be amplified to high copy number and are considered to be an important source of genetic diversity (Grandbastien, 2004). Hypomethylation associated with genomic stress largely affects the intergenic and intronic regions of the DNA,

particularly repeat sequences and transposable elements, and is believed to result in chromosomal instability and hypomethylation of regulatory DNA sequences activates transcription of protooncogenes, retrotransposons, as well as genes encoding proteins involved in genomic instability (Glover, 2006; Wilson et al., 2007). Retroelements represent evolutionary forces that establish and hone target gene networks of transcription factors in a species-specific manner. LTR class I endogenous retrovirus (ERV) retroelements impact considerably the transcriptional network of human tumour suppressor protein p53. A total of 1,509 of approximately 319,000 human ERV LTR regions have a near-perfect p53 DNA binding site. Human ERV p53 sites are likely part of the p53 transcriptional program and direct regulation of p53 target genes (Wang et al., 2007). Recent findings showed that key cell cycle checkpoint genes are important for genome stability at fragile sites. Altered sequences arising from chromosomal rearrangement and associated transposable element (TE) upregulation during 'cognitive stress' may result in neurospecific immune-like sequelae involving CFS as key participating regions. DNA double-strand break repair proteins were recognized 20 years ago as a major target of autoantibodies. Dysregulation of these processes can be considered to increase the risk for subsequently developing systemic inflammatory disorders through a central immunologically modified state and sensitization for increased stress responses in susceptible individuals. Because early changes may include misregulation of resident inflammatory myelomonocytic cells in the developing brain, this could be associated with prenatal–neonatal brain pathologies and neurobehavioural deficits (Dietert & Dietert, 2008).

### 5.2 CFS represent a network stress response

When data on CFS expression were analysed in a network context, it appeared that chromosomal fragile site associated genes function as part of a highly conserved stress response network (Re et al., 2006). The regulatory genome supplies an enormous computational capability with the capacity to process in parallel a vast number of regulatory inputs, comprising many thousands of processing units in the form of cis-regulatory modules. The interconnected cis-regulatory modules that control regulatory gene expression create a network that is the underlying mechanism of specification and illustrate the information processing that is done by the regulatory sequences (Ben-Tabou de-Leon & Davidson, 2007). AT islands in CFS have been shown to function as nuclear matrix attachment regions (MARs) both in vitro and in vivo (Jackson et al., 2003), which constitute the functional coordinate system for genomic regulatory regions (Liebich et al., 2002). DNA duplexes of AT islands are prone to base unpairing due to their unusual flexibility characteristics, which are necessary MAR attributes. Recent studies on the molecular mechanisms involved show that proteins of the nuclear envelope participate in regulation of transcription on several levels, from direct binding to transcription factors to induction of epigenetic histone modifications [Skalai et al., 2007]. MARs organize chromosomal loops in the interphase nucleus, are about 200 bp long, AT-rich, contain topoisomerase II consensus sequences and other AT-rich sequence motifs; often reside near cis-acting regulatory sequences, and their binding sites are abundant (greater than 10,000 per mammalian nucleus) (Blasquez et al., 1998). Cis-elements can be defined to include the repeat sequence units, the length and purity of the repeat tracts, the sequences flanking the repeat, as well as the surrounding epigenetic environment, including DNA methylation and chromatin structure (Cleary & Pearson, 2003). Contacts between cis-acting sequences through the formation of chromatin loops form the most basic level of organization that impedes or

permits access of factors to the genes (Dillon, 2006). It is suggested that this links to developmental remodelling of neuronal connectivity and differential network connectivity has been suggested to form the basis for species-specific network connections as key drivers of evolutionary change (Boldogkoi 2004). The behavioural phenotype manifests itself as an emergent property of such networks (Anholt, 2004).

### 5.3 Chromosomal breakage and network assembly, gene duplication and gene copy number variation

Analyses support a nonrandom model of chromosomal evolution associated with both recurrent small-scale duplication and large-scale evolutionary rearrangements (Hinsch & Hannenhalli, 2006). Similarly, the human brain appears to have developed anatomically by the divergent modification of pre-existing parts (Striedter, 1998) and new areas may have evolved as a result of processes likely to be linked with underlying extensive duplication of transcription factors (Babu et al., 2004) or genes. The functional characterization through analysis of the ontology of genes located at connected fragile sites clearly highlights that a great proportion of genes with significant annotated terms are involved in innate and adaptive immune responses and in particular in pathways characteristic of activated T lymphocytes (Re et al., 2006). From these findings it has been proposed that correlated breakage at fragile sites may originate in proliferating lymphocytes from a co-regulated modified expression of fragile genes; in this view the genes identified by ontological analysis may be new fragile genes; chromatin changes and DNA replication alteration at or near these genes would be produced by cellular processes connected with their co-regulation performed through still unknown mechanisms. This is supported by the observation that a number of the analysed cytokine-related genes show actual functional interactions in lymphocytes or other cell types (Re et al., 2006). Duplicate genes rapidly diverge in their expression profiles in the network and contribute to maintaining network robustness as compared with singletons (Chung et al., 2006) and according to modelling analyses, duplication plays an important role in feed-forward loop evolution (Cordero et al., 2006). Gene copy number variation has been considered to underlie a significant proportion of normal human variation including differences in cognitive, behavioural, and psychological features (Lee & Lupski, 2006).

Dynamic interactions between components of living cells (e. g., proteins, genes) exist on genomic, transcriptomic, proteomic and metabolomic levels. The levels themselves are heavily interconnected, resulting in complex networks of different interacting biological entities (Bosman et al., 2007). Some novel data suggest that a large amount of genetic variation exists in the regulatory region of genes within populations. In addition, comparison of homologous DNA sequences of various species shows that evolution appears to depend more strongly on gene expression than on the genes themselves. Furthermore, it has been demonstrated in several systems that genes form functional networks, whose products exhibit interrelated expression profiles. Finally, it has been found that regulatory circuits of development behave as evolutionary units (Boldogkoi 2004).

These data demonstrate that (1) Instead of individual genes, gene networks (GNs) are responsible for the determination of traits and behaviours. (2) The primary source of microevolution is considered to be the intraspecific polymorphism in GNs and not the allelic variation in either the coding or the regulatory sequences of individual genes. (3) GN polymorphism is generated by the variation in the regulatory regions of the component genes and not by the variance in their coding sequences. (4) Evolution proceeds through

continuous restructuring of the composition of GNs rather than fixing of specific alleles or GN variants (Boldogkoi 2004).

Unlike most optimization methods working from a single point in the decision space and employing a transition method to determine the next point, in a densely interconnected system genetic algorithms work from an entire "population" of points simultaneously, trying many directions in parallel and employing a combination of several genetically-inspired methods to determine the next population of points (Cantu-Paz & Goldberg, 1999). These aspects are likely to have been linked with evolutionary recruitment of an increasing number of gene promoters as members of progressively intricate gene expression networks employing different patterns of expression of stable household genes. Such principles may reflect the human ability to *combine and recombine* highly differentiated actions, perceptions, and concepts in order to construct larger, more complex, and highly variable units in a variety of behavioural domains including language, social intelligence, tool-making, and motor sequences (Gibson, 2002). It has been suggested that speech development and visual interpretation is characterized by multipart representations formed from elementary canonical parts (e.g., phonemes in speech, geons in visual perception) (Corballis, 1992), and in such new combinations similarly later gave rise to the introduction of iconic symbols used in art, writing and reading when information management became too complex for gestures and oral traditions.

## 6. Analytical challenges in building complex disease investigative models – network dynamics

The reductionistic approaches which have been successful in the early history of human genetics dealt with so-called 'single gene disorders' (increasingly a challenged concept), and currently fail to uncover the information required for insight into complex gene environment interaction such as required for studies in 'brain and behaviour'. Furthermore, bioenergetic metabolism as related to mitochondrial genetics (including both mitochondrial genes and nuclear genes involved with bioenergetic crosstalk) (Wallace, 2010) as well as epigenetic modification of DNA regulatory structures are considered to be increasingly important in neuroplasticity. Most of the gene identification studies have assayed for only one type of epigenetic marker. The problem of not evaluating the entire array of epigenetic modifications at specific gene promoters, along with the fact that most available gene chips fail to cover a large portion of the genome, means current technology has not yet reached the levels needed to fully assess the gene expression changes responsible for mediating many of the epigenetically-associated phenotypes in the adult brain.

### 6.1 Understanding the interactome

An excellent review of the topic was recently published in Nature Genetics (Barabási et al., 2011). The potential complexity of the human interactome (all the interactions between biological entities in cells and organisms considered as a whole), is daunting. The past decade has seen an exceptional growth in human specific molecular interaction data. Network based approaches to human disease have multiple biological and clinical implications. Networks operating in biological, technological or social systems are not random, but are characterized by a core set of organizing principles. Proteins that are involved in the same disease show a high propensity to interactly directly with each other. Thus, each disease may be linked to a well defined neighbourhood of the interactome, often

referred to as a 'disease module', representing a group of network components that together contribute to a cellular function and disruption which results in a particular disease phenotype.

### 6.2 Mapping complex conditions with multiple comorbid disorders through a 'diseasome' approach

Similarly, the systematic mapping of the network based dependencies between pathophenotypes and their disease modules has culminated in the concept of the 'diseasome' which represents disease maps whose nodes are diseases and whose links represent various molecular relationships between the disease associated cellular components (Barabási et al., 2011). Understanding such links not only helps us understand how different phenotypes, often addressed by different medical subdisciplines are linked at the molecular level but can also help us to comprehend why certain groups of diseases arise together. Diseasome - based approaches can be expected to aid drug discovery, in particular when it comes to the use of approved drugs to treat molecularly linked diseases. Single target drugs can be expected to correct some dysfunctional aspects of the disease module, but they could also alter the activity of molecules that are situated in the neighbourhood of the disease module, leading to detectable side effects. Analysis of drug target networks demonstrated that many drugs are palliative, that is they do not target the actual disease associated proteins, but proteins in their network neighbourhood. Finally, using network analytic capabilities, safer and more focused multi-target combinations can be designed e.g. for anti-inflammatory or anticancer drug combinations (Barabási et al., 2011).

## 7. Interface system pathology – pain hypersensitivity (fibromyalgia syndrome) as a diseasome

Epidemiological evidence suggests that an adverse prenatal environment permanently 'programs' physiology and increases the risk of cardiovascular, metabolic, neuroendocrine and psychiatric disorders in adulthood. Prenatal stress or exposure to excess glucocorticoids might provide the link between foetal maturation and adult pathophysiology (Turner et al., 2008). In a variety of animal models, prenatal stress, glucocorticoid exposure and inhibition (or knockout of) 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2)--the foetoplacental barrier to maternal glucocorticoids--reduce birth weight and cause increases in adult blood pressure, glucose levels, hypothalamic-pituitary-adrenal (HPA) axis activity and anxiety-related behaviours. In humans, mutations in the gene that encodes 11beta-hydroxysteroid dehydrogenase type 2 are associated with low birth weight. Babies with low birth weight have higher plasma cortisol levels throughout life, which indicates HPA-axis programming. In human pregnancy, severe maternal stress affects the offspring's HPA axis and is associated with neuropsychiatric disorders; moreover, maternal glucocorticoid therapy alters offspring brain function (Turner et al., 2008). Genetic variation in HPA axis genes was associated with programming might reflect permanent changes in the expression of specific transcription factors, including the glucocorticoid receptor; tissue specific effects reflect modification of one or more of the multiple alternative first exons or promoters of the glucocorticoid receptor gene. Intriguingly, some of these effects seem to be inherited by subsequent generations that are unexposed to exogenous glucocorticoids at any point in their lifespan from fertilization, which implies that these epigenetic effects persist (Turner et al., 2008). The Fibromyalgia Syndrome (FMS) can be viewed from a certain perspective as a

chronic pain/inflammation problem arising subsequent to a hypersensitized pain and/or stress memory in genetically predisposed individuals probably as early as intrauterine life. First degree relatives have a significantly increased risk to develop FMS. Foetal programming is expected to result in severe pathophysiological hyperreactivity when exposed to subsequent stressful stimuli. This, and much other contemporary research implies that foetal and perinatal stress could have long lasting sequelae in adult life and that it also involves inappropriate immune upregulation. The 'at risk' FMS genotype may represent a risk for several non-classical FMS outcomes as central stress induced hypersensitisation appears to cause subsequent susceptibility to posttraumatic stress disorder-like phenomena, chronic pain syndromes, mood disorders and several other adult onset diseases. These effects often include, but are not limited to, anxiety, depression, ADHD, substance use disorders, and tobacco dependence as well as a dramatically increased risk for a variety of mental disorders (Bhadra & Petersel, 2010; González et al., 2010; Natelson 2010). There may exist cross reactions between various emotional stress and pain responses which involve both the immune and nervous systems. These share quite similar processes for pattern recognition and memory consolidation, and may represent a useful perspective from which to regard aetiological relationships between conditions consistently occurring as comorbid disorders.

### 7.1 Chromosomal fragility in chronic fatigue/fibromyalgia syndrome (FMS)

In 1995, during research on chromosomal fragile sites at the University of Pretoria, my cytogenetics collaborator, Ingrid Simonic, found an increased expression of common aphidicolin-inducible chromosomal fragile sites in FMS/"chronic fatigue" patients as opposed to unaffected intrafamilial controls (Fig 1) (Simonic & Gericke, Unpublished data).

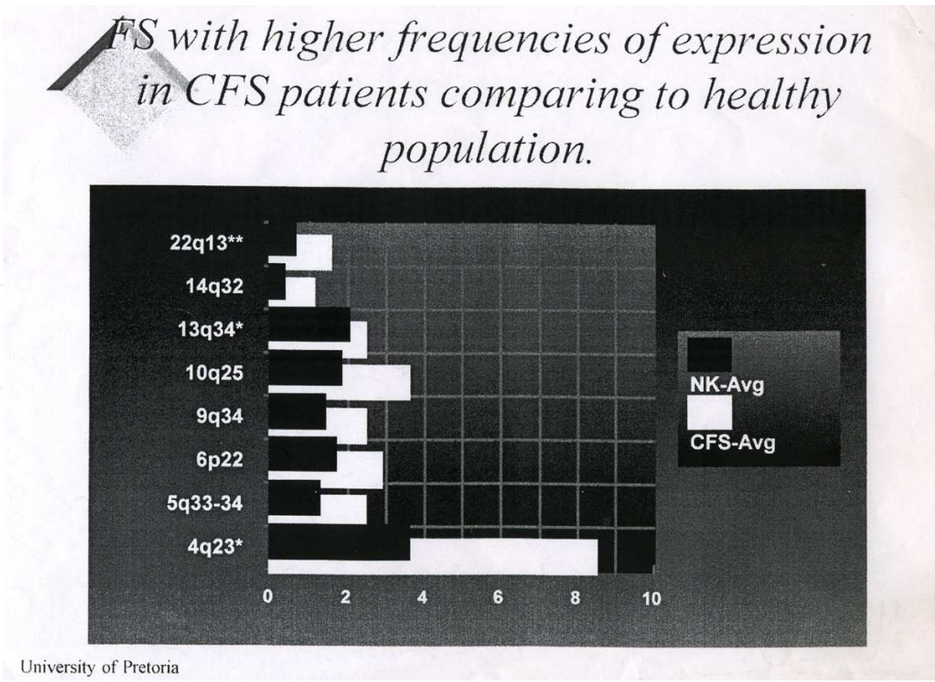


Fig. 1. Higher frequencies of some aphidicolin-induced common chromosomal fragile sites in FMS/chronic fatigue individuals versus first degree controls.

The involved sites included areas harbouring NF-KB genes, which are pro-neuroinflammatory factors (Fig 2). Several studies indicate that the nuclear factor-kappa B (NF-kappaB) -activation cascade plays a crucial role not only in immune esponses, inflammation, and apoptosis but also in the development and processing of pathological pain (Niederberger & Geisslinger, 2008). This could represent one aspect of a FMS diseasome.

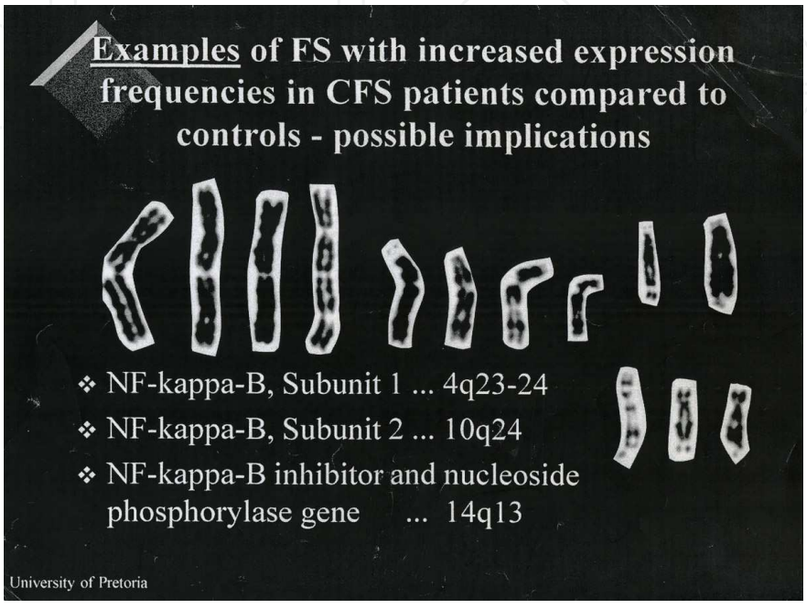


Fig. 2. Examples of induced chromosomal fragile sites in regions harbouring NF-KB genes.

### 7.2 A diseasome overlap with Persian Gulf War syndrome?

Chronic fatigue syndrome (CFS) and Persian Gulf War Ilness (PGI)/Persian Gulf War Syndrome (PGWS) and Fibromyalgia syndrome (FMS) are overlapping symptom complexes without objective markers or known pathophysiology according to the literature. When the cerebrospinal fluid proteome was examined to find proteins that were differentially expressed in this CFS-spectrum of illnesses compared to control subjects an identical set of central nervous system, innate immune and amyloidogenic proteins in cerebrospinal fluids were identified in two independent cohorts of subjects with overlapping CFS, PGWS and fibromyalgia. Although syndrome names and definitions were different, the proteome and presumed pathological mechanism(s) appear to be shared (Baraniuk et al., 2005). PGWS may be a syndrome especially occurring in FMS susceptible genotypes when exposed to specific genotoxicants or the stress of warfare. Of the 130 veterans who were evaluated clinically, 103 had unexplained fatigue, and 44 veterans met the 1994 U.S. Centers for Disease Control criteria for CFS (Mc Cauley et al., 2002). The number of Gulf War veterans who have developed the so-called Gulf War syndrome has risen to about one-third of the 800,000 U.S. forces deployed, and unknown proportions of those involved in the subsequent wars. Uncounted civilians and personnel of other nations that fought in Iraq and other wars since 1991 have also been afflicted (Bertell, 2006). Particulate depleted uranium (DU), widely suspected as one of the prime causes of PGWS associated pathologies, compounds were demonstrated to induce time and concentration-dependent cytotoxic (producing a toxic

effect on cells) and clastogenic (causing disruption or breakages of chromosomes) effects in human lung cells. The types of aberrations seen with treatment of particulate DU are consistent with those induced by other carcinogenic metals (Wise et al., 2007). Tests of 5 Gulf War Veterans in 2007 analysed by Wayne State University Medical staff revealed the 5 Veterans studied have severe chromosome damage. The damage uncovered is 10 times the level found in the normal population. The chromosome damage is similar to that seen when exposed to alpha radiation and could be related to depleted uranium munitions exposure.
In another study by Urnovitz et al., (1999), sera from Persian Gulf War veterans contained polyribonucleotides (amplicons) that ranged in size from 200 to ca. 2,000 bp. Sera from controls did not contain amplicons larger than 450 bp. DNA sequences were derived from two amplicons unique to veterans. These amplicons, which were 414 and 759 nucleotides, were unrelated to each other or to any sequence in gene bank databases. The amplicons contained short segments that were homologous to regions of chromosome 22q11.2, an antigen-responsive hot spot for genetic rearrangements. Many of these short amplicon segments occurred near, between, or in chromosome 22q11.2 Alu sequences. These results suggest that genetic alterations in the 22q11.2 region, possibly induced by exposures to environmental genotoxins during the Persian Gulf War, may have played a role in the pathogenesis of the Gulf War Syndrome. However, the data did not exclude the possibility that other chromosomes also may have been involved (Urnovitz et al., 1999). The fragile site-like nature of all of the breakpoint sites involved in translocations with the recurrent site on 22q11.21, suggests a mechanism based on delay of DNA replication in the initiation of these chromosomal rearrangements (Gotter et al., 2007). This breakpoint is located between two AT-rich inverted repeats that form a nearly perfect palindrome (a typical common fragile site structural characteristic (Politi et al., 2010). It remains remarkable that a known interface between environmental and genomic stress, the DNA double strand break, leading to altered transcriptional activity of genes suggested here to be involved with key PWGS-associated disorders, have not been considered before as a comprehensive study approach for PGWS.. Standard cytogenetic analyses will be inadequate, and a stringently controlled study of in vitro induced breakage is proposed in war veterans and unexposed controls, including first degree relatives.

## 8. Conclusion

Garcia-Campayo and co-workers (2009) took the optimistic view that imaging can take advantage of developments straight from routine individual biomarkers to multiple-scale biomarker profiles. “Imaging should predict treatment response, look at stratification for specific treatment modalities, and look at the characterization of an individual patient” (Garcia-Campayo et al., 2009). Browning et al., 2011 recently reviewed the debate about the nature of somatoform disorders (such as fibromyalgia) and posed the question: “Is there evidence of altered neural function or structure that is specifically associated with somatoform disorders?” These authors described studies reporting neuroimaging findings in patients with a somatoform disorder or a functional somatic syndrome (such as fibromyalgia) and found a “relatively mature literature on symptoms of pain” (and less developed literatures on conversion and fatigue symptoms). (Browning et al., 2011). Both the hippocampus (Emad et al., 2008; Wood et al., 2009; Fayed et al., 2010) and amygdala (Lutz et al., 2008; Burgmer et al., 2009; Valdés et al., 2010) have been implicated in FMS. To summarize, the literature suggests that early life is a period of increased vulnerability, although the effects of stress may be difficult to detect for years (as seems to be the case with

the hippocampus); stress-induced changes in amygdala (initial increases in activity and growth) are apparent earlier in life and more robustly than the hippocampus (decreases in growth), and later in life, when hippocampal changes are finally apparent, the initial amygdala volume increases may ultimately change to volumetric decreases (although it may remain hyperactive). Thus, through a combination of connectivity and volumetric studies, it would be possible to, in children as young as two years old, and extending through adulthood, examine the structural and functional networks that underlie the embedding of adversity.These brain areas represent important neuroanatomical structural markers that could be linked to the proposed stress memory interface pathways modifying the effects of early experiences on the developing human brain.

### 8.1 Genetic and clinical implications

The clinical hypothesis that needs to be investigated further is that foetal programming by intrauterine stress leads to stress hypersensitivity during later life insults in genetically susceptible individuals. The genetic susceptibility mechanism may be based on disruption of a stress hormone-immune recombination-brain fragilome 'interface' pathway together with modifying polymorphic variation in the more fixed associated genetic building bricks anywhere along this pathway (e.g. HPA axis and glucocorticoid genetic variation). Furthermore, such a complex set of changes should be analyzable according to modern integrative genetics analyses. The ability to correlate dynamic changes in cellular ROS levels with mitochondrial metabolism and neuronal network activity is already a promising step towards a detailed mechanistic understanding of redox- and ROS-mediated signalling in normal and diseased brain function (Funke et al., 2011), and this can be expected to contribute significantly to imaging of programmed stress disorders.

In order to gain further insight into human genomic flexibility and its role in individual neurodevelopment, as well as neurological and neurobehavioural disorder phenotypes, current cytogenetic information about fragile genomic regions needs to be augmented by techniques such as innovative next generation sequence variation data, transcriptomic data, epigenomic data and analysis of the interactome to circumvent previous problems in this regard. Assigning genes to context-dependent and potentially overlapping 'transcription modules' in fragile regions will provide functional predictions for numerous genes as had been done in yeast to identify relations between modules (Re et al., 2006) and present a global view on the proposed interface system transcriptional networks. CFS characteristics may underly many previous analytic dilemmas in assessing the neurogenetic response to the environment. For instance, megabase-long satellite sequences and CFS-associated contiguous segmental duplications hamper both physical and fine scale genetic mapping. Links with miRNA, altered methylation and the origin of copy number variation now indicate that CFS region characteristics may be part of chromatinomic mechanisms that are increasingly linked with neuroplasticity and memory. RNA is centrally involved in directing various epigenetic processes considered to occur in neurons, implying that the transcriptional state of the cell is the primary determinant of epigenetic memory. Changes in a small number of RNA regulatory proteins may thus generate a great diversity of biological outcomes.

The stage is now set to integrate transgenerational psychological stress research with, *inter alia* fragilomic and epigenomic studies and the extensive amount of available neuroanatomic imaging findings in prototypical antenatally programmed stress disorders. The aim would be to initiate the research and design of suitable imaging biomarkers to elucidate the role of

stress pathways of an interface system (hormones, antibodies and fragile sites) during physiological learning and memory processes, how such stress shapes the developing brain, and what spectrum of disorders may result when physiological activity thresholds are exceeded and pathological processes start appearing.
*"Data integration itself is not an end: it is designed to generate novel hypotheses and help to test them"* (Hawkins et al., 2010).

## 9. Acknowledgement

I wish to thank Dr Ingrid Simonic, who significantly contributed to a better understanding of the potential role of chromosomal fragile sites in complex multifactorial disorders in our earlier research.

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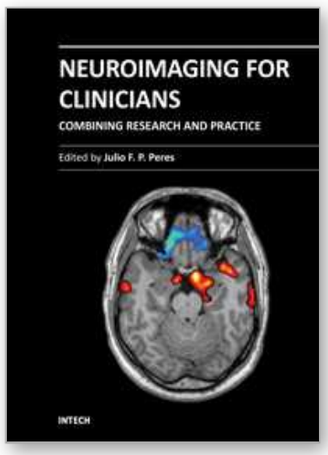


**Neuroimaging for Clinicians - Combining Research and Practice**
Edited by Dr. Julio F. P. Peres

ISBN 978-953-307-450-4
Hard cover, 424 pages
**Publisher** InTech
**Published online** 09, December, 2011
**Published in print edition** December, 2011

Neuroimaging for clinicians sourced 19 chapters from some of the world's top brain-imaging researchers and clinicians to provide a timely review of the state of the art in neuroimaging, covering radiology, neurology, psychiatry, psychology, and geriatrics. Contributors from China, Brazil, France, Germany, Italy, Japan, Macedonia, Poland, Spain, South Africa, and the United States of America have collaborated enthusiastically and efficiently to create this reader-friendly but comprehensive work covering the diagnosis, pathophysiology, and effective treatment of several common health conditions, with many explanatory figures, tables and boxes to enhance legibility and make the book clinically useful. Countless hours have gone into writing these chapters, and our profound appreciation is in order for their consistent advice on the use of neuroimaging in diagnostic work-ups for conditions such as acute stroke, cell biology, ciliopathies, cognitive integration, dementia and other amnestic disorders, Post-Traumatic Stress Disorder, and many more

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George S. Gericke (2011). Stress Shaping Brains: Higher Order DNA/Chromosome Mechanisms Underlying Epigenetic Programming of the Brain Transcriptome, Neuroimaging for Clinicians - Combining Research and Practice, Dr. Julio F. P. Peres (Ed.), ISBN: 978-953-307-450-4, InTech, Available from: http://www.intechopen.com/books/neuroimaging-for-clinicians-combining-research-and-practice/stress-shaping-brains-higher-order-dna-chromosome-mechanisms-underlying-epigenetic-programming-of-th

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