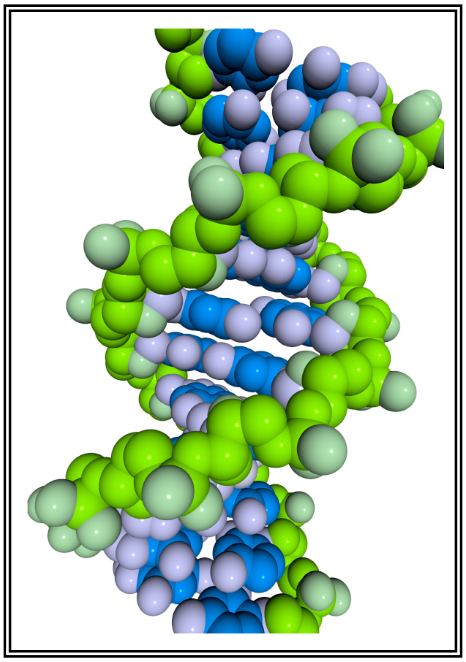
Some Thoughts about the Genetics of Being You

Richard Hill

Just when we thought our knowledge base had expanded exponentially with the introduction of brain plasticity, mirror neurons, and brains creating other brains, a new topic enters the conversation—genetics. As we used to think that the brain was immutable, so has been the thinking about our presumably unchanging DNA. It is turning out that genes are as capable of modification as the brain. Both have some level of fixation along with plasticity that allows wiring pathways and gene expression to change with experience over time. Experience has everything to do with what DNA does. Genetically identical twins have fascinating DNA-driven similarities, and equally fascinating differences influenced by the effects of their personal experience (Kaminsky et al., 2009).

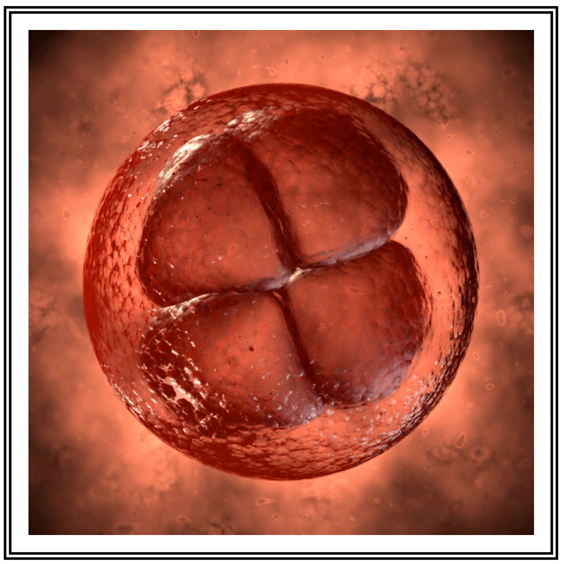


When we look at a brain with its 100 billion neurons and 1 quadrillion synaptic connections, plus neurotransmitters, neuropeptides, a trillion glial cells, and a host of other biochemical elements, we can see that it is very, very complicated and yet capable of astounding organization. However, the intricacy of actions and interactions, transcription factors, protein construction, genotype and phenotype structures, plus a mystifying array of biochemical components in the processes related to our DNA make the brain look like a child's Lego set. Nonetheless, this plethora of chemicals and processes organizes itself into the coherent structure that is our body, including our brain. Current discoveries in genetics are offering us an exciting new and deeper insight into the way things happen inside us, between us, and in concert with the environment we inhabit. Let's explore a few outer layers of the DNA onion in order to know a little more about ourselves and how we integrate our experience with others—person to person—into the deepest parts of our biochemical makeup.

Gene Primer

DNA, the molecule that acts as long-term storage for our genetic information and also regulates its use, is constructed from only 4 base chemicals that bind in pairs called nucleotides—adenine, guanine, cytosine, and thymine (always an AT:GC pairing)—which reside on the inner surface of two parallel, twisting, sugar and phosphate rails. After many years of examining genetic sections of DNA, the complete coding of the human genome in 2003 revealed some 2.8 billion base pairs and more than 23,000 protein coding genes (IHGSC, 2004). These numbers continue to be researched and reviewed, but have remained stable for several years. These numbers sound impressive until you learn that a single celled amoeba, the *amoeba dubia*, has 670 billion base pairs (Parfrey et al., 2008); the *populus trichocarpa,* or California poplar, has only 485 million base pairs, but 45,555 genes (Tuskan et al., 2006). We begin to sense the complex relationship between base pairs and the genes that result.

Some extraordinary research into genes, biochemistry, and even the effects of weightlessness in outer space has been made possible by the transparent nematode, *Caenorhabditis elegans*. Involved in three Nobel prizes and even surviving the explosive disaster of the Columbia space shuttle, the C. elegans has a very specific and predictable structure. Almost entirely determined by instructions from its DNA, the C. elegans has 302 neurons and 7,800 synaptic connections. In order to become the nematode it is from the simple fertilised egg of its parents (although in this case, just the one hermaphroditic parent), its DNA encodes around 20,100 genes. As we said, human DNA has only 23,000 genes (Linden, 2007). Let me give you a moment to make the same double take I did when I first read this. Yes, almost the same number of genes to determine a structure several trillion times larger and incalculably more complex than a nematode. How is this possible? Obviously, there must be a host of processes that grant those 23,000 genes flexibility of expression. For example, human genes can produce more than one protein through processes like alternative splicing (Luco, 2010) and duplication (Nakamori & Thornton, 2010) that allow for more combinations resulting in more possibilities with our relatively small number of genes.



The impact of experience on the organization and activation of the DNA code is visible in our diversity, on one hand, and also in the surprising process of evolutionary convergence on the other. Convergence is where different species in the same type of environment over a long period of time develop, or evolve, similar characteristics: the friction-grasping benefits of our fingerprints are also found on the fingers of apes and on the fingers of the Australian koala; the Australian platypus has a beak like a duck; prehensile tails co-evolved in New World monkeys, porcupines, marsupial opossums, and chameleons; the fish anti-freeze protein arose independently in the Arctic and the Antarctic; and Australia's koala bear is not a bear at all, despite its appearance (Wikipedia, 2010).

DNA, the helix-shaped lattice that carries our genetic information, is, without doubt, the foundational mechanism from which biochemistry is determined. It is from that biochemistry that biology emerges. The emergence of a species and each individual expression of that species is, however, more than just that initial code. Processes beyond the essential code of our DNA enable us to affect the final outcome of our biological structure depending on what is happening *to us* and *within us* as we grow. That brings us to the wonderful story of how a human being (almost) creates him/herself.

Let's start with the basics and look at how the body creates itself out of the cells that merge when sperm and ovum meet. Guided by the information in our genes, the number of these cells grows as the fertilized ovum divides in the safe, nutritious world of the uterus. These early cells are called stem cells and have yet to take on a differentiated existence. They are capable of becoming any cell of the body. In other words, they could respond to any segment of genetic information to become a specific cell. Within a week, the process of cell division changes when the group of just 32 cells embeds in the uterus wall. The cells that will form into a person become like a flat disc that begins to organize into a curve, eventually curling over to form a neural tube that becomes the spinal chord and brain (Tuan & Lo, 2000). At the same time, other cells begin to "commit themselves to a specific fate" (Gibson, 2009, p.8) as they become organs, limbs, and other musculoskeletal structures under the guidance of our DNA.

These are the first stages of differentiation, or specialization, of the cell. This brings to mind that in the process of complexity, differentiation must precede linkage, leading to a more integrated structure. As cells find their place and determine their purpose, they become the community of integrated biology we call our bodies. Once committed, the cell and all of the cells that replicate from it will conform to that commitment—once a liver cell, always a liver cell.

That poses a problem: if the DNA carries the pieces of genetic code for everything in the body and our full DNA is in every cell, then something must stop the DNA from expressing genes that are no longer required for the cell's differentiated purpose. It is necessary for many genes to stop functioning within that particular cell, and for this message to be "remembered" in future cell duplication. This *overlay of information onto* the genome is called the epigenome (Pray, 2004).

Epigenetics

Epigenetics involves heritable changes being made to the process of gene expression without changes being made in the underlying DNA sequence (Levenson & Sweatt, 2005). In other words, only a well-defined part of the genetic possibilities within the DNA are expressed and the rest are permanently shut off. In the language of geneticists, the universal DNA genotype is epigenetically changed to a cell-specific phenotype. The detail of epigenetic action is mind-numbingly complex, but the principles are quite straightforward. By adding or subtracting chemicals, it is possible to "silence" a gene or make it impossible for that gene to be expressed in that cell or any of its daughter cells. This is not exactly the same process we talk about when referring to turning genes on and off, which is more about utilizing genes that are readily available, but only in relation to particular needs at the time. Genes that are epigenetically silenced are taken completely out of the picture. (Having said that, these processes do have a wider involvement, but we'll keep it simple for the moment).

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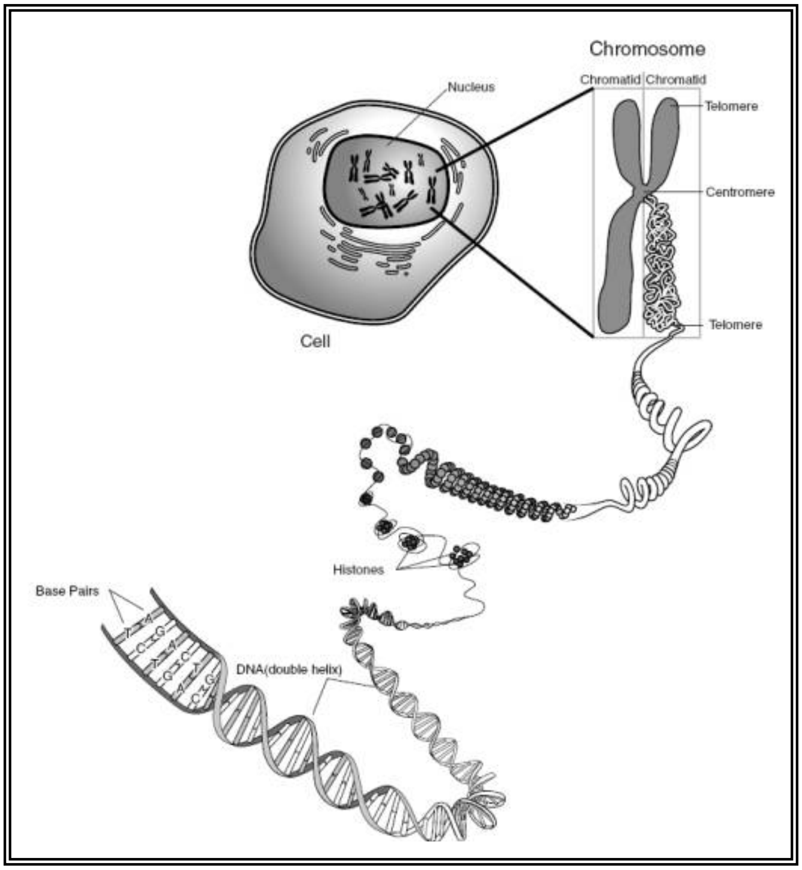
Let's take a closer look at the silencing process as it unfolds later in life. When the body needs something, which is usually in response to some experience or activity of living, both externally and internally, various chemicals which include things like peptides, hormones, and neurotransmitters become active and change the makeup of our "biochemical soup." Cells respond to these changes in a cascading process that eventually leads to the activation of transcription factors (which are sometimes called Immediate-Early Genes) that finally prompt a gene to be expressed. Transcription factors bind to a part of the gene called the promoter region (Boyd & Farnham, 1999). If the transcription factor could be stopped from connecting with the promoter region, then the gene would simply not "hear" the call and remain silent. That is exactly what happens in epigenetic silencing (Tycko, 2000).

It would be wonderful if there was just one chemical that did one thing to achieve this task, but no. There are numerous ways in which this can occur and sometimes it requires more than one process to be absolutely effective. This may be because there is such a complex array of chemicals floating around in the cell and the nucleus that it is far too easy for accidents to happen, so there are copious safeguards. It might also be that all these systems have developed over time and, as we know, evolution often just adds on top of previous developments. Regardless of this speculation, we need to look at how DNA is managed in the cell nucleus.

Adjusting the Microscope to a Finer Resolution - Histones, Nucleosomes, and Chromatin

When a cell is preparing for division, the chromosomes (the 23 pairs of packages that carry DNA in our cells) gather into their distinctive "butterfly pairs." For much of the time, DNA strands float, loosely coiled in nucleic fluid. Although very, very thin, each strand is quite long. Some are as long as 3½ inches. To squeeze itself down, DNA wraps itself around tiny rounded cubes of eight histone proteins creating a small unit of DNA, histones, and other factors that, taken together, are called a nucleosome (Pray, 2004). A collection of these nucleosomes is called chromatin

(Ehrenhofer-Murray, 2004), and they make up the butterfly wings of the chromosome, each wing individually called a chromatid.



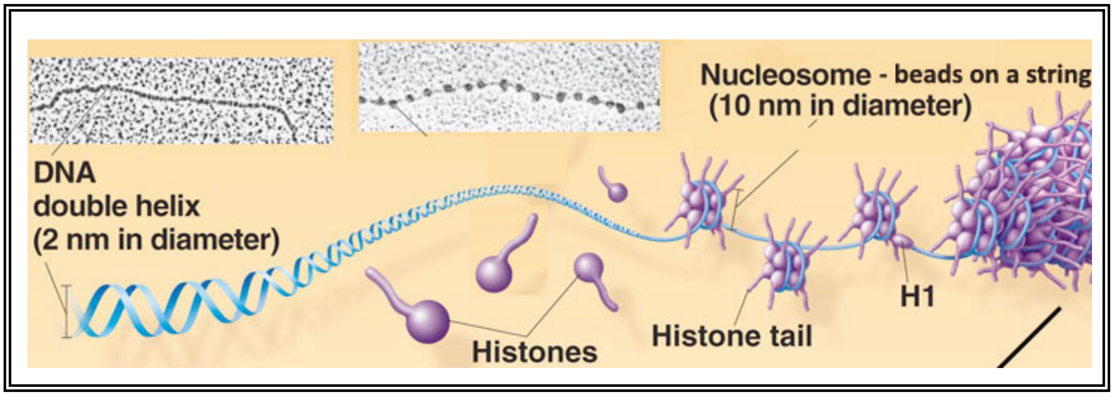
One way that a gene is silenced is when chemical alterations are made to tiny chemical tails that emerge from each of the eight histones. Addition or subtraction of these chemicals allows or disallows the transcription factors to attach to the promoter region. The most discussed processes are acetylation, phosphorylation, methylation, and ubiquitination. If we just look at the acetylation process, we see that when a histone tail is acetylated, the difference in ionic (electrochemical) charge between the histone and the section of DNA wrapped around it is neutralized. The larger the difference in charge between objects, the stronger the electromagnetic attraction. The effect of acetylation in neutralising this difference is that the DNA is looser and therefore accessible to transcription factors. When the histone tail is deacetylised, the difference in charge increases, which causes the DNA to wrap tightly around the histone, making it impossible for transcription to occur (Grunstein, 1997).

Another entirely different silencing mechanism is a change added onto the DNA code itself. In particular positions, usually near the promoter region in the gene (at what is described as CpG nucleotides), the cytosine “letter” of the DNA code is methylated which blocks the transcription factor from binding to the promoter region and, again, stops gene expression (Comb & Goodman, 1990). The crucial point here is that through a series of intricate and elegant processes that might remind us of a symphony, the information in our genes is constantly being brought into activity or silenced.

Going back to our initial development, as cells of the body take on their specific roles (differentiation), these epigenetic processes to silence genes that are not needed become permanent. This means that when the cell divides, the epigenetic overlay persists in the new (daughter) cells. Severe problems can occur if these genes are made available for expression, the greatest concerns being cancer and malformations in growth (Tycko, 2000). Most important for our discussion of gene plasticity is that in addition to these permanent changes, these processes of gene silencing and unsilencing are also designed to facilitate temporary changes in order to cope with a changing environment (Gibson, 2009). If the new environment persists, then it is possible for the epigenetic change to become permanent in a process of adaptation. This is the good news about being human—our capacity to adapt. It can also be the bad news. The persistent problems of living in a world that is different from the evolutionary development of our DNA (different food, sedentary lifestyle, performance and status stress and anxiety) may be causing epigenetic changes to our DNA (adaptations) which can increase our susceptibility to illness, disease, and affect dysfunction (Gibson, 2009): adaptation to a persistent dysfunctional experience is most likely to produce a dysfunctional organism.

Attachment, Environment, and Experience

Armed with our "in principle" understanding of gene expression and gene plasticity, we will look at some of the research that tells us about how we create our "felt sense" of being an individual—on the genetic level. There is not a lot known about the behavioral and affective implications of epigenetic processes. Most of the research is being done in regard to disease and, more recently, in relation to individualised affinity to prescription drugs. We are, as therapists, more concerned with the quality of life resulting from difficult and even traumatic experiences in childhood and as life goes on. We are all well educated in the importance of good attachment experiences from shortly after conception onward. We now know much more about how insecure attachments become embedded (or imprinted) in the neurology of our brain and require some effort to reframe and retrain toward a more satisfying and integrated life. Does it go deeper than just our neurons? Preliminary work with rats suggests this to be true.



Moshe Szyf, from McGill University in Montreal, has been involved with several other researchers in the investigation of what happens epigenetically to rat pups who have "good" mothers (high licking and grooming - HLG) and "bad" mothers (low licking and grooming - LLG). The story is much more than just that behavior triggers genes. There is a cascade of chemicals that respond, react, induce, and finally trigger gene expression. The pleasant response to HLG maternal care increases serotonin, as you might imagine, and it is this increased potency in the biochemical milieu that activates other proteins and then binding factors and growth factors that positively activate a very particular gene. These biochemical cascades can also enable epigenetic processes that act like a genetic "memory" of the quality of life the organism can expect. Secure attachment practices, like HLG, will demethylate the CpG nucleotide and acetylyze the histone tails of the glucocoticoid receptor (GR) gene (Weaver et al., 2004; Meaney & Szyf, 2005). In contemplating this, we might see the parallel to the creation of implicit mental models through repeated experiences of attunement in secure attachment.

What do these genetic changes have to do with secure attachment and positive affect? Everything, but it is a little complicated. Stress is marked by increases in cortisol through activity of the HPA axis. What we may not realize is that this is a dynamic process. Cortisols also return to the hippocampus as information that the stress response can be moderated. The returning cortisols are "read" by glucocorticoid receptors in the hippocampus. How many receptors are available depends on how open the GR gene is for transcription. The rat pups from the LLG mothers had methylation of the GR gene and so had low numbers of glucocorticoid receptors in the hippocampus. As I mentioned earlier, genes create the biochemistry from which the biology emerges and from which behavior is determined. Rat pups from LLG mothers were epigenetically changed into animals that expected an "insecure attachment." Being less able to modulate the stress response means they were less able to handle stress, less able to enjoy life, and more likely to become depressed, AND this quality was permanently written onto their DNA by an epigenetic overlay that will reproduce throughout the pup's lifetime (Szyf, 2009; Meany & Szyf, 2005). Post-mortems of human suicide victims who had suffered childhood abuse also revealed methylation of glucocoticoid receptor genes and other promoter genes in what is a more complex system than rats (McGowan et al., 2009). It is a genetic memory of insecure attachment that continues to underwrite everything in the biology above it, just as limbically held implicit memories influence thoughts, feelings, perceptions, and behavior.

We might ask if these epigenetic changes will persist through the generations. Research is in a preliminary stage, to say the least, and these comments are speculative, but, in mice, insecurity of attachment that causes the silencing (methylation) of the GR gene may be inherited through as many as two generations, although in humans, it appears that there may be a more complex variability with the changes persisting in some people, but not others (Meaney, 2001; Whitelaw, 2006; Morgan, 2008). Nonetheless, it does point to the importance of helping people rectify their attachment prior to having children. We can also ask, “Is this ‘attachment memory’ changeable at the genetic level within an individual’s lifetime?” The preliminary answer seems to be, “Yes!”

When the pups from LLG mothers with methylated GR genes were stimulated by a HLG biochemical milieu, they were epigenetically transformed to unmethylated and acetylized GR genes as if they had never had a difficult early life. This took a little time, but a persistent new experience—and I suggest that therapy is a persistent new experience—revised their biological capacity to respond to stress. Amazing!

Some of the other behavior and affect research in epigenetics includes: social adversity (McGowan & Szyf, 2010); memory formation (Livesson & Sweatt, 2005); extinction of conditioned fear (Bredy et al., 2007); mood disorders (McGowan & Kato, 2008); maternal behavior (Weaver et al., 2004); and early life environment (Syzf, 2009). This is just a tiny gathering compared to the work done on disease, but the door has been opened.

What We Are Doing Now

One of the most prescient thinkers about the involvement of biology in our psychology is Ernest Rossi, PhD. Beginning his academic career in biology and chemistry, but gravitating toward the study of the human experience, Rossi is a protégé of Milton H Erickson, and was the first person to search for and discover the biological processes underlying Erickson’s practices.

In 2002, just after completing one of his many books, *The Psychobiology of Gene Expression* (Rossi, 2002), he woke to find that he had been “brutishly clubbed in the head” (Rossi, 2004) in his sleep. A stroke had dramatically changed his experience, but few people were as well prepared for the processes of brain plasticity and positive gene expression as Rossi. His recovery is a testament to the focus and determination that is possible when we not only know what to do, but why we do it. His recovery may inspire us, but his continuing work is an even greater cause for astonishment. As a member of his International Psychosocial Genomics Research Group, I am honored to be involved in the unmasking of this wondrous mystery of our genes.

In 2009, Rossi and some of the research group conducted an in-principle experiment into the gene expression response to his Mirror Hand therapeutic process (Rossi et al., 2008). For those unfamiliar with this process, it is an implicit hypnotherapeutic and psychotherapeutic process developed by Rossi based on his experiences with Erickson. The process does not utilize the suggestive techniques in many forms of hypnosis; instead, it is very much an interoceptive, reflective focus of attention where the therapist acts mostly to support and encourage the client’s experience. The hands are used as an external point of observation to reflect the opposite elements of the client's dilemma (Rossi, 2002). There is some similarity to Daniel Siegel's Hub and Wheel mindfulness meditation (Siegel, 2010). The client is able to be aware of the issues that have been externalised into the hands. They are able to be aware of their concerns and they are able to allow the mind, brain, and body to respond, react, and reflect. At the conclusion of a therapy session, it is not unusual for neither the client nor the therapist to be able to accurately verbalize everything that has been achieved because so much of the processing takes place at the implicit level below conscious awareness. It is clear, however, that over the next few days, there is continued processing as demonstrated by the resolution that emerges.

Rossi wanted to see if there was a measurable response that could validate the phenomenological reporting by the client that wonderful things had occurred. It's not that we should not believe our clients, but Rossi wanted to be able to establish a point of reference beyond just subjective experience and belief. As a reflection of the extraordinary enquirer that he is, Rossi sought to look into the very depths of gene expression. The resulting information is more than we can discuss here, but just one important element in relation to our discussion is the discovery that the Immediate-Early Gene (and transcription factor) ZIF268 is expressed during this process (Atkinson et al, 2010). ZIF268 is the same transcription factor expressed in the rat pup research that activated the glucocorticoid receptor (GR) gene. This gives us a reasonable line of insight to suggest the possibility that non-invasive therapies such as therapeutic hypnosis and psychotherapy generate gene expression (and possibly permanent epigenetic modification over time) that will alter the biology and the biochemistry that underlie processes in the brain and the body. Again, the parallel with the process of changing a new state of mind into a trait of being through repetition comes to mind. Given that we are self-organizing, complexity-seeking beings, it is not surprising that fundamental processes and simple generating rules are used throughout the complex system of our body for different purposes and for different ends. Epigenetics may be a complex system, but the principles, the recipe, are quite simple. I am not at all surprised to find that processes at different levels from gene expression to neural integration share common patterns.

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The implications are enormous and exciting. We need additional rigorous research to expand what we are learning. If we continue to discover gene expression patterns and epigenetic changes that result from non-invasive therapies like psychotherapy, hypnosis, mindfulness, compassion, integration, and the implementation of a flourishing lifestyle (positive psychology and lifestyle medicine), then we may be able to verify and validate the benefit of mind-to-body healing practices. Most importantly, we will be able to further establish the heartening, hopeful reality of gene plasticity. We may be able to optimize the expression of our DNA as we support increasing neural integration through both interpersonal connection and increased mindful awareness. When gene expression, gene plasticity, and neuroplasticity all move in the direction of maximizing coherence, this adaptability can build a deep and effective foundation that supports resilience, resolution of maladaptations, and a flourishing life.

Conclusion

Brain plasticity has revolutionised our thinking about our capacity to make positive changes in our lives. Mirror neurons have opened a doorway onto a huge field of interactional and person-to-person supports for neural integration in therapy and our personal lives. Now we have a new window into the even deeper foundation of what enables us to create and transform our individual existence.

Epigenetics is one of the ways that the body writes down and memorizes our ongoing life experience. What we do, when we do it, and how we feel about it while we are doing it contribute to the way experience utilizes the building materials in our DNA to construct the person that we see in the bathroom mirror and in the mirror of our friends, family, and loved ones. As the wise old acupuncturist said to the mystified Westerner as he inserted needles for headache into the hand and for kidney problems into the feet, "What? You crazy? Look! All connected!"

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Gene Plasticity and Making Memories

Memory formation and consolidation require us to create new synaptic connections and even new neurons in what we now call "neuroplasticity." Research from Miller and Sweatt (2007), from the University of Birmingham, shows that there is also a dynamic, activity-dependent plasticity at the genetic level. In experiments with rats (humans are so difficult when it comes to electric shocks and vivisection), they found that the *PP1* gene that *inhibits* memory formation is generally set to the ON or epigenetically unmethylated state. An essential gene for memory formation and consolidation, *reelin*, is generally set to the methylated OFF state. We can't be remembering everything at once or our brains would explode! Memory formation was turned on when the rats were remembering context and location when given electric foot-shock. *PP1* was silenced by methylation, and *reelin* was unmethylated, allowing its gene expression. Within a period of 24 hours, both genes returned to their baseline methylation state. This shows that epigenetic changes can occur dynamically, in response to activity (stimulus), and that as conditions evolve, the epigenetic change is reversible.

When we ask a client, "What's been happening?", through both behavior and words, they "speak" about the things they remember. What they offer tells us what they consider to be contextually relevant in their lives. We are listening to the verbal, physical, and gestural representation of their mental state—both explicit and implicit. Since explicit and implicit memories are formed using the same processes of neuroplasticity, the determining factors are which cells and where in the brain memory-forming gene expression and epigenetic plasticity is expressed. Also amazing is that this is happening at a single-cell level, so some parts of our brain can be remembering and others not, depending on need, stimulus, and other factors. Exactly what this all means only time and research will tell. I hope that you are as keen as I am to stick around and find out!

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