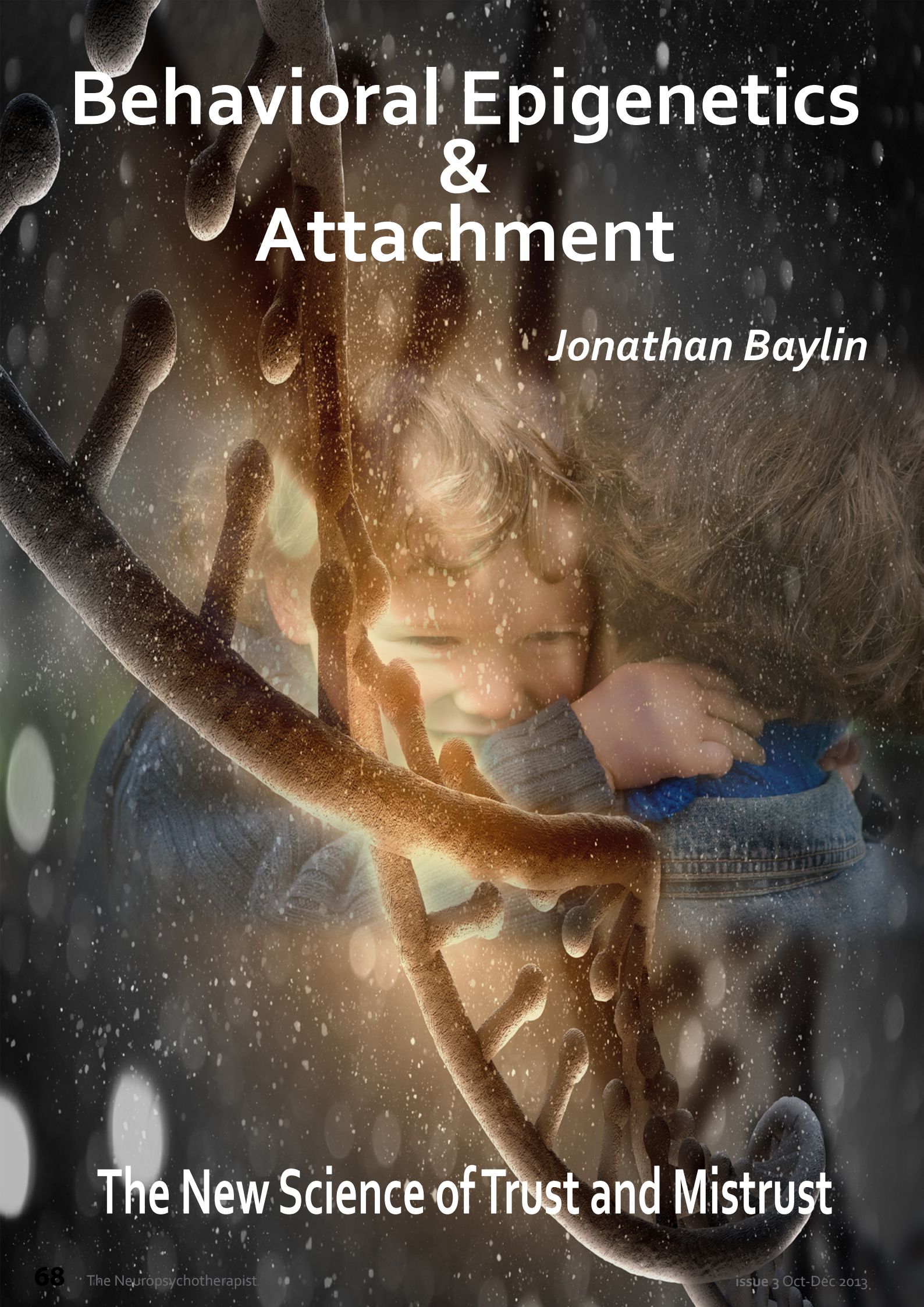
Behavioral Epigenetics & Attachment

Jonathan Baylin



The New Science of Trust and Mistrust

"…the perception of safety is the turning point in the development of relationships…"
Stephen Porges, 2011

"The reality of the functional genome does not admit to main effects of either gene or environment, but rather to a constant interaction between the DNA and its environment"
Michael Meaney, 2010

One of the hottest areas of neuroscience is the study of how life experience affects patterns of gene expression in the brain, what some call *behavioral epigenetics* (Weaver, 2004; McEwen, 2012). Of great relevance to therapists interested in attachment, this fast growing body of research is revealing how early life experience can influence brain development towards either social engagement or self defense. Researchers are uncovering experience-dependent effects on the development of the brain during the sensitive period for attachment-based learning in animals, work that has now been extended to humans. Furthermore, epigenetic research is exploring the potential of reversing the effects of poor parental care by altering patterns of gene expression in the brain after the sensitive period for attachment has passed (Landers and Sullivan, 2012). Clearly, this research has huge implications for the whole field of mental health.

Epigenetic Effects of Early Care On the Child's Stress Systems

Ground breaking studies by Michael Meaney and his colleagues (Kaffman and Meaney, 2007); Meaney, 2010) laid the foundation for studying the effects of differences between the quality of early maternal care and patterns of gene expression in the brains of offspring. This seminal work showed that naturally occurring differences in the quality of maternal care within the first week of a rat pup's life trigger different patterns of gene expression in the regions of the brain that support both self defense and social engagement. Young rats who are licked often and nursed in a certain position show a different pattern of gene expression in their hippocampus, prefrontal cortex, and amygdala than pups who do not get as much of this "enriched" stimulation. These differences in gene expression enable well cared for rats to be more social, less fearful, and faster to approach and explore new things than their less well cared for peers.

In the well licked babies, the gene responsible for the corticosterone stress hormone receptor, called the GR, is more highly expressed (or in technical terms, less methylated) in the hippocampus than it is in the less licked rats. This means that the well cared for pups acquire more GRs in their hippocampus. These hippocampal GRs are an essential component of the stress response system as they help turn off the stress response after a stressful experience. In the *low licked* offspring, the stress response system stays active longer, facilitating self defense at the cost of growth and social connectedness.

Epigenetic research that began with rodent studies has since been extended to both non-human primates and humans. Maternal licking in rats is a form of tactile stimulation similar to grooming behavior in primates and to all forms of "good touch" in humans. Human studies show that certain qualities of touch activate the insula, anterior cingulate cortex (ACC), and orbitol regions of the brain while calming the amygdala in ways that promote well being, trust, and social engagement—very much like licking does in Meaney's rat pups. While studying gene expression patterns in

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human brains is more difficult than it is with rodents, where brain tissues from different regions can be readily examined, methods for behavioral epigenetic studies in humans are being developed.

An intriguing study by Meaney's group (McGowen et al., 2009) used postmortem brain tissue to explore patterns of gene expression associated with childhood abuse in a group of suicide victims (McGowan et al., 2009). The pattern of gene expression seen in the brains of those individuals who had experienced abuse in early childhood matched the pattern of methylation in the rat studies, showing gene suppression in the equivalent promoter region of the GR gene. In other words, the pattern of gene expression was consistent with epigenetic programming of the human brain by early life adversity.

In addition to showing that early life experiences with attachment figures activate different patterns of gene expression (and therefore, protein synthesis and brain structure) during the initial period for attachment-based learning, epigenetic research is also exploring the potential of reversing early life patterns of gene suppression associated with separation, early abuse, and neglect. This research includes both environmental interventions (Environmental Enrichment) and pharmacological methods such as the administration of demethylating drugs to unblock methylated promoter regions of genes in animals exposed to poor care early in life. Both types of interventions have shown some capacity to alter the effects of early life adversity on gene expression in brain regions such as the hippocampus. While epigenetic effects triggered by social experiences are strongest during the sensitive period for attachment-based learning, experience-dependent gene expression continues throughout life (Weaver et al, 2004). This exciting line of research has strong implications both for psychotherapy and psychopharmacology.

Gene Expression, Trust, and Mistrust

The social engagement and social defense systems are developing early in life and both are affected by the nature of caregiving that infants of various mammalian species receive. Epigenetic research is showing that differences in the quality of early care have differential impact on the patterns of gene expression in these two systems, channelling brain structure and functioning along different trajectories. In effect, epigenetic mechanisms, whereby the environment impacts brain development, is nature's way of helping to ensure that the young adapt to the specific kind of social world they are likely to be living in. If this first "environment of care" is safe, the young brain will be sculpted or "programmed" for living in connection with other people. If the early environment exposes the young to harsh, insensitive treatment by attachment figures, the young brain will be epigenetically sculpted for surviving (and reproducing) in a world in which it is vital to be hypervigilant, slow to trust, and quick to deploy one's defenses. While both of these developmental scenarios of "biological embedding of early experience" (Hertzman,2012) are initially adaptive, a wealth of research on attachment formation shows that early experiences with sensitive, nurturing caregivers promotes a pattern of brain

development supportive of emotional resilience, empathy, and cognitive flexibility (National Scientific Council on the Developing Child, 2008).

Children who are forced to adapt to high levels of adversity very early in life when the brain systems for social engagement and self defense are under construction are at risk for developmental stress disorders, including depression, social anxiety, and PTSD (Heim and Nemeroff, 2002). In brain terms, this means that the development of the circuit that connects the prefrontal cortex to subcortical regions, especially to the amygdala, may be compromised by over activation of the child's stress response system early in life. The development of the fronto-limbic system connecting the lower regions of the prefrontal cortex, including the orbitol region and the ventral ACC, to the amgydala forms the core neural substrate for self regulation throughout life. When the initial development of this circuit is suppressed for any reason, it is more difficult later in life to regulate emotions, behavior, cognitions, and attention. As a result of these regulatory difficulties, it is harder for the individual to learn from new experiences and to change one's mind about the meaning of old experiences. Children who have to adopt an early life survival strategy of premature self reliance and defensiveness are vulnerable later in life to all kinds of health problems because of their chronic exposure to high levels of stress hormones. In the brain, chronic activation of the stress response systems can have toxic effects, especially on the hippocampus and the prefrontal cortex (McEwen, 2012), while promoting chronic hyper-activation of the amygdala.

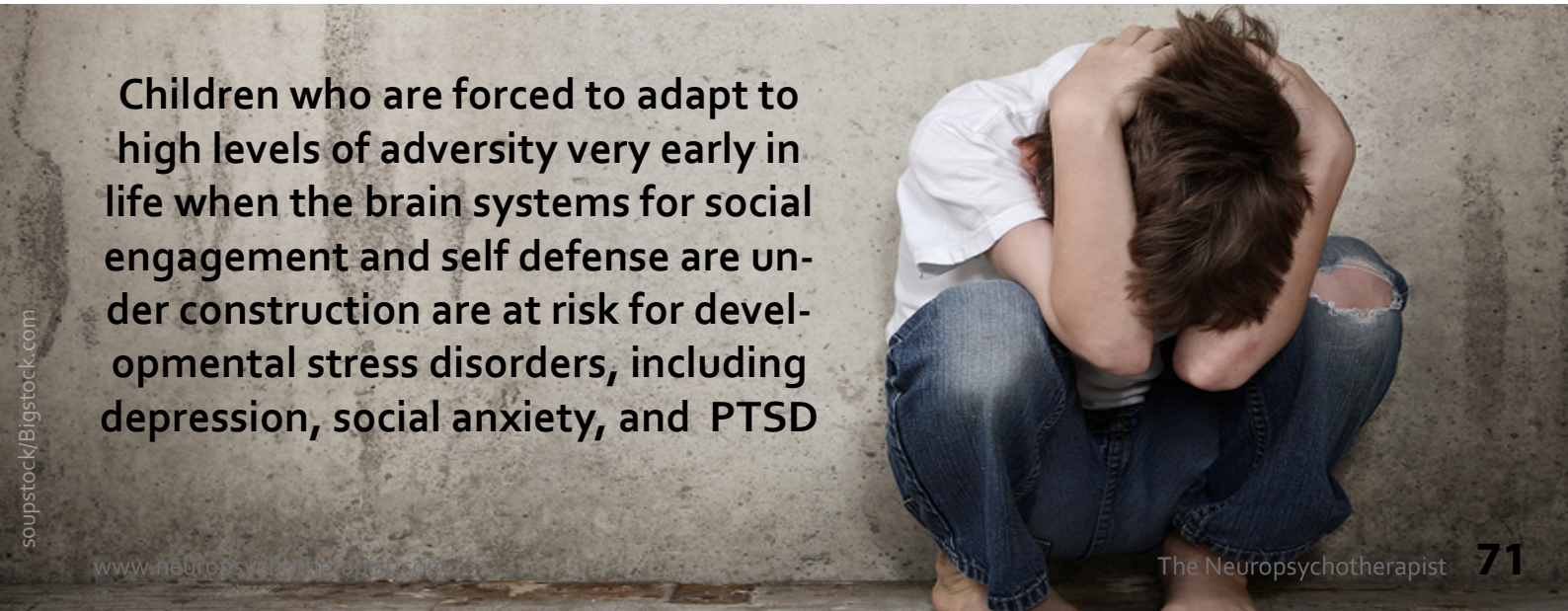
This developmental scenario of chronic stress is a common one for children exposed to abuse and neglect early in life. Having an underdeveloped fronto-limbic system biases these children towards hyper-reactivity to aspects of their environment that they perceive as threatening. This includes a strong tendency to perceive other people as untrustworthy, based on prior learning that has become the basis for habitual ways of responding to attachment figures. In common parlance, these kids are more prone to "flipping their lids" and either blowing up or freezing in fright when they detect signs of negative intentions or rejection, especially in other people's facial expressions and voices.

Appraising Safety and Threat: A Two Level System

The process of shifting between social engagement and defensive states depends heavily on the way we appraise the level of safety or threat posed by other people in our environment (Porges, 2011). This appraisal process occurs on two basic levels:

1) an unconscious, or implicit, ultra rapid level based heavily on the functioning of the amygdala and its ability to activate approach and avoidance responses to other people and

2) a conscious, slower appraisal system based on prefrontal regions of the brain that can modulate and inhibit the implicit, fast acting "first pass" appraisal system.



Porges calls the implicit, subcortical appraisal of safety and threat "neuroception". The ability of the prefrontal regions to modulate the neuroceptive process typically increases with age and brain maturation into adulthood; however, this process of developing a robust fronto-limbic system is also significantly affected by early life experiences with attachment figures, i.e., by epigenetic processes.

Epigenetics and The Amygdala

The amygdala is functional very early in life, providing infants with a rough and ready, implicit way of detecting threats in the social environment. However, nurturing, responsive parenting buffers the defensive reactions from the amygdala, in part by decreasing the release of stress hormones such as cortisol and norepinephrine while promoting the release of calming chemicals such as oxytocin in this region. Social engagement involves eye contact, the ability to read other people's facial expressions, the ability to extract emotional meaning in other people's voices, and the ability to put emotion into one's own voice. Different types of social stimuli all pass through the amygdala early in the sequence of sensory processing in the brain. How the amygdala responds to this information biases the young child towards either social approach or social avoidance. The role of the amygdala as a switching mechanism between attachment learning and avoidance learning is beautifully described by Landers and Sullivan (2012) and there is a wealth of data that strongly indicates a similar process in humans (Caldji et al., 2003).

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The amygdala is a creature of proximity in the sense that the closer something comes to us, either in space or time, the stronger the potential reaction of the amygdala, especially to something perceived as threatening or stressful. The amygdala appears to be part of the brain system that monitors "personal space" at about an arm's length from our bodies, basically treating this space as an extension of ourselves. This helps to understand why mistrustful children are likely to become more defensive the closer we try to get to them. Some children, with insecure attachment experiences, often respond dramatically differently to strangers or people who are more distant from them than to attachment figures who try to come very close. They are responding from a neurobiological defensiveness.

If a caregiver is being neglectful or causing pain, the child's amygdala starts to react to the caregiver as, in part at least, a source of pain and fear, setting up the potential for chronic conflict between approach and avoidance tendencies. The amygdala is strongly connected to the stress response system, or hypothalamus-pituitary-adrenal (HPA) axis, that activates the endocrine circuitry and ultimately engages the adrenal glands in producing stress hormones such as cortisol. It is also strongly connected to the brain's vigilance system that operates through the release of norepinephrine (NE) from the locus coeruleus (LC). When the amygdala detects a potential threat, it triggers the release of NE from the LC, ramping up attention to the possible threatening object or person. Through back projections to all sensory processing regions, the amygdala can intensify sensory experiences if it detects something as emotionally relevant, ramping up attention to that thing or person. Through its connections with the stress/defense systems—the HPA axis that produces stress hormones and the sympathetic and parasympathetic defense systems that support fight,

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flight, and freeze reactions—the amygdala can orchestrate the process of keeping the brain and body on high alert, promoting self defense over social engagement.

A number of genes are now known to be targets for epigenetic effects in the amygdala. These include GABA receptor genes, the gene for the oxytocin receptor, genes that express proteins involved in the growth of connections between the amygdala and other brain regions, and genes for corticotrophin-releasing hormone (CRH), the chemical that triggers the neuroendocrine stress response system. Research has begun to target the GABA system in the amygdala as an extremely important mechanism for epigenetic effects of early experience on emotional resilience and vulnerability (Cadji, Diorio, & Meaney, 2003; Diorio and Meaney, 2007).

The $GABA_A$ Receptor in the Amygdala

In the amygdala of well cared for rats, the gene for the $GABA_A$ receptor shows different patterns of expression compared to the less nurtured peers. This is important because GABA is the main *inhibitory* chemical in the brain. The action of GABA in the amygdala makes it possible to modulate defensive reactivity that otherwise can set off the fight, flight, or freeze responses within milliseconds of detecting a potential threat. The amygdala specializes in avoidance learning, orchestrating the process of learning to associate social stimuli with pain, danger, or distress. By having more sensitive $GABA_A$ receptors in their amygdala, the well licked rats have more power to "veto" output from the central region of the amygdala to the stress/defense systems.

The $GABA_A$ receptor is composed of several different subunits and the genes for these subunits are targets for epigenetic programming by maternal care (Caldji, Diori, and Meaney, 2003). In the first week of a rats life, maternal care is associated with differences in $GABA_A$ receptor subunit expression and these differences are intriguingly related to fearful behavior throughout the life of these animals. According to this research, "the adult offspring of high licking-grooming mothers show significantly higher levels of $GABA_A$/Benzodiazepine receptor binding in the basolateral and central nuclei of the amygdala and the locus coeruleus. These findings provide a mechanism for increased GABAergic inhibition of amygdala-locus coeruleus activity" (Caldji et al., 2003, p.1957).

In poorly nurtured rats, suppression of the gene for $GABA_A$ receptor subunits in the amygdala leads to less sensitive GABA receptors, which, in turn, makes the amygdala more highly reactive to perceived threats. Also, because higher brain regions in the prefrontal cortex modulate the amygdala by activating GABA receptors in the amygdala, the lower sensitivity of the GABA system in the amygdala reduces the capacity of the prefrontal regions to dampen amygdala reactivity.

This is a structural and functional design to make someone more highly reactive to stress, but unfortunately, also more vulnerable to stress-induced disorders of all kinds, including PTSD, depression, and social anxiety. In essence, people with reduced GABA activity in the amygdala are more "amygdaloid" in their reactions to all kinds of stressors—they have difficulty regulating negative emotions, actions, and thoughts. These individuals are likely to have a negative reaction to novelty, being more at the mercy of their rapid appraisal system that is biased towards avoidance of new things in a seemingly "better safe than sorry" approach to life. With less ability to inhibit the activity of the amygdala, it is harder for these people to "get above" their quick reactions to things and to other people. This makes it harder for them to change their behavior in the light of new experiences.

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The Oxytocin Receptor in the Amygdala

Oxytocin (OT) plays several roles in humans and other mammals:

1) promotes social approach behavior

2) facilitates formation of social memories

3) enhances the ability to read other people's minds, facilitating empathy and "mindsight" and

4) reduces stress reactivity and self defensiveness (Carter, 2007).

All of these functions are made possible by the presence of the oxytocin receptor (OTR) in a wide variety of brain regions that are involved in social and emotional aspects of functioning. The gene for the OTR is a known target for epigenetic effects, meaning that early life experiences affect the level of expression of the OTR gene in the brain. Furthermore, researchers have found a significant relationship between the density of OTR receptors in key brain regions in the limbic system, and individual differences in social affiliation, empathy, and "mind reading" ability in humans (Andari et al., 2010; Kumsta et al., 2013).

The amygdala is a key region of the brain for oxytocin activity at OTRs. Considering both animal and human studies, it is clear that there is an important process of environmental tuning of the structure and functioning of the amygdala and the genetic expression of the OTR gene in this area. This research is extremely interesting in terms of understanding how good care buffers the child's stress systems and promotes the development of secure attachments and pro-social behavior. By activating the oxytocin system, sensitive parenting helps to quiet the amygdala and facilitate bonding and trust.

Based on this research, we can see how early experiences with attachment figures can promote either secure attachment based on deep safety being close to an adult or insecure attachment that depends upon a certain level of vigilance or at least ambivalence about being close to others. For children who are exposed early in life to abusive and/or neglectful attachment figures, it would be maladaptive to have a high level of gene expression of the OTR gene in the amygdala because this would promote pro-social behavior and a tendency to approach unreliable

attachment figures in a trusting, relaxed manner, a potentially dangerous behavior trait. It would be adaptive for these children if their brains produced fewer OTRs and GABA receptors, making it easier neurobiologically to "play defense" around others.

Targeting The Neuroceptive System: An Epigenetic Model of Attachment-based Intervention

Since the amygdala is a major switching station in the brain between the social engagement system and the self defense system, it makes evolutionary sense that this region is a major target for epigenetic effects of good and poor relationships. The question for intervention then becomes "what kinds of relational processes have the power to alter early patterns of gene expression in the amygdala so as to shift its functioning towards social engagement and away from reflexive defensiveness?" This shifting of the neuroceptive system can be seen as the key to helping defensive children (and adults) shift from core defensiveness and mistrust towards social engagement and trust.

Reversal of Early Epigenetic Effects

The task for a model of therapeutic intervention is to determine what kind of new experiences, beyond the sensitive period for attachment formation, can alter the early patterns of gene activity that supported self defensive living. In animal research, there is a line of recent research that is studying this very question, exploring the kinds of later life experiences that can shift patterns of gene expression in the direction of less defensive, more pro-social behavior. This research deals with so called *environmental enrichment*.

Environmental Enrichment and the Re Opening of Attachment-based Learning

The key to helping mistrustful children learn to trust is to somehow re-engage them in attachment learning when they have passed the sensitive period for this process. Environmental enrichment involves creating opportunities for novel social experiences, which can "jiggle" the brain into a state of alertness, surprise and curiosity and launch a process of renewed social learning that can alter old learning that is no longer adaptive. This involves surprising a mistrusting child with openness rather than responding in a predictably defensive way to mistrusting behavior.

Re-engaging the child's brain in new attachment-based learning requires that the child experience an immediate disparity or incongruity between the caregiver's behavior in the moment and the kind of reactions predicted by the child in a "mindless" state of mistrustfulness. Novel experiences with caregivers can trigger the process of tagging brain cells for further gene expression, a process involving what are called Immediate Early Genes or IEGs. Brains are in the business of making sense of experiences by comparing new and old experiences, determining rapidly if there is "news of a difference" and if so, starting a process of trying to resolve the disparity. So creating disparity, surprising the brain, presenting the brain with a mystery, would appear to be essential to altering patterns of gene expression in a therapeutic direction.

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The neuroscience literature on sensitive periods and post sensitive period learning shows that different brain processes are involved during these different periods. During a sensitive period, learning is highly efficient because the brain is in a state of high arousal and receptivity, making it easy to

learn simply from continued exposure to recurring experiences with an attachment figure. Sensitive periods are a time in brain development when there are high levels of neurotransmitter activity in the brain, including high levels of dopamine, serotonin and norepinephrine. This high level of arousal facilitates all kinds of learning. The sensitive period for attachment in humans is probably the time between birth and around 18 to 24 months. Once this period has passed, attachment learning probably requires intensive, highly arousing, attention-demanding experiences to re open the "gate" for engaging the brain in this kind of learning and for facilitating the unlearning of old patterns of relating to unreliable caregivers. The new attachment figure has to somehow co-create with the child experiences that are novel, surprising, beyond the "same old, same old", triggering unpredictable reactions in the child. While all kinds of learning are more difficult after a sensitive period for that type of learning has been closed, neuroscience suggests that post sensitive period learning is quite possible if given the necessary experiences and stimulation.

PACE: A Formula for Epigenetic Reprogramming of the Child's Neuroceptive System

PACE[1] (playfulness, acceptance, curiosity, empathy), (Hughes, 2009) appears to be a formula for re-engaging the child's brain in attachment based learning, based on a growing body of evidence from attachment-focused treatment around the world. From a brain based perspective, PACE can be seen as a formula for promoting the kinds of epigenetic changes in a child's brain that could facilitate the shift from defensiveness to openness. Clearly, from the research described earlier, the important brain targets for these changes would be selected genes in the amygdala, the hippocampus, and the prefrontal cortex (PFC). How might PACE trigger changes in gene expression in these key brain regions?

PACE has the potential to do two important things that could promote epigenetic changes in a child's brain:

1) dampen the reflexive defense system by promoting oxytocin flow into the amygdala and

2) turn on excitatory neurochemistry, especially dopamine, to support new learning (engaging what Panksepp calls the "seeking system"), and a state of curiosity about the new attachment figure that reopens the child's mind to attachment-based learning.

PACE and the Amygdala: Shifting From Self Defense to Openness

A major goal of a brain based approach to helping defensive children form secure attachments to trustworthy caregivers would

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1. Dyadic developmental therapy, developed by Daniel Hughes, principally involves creating a "playful, accepting, curious, and empathic" (PACE) environment. The therapist "co-regulates" affect and "co-constructs" an alternative narratives with the child by being attuned to the child's "subjective experiences". *Ed.*

be to alter the pattern of activity in the children's defensive brain circuitry. Since the amygdala plays a leading part in orchestrating this defensive way of relating, it is essential to target the amygdala for therapeutic modulation, for shifting the amygdala's bias towards self defensive behavior towards social engagement. By being playful, accepting, curious, and empathic, the adult may be able to de-activate the child's defense system, at least transiently. This transient buffering of the child's defense system would very likely activate the immediate early gene system to tag brain cells in the amygdala, alerting them, in a sense, that there is "news of a difference", that this adult seems different from other adults who presented a threat in the past. This "news of a difference", would, in turn, likely activate:

- the hippocampus to help compare the present experience to the past;
- the lower region of the PFC;
- the orbitol region, which specializes in learning and remembering social contingencies and in "reversal learning";
- and the ACC that is vitally involved in fear "extinction" and in resolving conflicts between old, habitual ways of reacting and new ways of behaving.

This sequence of brain activity would very likely create a state of mind conducive to altering patterns of gene expression in the fronto-limbic regions—the foundational system for social and emotional functioning.

In sum, the rapidly growing field of behavioral epigenetics of early life experience, combined with research on processes for reversing adverse epigenetic effects, provides a new window into the neurobiology of relationships and the underlying mechanisms of therapeutic change. Furthermore, beyond the social processes discussed here, epigenetic processes are now known to be associated with a wide range activities, including exercise, the sleep/wake cycle, and, intriguingly, certain mindfulness practices that promote expansion in a region of the brain associated with self reflection and compassion (Davidson et al., 2003). Combining the research on various kinds of epigenetic processes, we begin to see an emergent integration of relational processes, intrapersonal processes, and pharmacology that could be the foundation for a more effective model of mental health interventions. With a deeper understanding of how experience becomes embedded in our brains and bodies, we can learn to target epigenetic changes that promote greater resilience and capacity for human connection.

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