Hippocampal Regeneration and Treatment of PTSD and Depressive Patients

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After eight of their ververt monkeys had died spontaneously during a four-year period, the staff of the Institute of Primate Research in Kenya developed an opportunistic research project when all their autopsies found multiple gastric ulcers and a high incidence of bite wounds. The ulcers - and the bite wounds that came from their dominance struggles in caged group housing – were seen as evidence of significant levels of stress, especially as all but one had bred in the wild and had roamed as agricultural pests before capture and housing in the outdoor cages of the Institute. Six colony-born ververt monkeys, similarly housed, and euthanized as part of an experimental program, formed a convenient comparison group, especially as their autopsies revealed no ulcers and a low level of bite wounds (Uno et al., 1989). Because of the known link between stress and glucocorticoids, the investigators hypothesized that glucocorticoids had played a major part in the development of the ulcerated monkeys.

The investigators were particularly interested in the effects of stress on the brain morphology of these ulcerated primates in the hippocampus region. A histological examination found pronounced neural degeneration in the CA3 area of the hippocampus, which was also smaller in the ulcerated than the non-ulcerated monkeys. In the ulcerated monkeys the CA3 pyramidal neurons were shrunken, sparse, and damaged – as evidenced by "irregularly shaped perikarya associated with dispersed Nissl bodies and trophic dendritic branches" (Uno, 1989, p. 1708). These results were consistent with rodent

studies on neural degeneration. For example, Watanabe et al. (1992), after restraining rats on a daily basis, discovered atrophy of the apical dendrites of the CA3 hippocampal pyramidal neurons, and Mizoguchi (1992) also demonstrated a significant loss in the CA3 and CA4 hippocampal pyramidal neurons in rats stressed by daily restraint and water immersion.   These anatomical and cellular damage patterns in primates and mammals were consistent with what was thought to be a glucocorticoid-induced-neurotoxicity. Fortunately for us, this neural degeneration is only half the story, for neural regeneration also takes place in the hippocampus, and near the olfactory bulb (subventricular zone) (Bjorklund, 2000).

The mounting evidence of neural damage from chronic stress challenges psychotherapy to demonstrate its capacity to play a significant part in healing such structural damage. Although it has long been accepted that psychotherapy can ease emotional distress, reduce cortisol levels, and help prevent neural degeneration, the effectiveness of long-term intensive psychotherapy of patients with neural damage, has never been convincingly demonstrated to the medical world. So, with reports of neural degeneration in the neuroscience literature over the last few decades and with the dethroning of Classical psychoanalysis as the preferred treatment for severe mental disorders, the time has arrived for an empathically-oriented long-term psychoanalytic psychotherapy to demonstrate its ability to permanently heal such severe self-disorders as Post Traumatic Stress Disorder (PTSD) and major depression.

For example, Meares et al., (1999) reports an outcome study of the treatment of 30 severe self-disorder patients (borderline symptoms) who showed a significant decrease in DSM III criteria after twelve months of treatment, compared with 30 similar patients on a waiting list during the same period. The treatment used an empathically-oriented form of psychotherapy (carefully supervised medical Interns) twice a week. Bateman and Fonagy (2001) also report that a partial hospital program of individual and group psychoanalytic psychotherapy for borderline patients had significantly reduced their symptoms compared with a randomized control group who were given standard psychiatric care. The symptoms reduced were as follows: anxiety, depression, self-mutilation, suicidal attempts and outpatient consultations. Such results as these in these two studies, while readily believed by experienced practitioners in the psychotherapeutic community, have limited influence in a medical milieu that is committed to rigorous forms of objective measurement, randomization, and experimental design. Outcome research similar to the Meares and Bateman studies using measures of neural regeneration, such as hippocampus size would, however, clearly demonstrate the value of psychotherapy for self-structural change (and neural change) - not just a reduction in symptoms - as worthy as this is - when conducted by competent practitioners or trainee practitioners carefully supervised by experienced supervisors.

Why the emphasis on hippocampus size as a measure of a structural effect for psychotherapy? To understand the importance of hippocampus size we shall examine evidence for (a) neural degeneration and then (b) neural regeneration, before discussing

(c) the need for a neural regenerational treatment of PTSD and severe depression that includes psychotherapy.

A. Hippocampal Neural Degeneration

Measurement of the effects of neural degeneration in the hippocampus has been facilitated by the use of MRI (Magnetic Resonance Imagery). Gurvitz et al., (1996) studied seven Vietnam veterans with combat experience who developed PTSD (Post Traumatic Stress Disorder), and compared them with seven veterans with combat experience and without PTSD, and also with eight veterans without combat experience and without PTSD. This study found a convincing 26% decrease in the hippocampi size of the combat veterans with PTSD compared with both the combat veterans without PTSD and veterans without combat and PTSD. Such a result not only supported the idea that a shrinking hippocampi volume reflects neural damage, but importantly, revealed that combat stress alone does not lead to significant neural degeneration.   This means that traumatic situations that trigger a stress response do not necessarily lead to neural death. How come? Such a result challenges the psychotherapeutic community to understand its work in a way that is consistent with this neurological evidence.

The small size of the Gurvitz groups made it a de-facto pilot study. The sample size problem was corrected by a meta-analysis of twelve MRI studies on depression, covering 434 patients and 379 comparison subjects, where again, smaller hippocampi sizes of patients confirmed the Gurvitz result and demonstrated that MRIs can effectively

measure brain degeneration (Campbell et al., 2004). In this meta-analysis, Campbell noted that although the overall results were significant, three of the twelve studies showed no significant differences in hippocampi volume between depressed patients and comparison subjects. As these three studies had patients with a low mean age (Rush et al., 2001; Posener et al., 2003; Vakili et al., 2000), they pointed to the possibly of a chronicity factor in neural degeneration. This observation was consistent with the finding of Sheline et al. (1999), that hippocampus volume was positively correlated to the duration of a depressive illness. So Campbell concludes that degeneration occurs as a result of a long period of chronically repeated experiences of stress rather than a few extreme episodes of neurotoxic biochemistry. A chronic stress view of brain degeneration is further supported by the DeBellis team's (1999) study of 44 abused but not chronically stressed children who had clear symptoms of PTSD, but who showed no significant reduction in hippocampus volume, compared with 61 non-abused children. So Bremner (2002) concludes that "chronic exposure to stress over many years may be required for hippocampal atrophy" (p. 118).

Sapolsky (2000) is a major proponent of the idea that excessive secretions of the glucocorticoids are involved in brain deterioration, especially in the hippocampus. He thinks that neural damage in both PTSD and depressed patients points to excessive levels of glucocorticoids, because they have been found to be responsible for morphological diminution in Cushing's syndrome. Cushing's syndrome "arises from …hypercortilism" [the excessive production of cortisol] (p. 927), which these Cushing syndrome patients experience for periods of months to years, leading to loss of hippocampi volume. For

example, Starkman et al. (1992) studied 10 men and two women who had Cushing's syndrome and a significant decrease in hippocampi volume. He found that the severer the hypercortilism the greater the atrophy of the hippocampi. He also reported that a decline in memory, as measured by verbal paired associate learning and verbal recall testing, was correlated to the loss in hippocampi volume.

In a follow-up study of 22 Cushing's syndrome patients, Starkman and colleagues, (1999) found further confirmation of hippocampi shrinkage and elevated cortisol levels when they re-measured the hippocampi volume 16 months (on average) after the patients had their tumors surgically removed. Importantly, their glucocorticoid levels were not only reduced, but 18 of the 22 patients had a statistically significant increase in hippocampi volume as <u>evidence of the reversibility of brain degeneration after corrective surgery</u>. This reversal with Cushing's syndrome patients also suggests the possibility that treatment of patients with PTSD and depression involves neural regeneration.

The role of glucocorticoids in the stress response has a long history in physiology. After surveying the enormous research literature on the glucocorticoids - there are over 400 references in their paper alone - Sapolsky and colleagues (2000) note the complexity with which the glucocorticoids influence the body's systems in different ways: cardiovascular, hemorrhaging, immune, metabolic, neurological or reproductive. The glucocorticoids may repress one system, stimulate a second, give permission to another,

or prepare yet another, all for the purpose of mobilizing an organism's sympathetic nervous system for an immediate maximum effort.

Southwick and colleagues (1990), however, offer an important revision of the glucocorticoid theory, that the glucocorticoids are in a protective rather than damaging role, inhibiting and eventually shutting off the excitatory response, to prevent damage to the human organism. In this revised model, damage to the glucocorticoid receptors will lead to neural damage. Southwick proposes that a "simultaneous activation of catecholamines [epinephrine, noreprinephrine] and glucocorticoids stimulates acting coping behaviors, whereas increased arousal in the presence of low glucocorticoid levels provokes fight or flight" (van der Kolk, 1995b, p.223).

The possibility of the protective function of the glucocorticoids in a stress response is confirmed by research findings of low cortisol levels in patients with PTSD. For example, Resnick and colleagues (1995) investigated the blood cortisol levels of rape victims with a previous history of rape (15 ug/dl), and victims without a previous history (30 ug/dl) and found that those with a previous history of rape had a blunted cortisol response. Also, as Yehuda and colleagues (1995) found, Holocaust survivors have an enhanced sensitivity to the glutamate neurotransmitter because their lower cortisol levels, when they are under stress, leaves their glutamate neurons less protected from excessive use. Consequently they view PTSD as primarily a hyperarousal disorder in which patients often resort to dissociation. Such a hyperarousal view, consistent with the experiences of psychotherapists, may reflect a biochemical disregulation, which could

explain why such hyperaroused patients need the compensation of external behavioral and social controls.

De Kloet (1998) explored why low cortisol levels may occur in highly chronically stressed people. Research shows two types of neural receptors for cortisol – the mineralocorticoid and the glucocorticoid – as noted by Selye (1952). The function of the mineralocorticoid receptors (MR) is to maintain the metabolic level in the brain, whereas the glucocorticoid receptors (GR) cope with emergency metabolic states. These MRs and GRs have separate functions because cortisol has a ten times greater affinity to the MRs than the GRs and does not bind to GRs until the MRs are occupied. This means that under mild or moderate levels of stress the GRs are unbounded. Only with high cortisol levels does cortisol also bind with the GRs, which then activate the GRs to decrease the cortical stimulation of the MRs, which then brakes the excitation of the neurons in the CA3 area of the hippocampus.

De Kloet summarizes that depression occurs from a permanent imbalance of the MR/GR system as a result of neural or receptor damage from stress. Such neural damage leads to cell degeneration, apotosis, and eventually shrinkage of the neural volume of the hippocampi.

B Hippocampal Neural Regeneration

One of the most remarkable shifts in modern neuroscience has been the discovery that a brain regenerates neurons in adult life. Although the idea of neural regeneration surfaced over a century ago (Hamilton, 1901; Hatai, 1901), the early findings of neurogenesis, like many important discoveries, were ignored because they did not accord with prevailing belief. For several centuries it has been believed that human brain cells couldn't divide (non-mitotic) and therefore, couldn't be replaced. But it has become increasingly difficult to believe this non-dividing (mitotic) cell model of the human brain because it ignores the knowledge that all organisms have some cells dividing, adding size or repairing cell damage; ignores that mammals have replicating cells in the blood, skin and gut, where stem cells contribute to cell replacement; and ignores that insects, fish and amphibia have replicating neural cells. Why not humans?

Hebb (1949) made a dent in the belief in non-mitotic brain neurons when he demonstrated synaptic growth and postulated a theory of a limited neural plasticity, without tackling the issue of new neurons. It was only after Altman (1962) took the step of publishing evidence of neural regeneration that a modern, full-blown theory of structural brain plasticity emerged. This mitotic view was reinforced by the important discovery of axonal elongation and synaptic reorganization in response to injury (Raisman, 1969; Moore 1971; and Lynch, 1973), and then by the electron microscope observation that thymine labeled rat cells formed in the granular layers in the dentate gyrus of the hippocampus, and in the olfactory bulb (Kaplan, 1977).

Greenough's (1978) studies of enriched environments then demonstrated that experience alone could promote pre-synaptic and post-synaptic change and broadened interest in studying neurogenesis. Support for neural cell mitosis (Gage, 2002) emerged with the discovery that neural stem cells can renew the adult brain throughout life by differentiating into new neurons and glial (neuron support) cells, as indeed happens in early brain development. Such stem cells have been found in two regions of the mammalian brain: the subventricular zone (olfactory bulb)(Reynolds and Weiss, 1992; Richards et al., 1992) and the dentate gyrus of the hippocampus (memory). This discovery of brain stem cells is supported by Gage et al (1995), who demonstrated that brain precursor cells have the capacity for *in vitro* neurogenesis, because of the presence of glial and neuronal cell markers when precursor cells are stimulated by the fibroblast growth factor (FGF-2). Gage also reports *in vivo* results, that "Upon implantation into the adult rat hippocampus, [precursor] cells migrate and differentiate into mature neurons or glia, depending on the terminal site of migration" (p. 11,879). His study confirmed that neurogenesis occurred in the hippocampus.

Then when Suhonen (1996) grafted developing cells from the hippocampal region into the subventricular zone, he found they migrated into the olfactory bulb where, influenced by the olfactory field, differentiated into olfactory neurons. This clearly demonstrated the multipotentiality of precursor cells, and that neither neurons nor glia are specific to location or function. Of this study Palmer (1997) says,"[developing neurons} may have a phenotype plasticity more akin to the immature stem cells present in early development" (p. 389). Further, by cloning retro-virally-marked cells and using DNA

analysis, he demonstrated that cells were derived from a single precursor, thereby

reinforcing the idea that both glial and neuronal progeny are generated *in vivo* from a

common stem cell reserve.

Along with acceptance that neurogenesis takes place in several regions of the

mammalian brain during adulthood, research sought biochemical markers to measure the

extent of neurogenesis. For example, Cameron (1991) demonstrated that newly born

cells, migrate from the hilar region to the granular layer as rapidly as 24 hours following

DNA synthesis. Rakie showed that evidence for cell regeneration comes from the

presence of radial glia cells, which guide migrating neurons to their destinations (Rakie,

1981). After this migration, radial glia differentiate into mature astrocytes (Pixley and de

Vellis, 1984

Neurogenetic markers have been found in the hippocampus. Cameron et al.

(1993), for example, demonstrate that new cells in the granular cell layer express the

neuronal marker - enolase. Kuhn et al., (1996) report that newborn granule cells from the

adult rat express 'NeuN" (Mullen et al., 1992), and also report the marker "calbindin-

D28k," a calcium binding protein that is commonly expressed by mature granule cells. In

a further study by Cameron et al., (1995), the focus was on the N-methyl-d-asparate

(NMDA) receptor, a subtype of glutamate receptor. When a glutamate antagonist

blocked these NMDA receptors and the new neuron cell rate increased, investigators

concluded that damage to NMDA receptors regulates cell birth. This suggested that

<u>prolonged excessive levels of the neurotransmitter glutamate, not exposure to cortisol</u>

<u>may be the most serious source of damage to neurons.</u>

The search for neuronal growth markers continues. An accurate means of measuring neurogenesis in living humans will advance many areas of neuroscience. And a reliable test of neurogenesis would especially enable psychotherapy to demonstrate the efficacy of its long-term work with severe self-disorders, and particularly with PTSD and severe depressive patients, who have been shown to have severe hippocampi volume loss as a result of neural damage. This is not a new idea. Kandel (1979) of *Californica Aplysia* fame, predicted that if psychotherapy works, it changes cellular structures. He (1998) says, "insofar as psychotherapy is successful in bringing about substantive changes in behavior, it does so by producing alterations in gene expression that produce new structural changes in the brain" (pp. 465-466). And recently Fuchs (2004) predicts that neurscience's discovery of correlates to mental disorders will eventually be accompanied by correlates to therapeutic changes.

Before examining the question of psychotherapy's potential to stimulate neural regeneration with PTSD and severely damaged depressive patients, we need to ask the question, what triggers neurogenesis? The answer from the Cameron (1995) study has been that neural damage, through damage to the NMDA receptors, triggers neurogenesis! This suggests that neurogenesis is a part of a process of neural repair, which has enhanced the evolution of the mammalian, primate, and human brain. When the neural death rate is low, there is a low level of regenerative activity, but if some other form of

neural injury occurs, the amount of regeneration increases. Such a capacity for neural damage to trigger neural regeneration, is also suggested by the work of Raismann (1969) Moore (1971) and Lynch (1971) and brain injury, and has received support from studies where electroconvulsive therapy (ECT) and antidepressants stimulated neurogenesis.

Nibuya (1995), for example, found that ECT increased the expression of brain-derived neurotrophin (BDNF) and its receptor trkB in the hippocampus, a clear sign of neurogenesis. BDNF, which is abundant throughout the brain, promotes the growth and development of immature neurons and enhances the survival and function of adult neurons. Nibuya also found an increased expression of BDNF after a continuous 21-day treatment (chronic) of antidepressants on rats, which included three major types of antidepressants - a MAO inhibitor, a norepinephrine SRI (selective reuptake inhibitor), and a serotonin SRI. Interestingly, however, three other treatments using a psychoneuroleptic, morphine and cocaine did not increase the levels of BDNF mRNA in the hippocampus.

Because previous research showed that CREB (cAMP response element binding protein) regulated the BDNF and its receptor, Nibuya and colleagues (1996) studied CREB and found that antidepressants increased the expression of it and the induction of BDNF and its receptor in rat hippocampi, and increased the survival and functioning of the neurons.   In another study, Mallei and colleagues (2002) found that chronic treatment using antidepressants increased the fibrblast growth factor (FGF2) in the hippocampus, a

neurotrophic factor expressed by the glia cells. This result means that neurogenesis involves the expression of both neuronal and glial neurotrophic factors.

This research into neurotrophic factors and markers for neural regeneration can be used to make the case that ECT and antidepressants are successful in overcoming depression through the production of new neurons. Such a view represents a shift from the strategy of changing the level of neuromodulators in depression, towards a replacement of the neurons themselves. A neuron replacement theory has its difficulties, however. For as Magavl (2000) points out, what triggers an increase in neurogenesis are the signaling molecules of the cells neighboring those damaged. In other words, these neurogenetic growth markers signal that some form of injury has occurred.

Neuroscientists are now studying cell regeneration by creating lesions in the brains of rats. These brain lesions are created by injecting a toxic substance such as chlorin (Magavl, 2000) or iboteric acid (Gould, 1997) or even a saline solution (Gould, 1997); by generating epileptic seizures through electrical kindling from mimplanted electrodes (Bengzon, 1997)(Parent, 1997); and by creating a loss of blood (ischemia) by clipping the carotoid arteries of gerbils for a number of minutes (Liu, 1998). All these studies provide evidence for a view that an "increase in proliferating cells occurred as a result of granule cell death" (Gould, 1997, p. 432). But if cell damage or death is a trigger of neurogenesis, what amount of damage is needed to trigger it, and what amount is excessive enough to create more brain damage than new cells? For example, Parent (1997) raises questions about the mossy fiber patterns of the new neurons in the dentate

gyrus, suggesting the possibility that excessive or continued treatment by ECT and antidepressants may damage a new neurons' capacity for healthy connectedness.

As Gould (1997) found small amounts of injected saline did not trigger neurogenic markers, but moderate amounts did, do we have some kind of optimal theory of brain damage and regeneration similar to the Yerkes and Dodson (1908) inverted U relationship between two variables. Under a neuroregenesis model of treatment for depression, the goal will not be to increase the neurotransmitters, but create just enough neural damage using ECT and/or antidepressants, or stress from some psychotherapy sessions to trigger neural regeneration. The risk of this strategy, however, is that excessive amounts far beyond what is necessary to trigger neurogenesis may create neural damage greater than any regenesis can possibly repair. Interestingly, a brain damage-regenerating triggering scenario fits the fact that antidepressants take a few weeks to have an effect, possibly because new neurons need time to mature and make a difference.

The neuroregenerational model suggests that if ECT and/or antidepressants have not triggered an improvement after a number of months, increasing the amount of treatment ECT or medication could increase damage to the neurons without concomitant neurogenesis and, hence, lead to more permanaent forms of depression. Such an increase is based on the neuromodulator deficiency model's assumption that no improvement after some months of treatment means there is still an insufficient amount of the neuromodulator in the synaptic cleft. But a neurogenesis model of depression means that

if a patient does not improve under ECT or antidepressant treatment, there is a need for psychotherapy treatment, not an increase of the ECT or medication in hopes that something will work.

Psychotherapy itself faces a similar treatment dilemma. In the initial stages of the psychotherapy, there may be enough stress to trigger neurogenesis, but the treatment relationship triggers threatening transference fears, and if these do not abate, psychotherapy may also produce more neural degeneration than regenesis. But even when psychotherapy, ECT or antidepressants have successfully triggered neurogenesis at a greater rate than neurodegeneration, neurogenesis still leaves a person vulnerable for a later depression. For although the negative past experiences encoded in patterns of damaged neurons may be destroyed, the new neurons that replace them need to be dendritically connected and integrated into the old neural networks. Just as the neurons of a new born baby will soon die in a Darwinian type of selection from disuse or lack of an empathically attuned mother's responsiveness, so newly generated neurons may be insufficient to prevent future depression from stress until newly developed dendrites make connections as a result of empathically attuned responsiveness from significant others or psychotherapists. One patient, for example, presented for psychotherapy after his antidepressant treatment had reduced his depression, because he wanted "his soul back."

The most important feature of the neural regeneration theory of depression and PTSD is that it challenges all treatment modes - ECT, antidepressants, and psychotherapy

- to demonstrate that successfully treated patients have a structural change as shown by an increase in the size of the hippocampi. If and when this increase can be demonstrated, the treatment of PTSD and severe depression will have taken an immense step forward and many of the issues between the various treatment modes have the potential to be resolved in a more co-operative approach to the welfare of patients.

C. Psychotherapy with PTSD and Severe Depressive Patients

This section focuses on understanding patterns that typically emerge in the interaction ("co-transference") with PTSD and depressive patients, primarily because of their self-organization. Even though PTSD patients develop different relational patterns and co-transferences than depressed patients, the common link between these two clinical syndromes is an experience of extreme helplessness, whether this helplessness comes from experiences of intrusive terror and over-stimulation in the former, or experiences of disinterest, neglect and deadness in the latter. First, we seek to understand the co-transference with the PTSD patient

Antigo, the small, Langlade County Seat, has nothing to distinguish it from many of the other towns of Northern Wisconsin - seemingly. I drove through it on several fly-fishing trips to the nearby Wolf River, to its famous Oxebow bend, but never noticed the McCandless, Zorbel and Bradley Funeral Home. Not that I would have connected John Bradley, its owner, to the famous navy medical corpsman of the horrific battle for Iwo

Jima (Bradley, 2001), where two out of every three U.S. marines were killed or wounded, and where corpsmen were exposed to both the dangers and the worst of the gruesome carnage!

Four days after the marines landed, John Bradley and five other members of the second platoon, Easy Company, were photographed on top of Mt Suriarchi, a 550 foot volcanic crater, as they uprighted a steel pole with an attached U.S.flag and unwittingly achieved instant hero status. In the minds the American public, this picture more than any other, represented the bloody sacrifice and courage of the U.S. in World War II.   The interest of this paper, however, lies with the fate of the three flag raisers still alive after the island was captured. Of these three survivors of Iwo Jima, two died relatively young (Ira and Gene) - and there was "Doc" Bradley.

After the battle, the three had gone on a war bonds tour of 33 cities where they were hailed as heroes. Ira and Gene used the heavy consumption of alcohol to cope with the stresses of the tour, probably as a result an exacerbated of the PTSD by their hero roles. In contrast, John Bradley defended against the corrosive effects of constant adulation by referring to the "real heroes of Iwo Jima" as the marines buried there. Back in Wisconsin, he adopted a dissociating strategy, avoided publicity, refused to talk about the war, married his childhood sweetheart, and quietly got on with his life. He underwent mortician training, prospered as a funeral director, became a pillar of the Antigo community, showed no signs of PTSD, and never shared his Iwo Jima ordeal with his wife or family. His defenses against reliving the memories of the war extended to his

children, who were coached to tell intrusive telephoning reporters that their father had gone fishing in Canada – notwithstanding the fact that John never fished. Even so, John's dissociation was not complete, initially. For four years after Iwo Jima he wept nightly in his sleep.

From clinical experiences with PTSD and depression patients (severe self-disorders), the difference strategies between John and the other two survivors is understandable. In discussing the PTSD syndrome, van der Kolk (1996) describes PTSD patients as organizing "much of their lives around repetitive patterns of reliving and warding off traumatic memories, reminders, and affects" (p. 183). This was not so with John Bradley. The John Bradleys of this world rarely seek psychotherapy, as they are able, through dissociation, to put the past behind them. They are not crippled by the experience of trauma, because they let go of the past and get on with their lives, which is the classical theological meaning of forgiveness. In contrast, the Iras and Genes of this world are unable to achieve this letting go. They can't forgive because they are consumed – either by a conscious or unconscious need for revenge, or from attempts at self-repair – by reliving their traumatic memories. One patient for example, who had been severely beaten as an infant by a brutal mother, initially feared losing these memories of abuse because she determined not to be cheated out of the hoped-for revenge on her mother. Consequently, by deliberately rehearsing of these memories, she kept herself in a constant state of stress, which I now believe fostered more neural degeneration than neural regeneration.

Although it is broadly accepted that persons can be re-traumatized by events similar to an original trauma, an overemphasis on traumatic events "out there" may disavow the power of memory to trigger re-trauma too. As my "lehrmeister" (teacher), a patient who was physically beaten through babyhood and childhood, helped me understand how iatrogenic the uncovering of the unconscious with traumatic self-disorders can be. For weeks after she uncovered each painful memory, her sessions would be unproductive until she recovered from her distress. It was not my empathic failure during these unproductive periods that fragmented her – although this sometimes happened – but her strategy of attempting to rid herself of traumatic memories through sharing them. As the treatment progressed, she increased her resistance to recalling her painful past, and after we noticed that her "resistance" resulted in less distress and more adaptive behavior, we both realized its significance and I was able to affirm her resistance as a healthy expression of self-agency.

Miss B was another middle-aged person who presented as a terrified, highly stressed PTSD patient. As she had failed to develop a therapeutic relationship with several previous therapists, it soon became obvious that the major issue was whether she could develop a trust of me (Brothers, 1995). She was a social worker who had been raped as a child, and now wanted to overcome the damage to her life. She questioned me about my background and training. Had I prior experiences with traumatic patients? As the pattern of questioning became an interrogation during the initial sessions, it became obvious that she was using this technique to avoid revealing herself until she developed some trust in me.

After a number of sessions, Miss B presented me with a nude, pink plastic doll, about eight inches tall, which she had bought for 25 cents in an Opportunity Shop. When I asked her why she had brought the doll, she shrugged her shoulders and declined to talk about it. So I made the general comment that she had made an important gesture with the doll, the meaning of which would become clearer in later sessions. This satisfied her because it contrasted with the feelings of being pressured by her previous therapists to talk. At the end of the session she had me place the doll in the room's closet. By the next session, I had my non-verbal response.

In a nearby Opportunity Shop, I found an old wicker basket type tissue box cover that could be used as a doll bassinet. It cost a dollar. So when Miss B asked for her doll from the closet during the next session, it was lying in the miniature basket, tucked in, with a serviette as a blanket. Totally surprised at first, Miss B's face lit up in delight. Importantly, she had a decreasing fear of me in the succeeding sessions, despite an occasional session where she re-adopted her interrogating style. Eventually, after about 100 sessions, Miss B had developed enough trust to be comfortable with our therapeutic relationship. As she became more trusting, she increasingly shared her past, which included being placed in a institution from when she was six month's old until she was two years of age when her mother fragmented and could not cope. She also included meager details of a rape by two teenage boys when she commenced school, and her shattering humiliation when she attempted to tell her mother what had happened, and her mother discounted her story.

In later sessions, each time Miss B shared more of her story she became extremely distressed and needed me to function as a soothing "selfobject" (Tolpin, 1971). Believing that the repetitive pattern of extremely distressing periods may be contributing to neural degeneration, I emphasized that I only wanted to know about her past if and when she was ready to talk about it. This uncovered her belief that trauma was only overcome by talking about memories, which she attempted despite her intensified feelings of terror. She forced herself to talk about these memories because she believed the sooner she did this, the sooner she would heal and finish the psychotherapy. She then realized that she was continually being re-traumatized by the memories that were being stimulated by her concept of treatment.

Based on my work with traumatized disorders, and the neuroscience literature on chronic stress, the Gurvtiz (1996) result - that exposure to the trauma alone does not automatically lead to PTSD or significant brain damage (smaller hippocampi) - makes sense. Combat exposed PTSD patients seemed to not have the ability to utilize a controlled form of dissociation, and so developed chronic stress from continual over-stimulation of the sympathetic nervous system from memories of traumatic events. In contrast, those combat veterans who could turn off their traumatic memories, the natural processes of brain regeneration eventually allowed new neurons, new glia, and new dendrites to develop - and healing to gradually take place.

Miss B also reflected Kohut's theoretical understanding of a "vertical split" (Kohut, 1971, 1977, 1984) in her self-organization. In her defensive self-state she was organized around prevention of re-traumatization, even though such a foreground self-organization constricted her background self-organization from creatively reaching out and experiencing enjoyment. After she felt more secure and her creative self-organization moved into her foreground and her defensive self-organization receded, Miss B was motivated by her improved feelings to attempt a repair of her traumatic memories. In so doing she re-traumatized herself, especially as she attempted to make repairs herself without the aid of a psychotherapist/selfobject. Feeling re-terrorized by her traumatic memories, she then switched her defensive self-organization into the foreground and her creative self-organization into the background. This case and other PTSD cases, suggest that persons with narcissistic behavior disorders (Kohut and Wolf, 1978) are more prone to develop PTSD after becoming chronically distressed.

Chronic depression is another syndrome with evidence of neural degeneration and a lowered capacity to regenerate new neurons in the hippocampi. How does successful long-term psychotherapy contribute to their treatment? What is the co-transference that emerges with such cases? How could psychotherapy with depressive patients foster re-generation. For, unlike treatment with PTSD patients, the severely depressed patients do not have the need to self-repair, they withdraw into inactivity. How do such patients interfere with the natural processes of neural regeneration so they steadily become increasingly brain damaged? Like the PTSD patients, depressed patients feel hopeless and despairing. They are organized around feelings of hopelessness that are connected to

experiences of emotional neglect and isolation that began early in life. Miss A is a composite of a number of patients. She is a middle-aged ex-nurse who was so depressed and suicidal when she presented for psychotherapy that she could scarcely say a word. In former times she may have been diagnosed as catatonic   When the female psychotherapist suggested that antidepressants could possibly assist with the psychotherapy, Miss A responded that several psychiatrists in the past had prescribed antidepressants - tricyclics, MAO inhibitors or SSRIs – and none had made enough difference for her to tolerate the significant side-effects.

Miss A indicated that although she was not a believer in psychotherapy, she had decided to try it as her last hope. In the succeeding sessions a pattern developed in which Miss A would share a little about what happened during the week to make her miserable, and then lapse into a hopeless silence. After several months of these sessions the psychotherapist found it increasingly difficult to tolerate the patient's pattern of long silent periods, although she thought the patient was attempting to convince her that she was not worthy of interest and was trying to induce hopelessness in the therapist so as to give up on her. The therapist, influenced by Brandchaft (1988), eventually interpreted that the patient may want her to feel unconsciously hopeless about the case, and to give up. Impassively, Miss A said she found this "an interesting idea" and lapsed into silence.

Two days later, the therapist received a short note in the mail from Miss A in which she shared a lot more information about herself. In the next session Miss A was

slightly more talkative after the therapist indicated how pleased she was to receive the note, and then added that, as she found Miss A interesting, she did not believe she would abandon her. During the next two years, after some sessions Miss A sent notes in which she shared her feelings, particularly when the therapist angered her through misunderstanding. Gradually, however, there was a shift from writing notes to sharing more of her feelings in the sessions.

From the material that Miss A eventually shared, the psychotherapist was able to piece together a story of abject humiliation. As happened with the case of Miss B, the psychotherapist did not delve into details about Miss A's humiliating incidents to avoid shaming her, although she made it clear that she was interested in what the patient wanted to share. The psychotherapist understood Miss A had formed an "alterego" twinship (Kohut, 1984), in which the therapist's hopefulness for Miss A's treatment substituted for the repressed, split-off hopefulness in the patient. The psychotherapist also believed that her sustained hopefulness and interest gently stimulated Miss A's Sympathetic Nervous System (HPA axis), inhibited neural degeneration, and enabled natural neural regeneration to take place. After four years of the therapist's genuinely sustained interest, Miss A, although still depressed at times, was no longer suicidal, was more socially interactive, and more hopeful. Then Miss A decided to have a "break" from the therapy.

In response the therapist felt that a few more years of sustained treatment would be necessary for further neural regeneration to take place and the chances of a more

permanent improvement. She also wondered if the patient was beginning to experience

the length of the treatment as an imprisonment, and therefore as a punishment, and was

taking a temporary break in sessions to alter this misperception. Furthermore, the request

for the break was seen as one more test of whether the therapist was still interested in

Miss A. So, the psychotherapist agreed with Miss A that a break in the psychotherapy

sessions could be a good idea, but hoped that Miss A would eventually return for further

treatment to reinforce the gains that had been made.   By mutual consent the sessions

were suspended.   Within four months Miss A had returned, and with a renewed

commitment to further treatment.

D. Conclusion

With such long-term cases if successful, there is a significant shift in the patients'

subjective experiences, and a significant improvement in the ability to function in society

without feeling distressed. Along with such subjective and behavioral shifts, one would

expect, if Kandell is correct, that these improved subjective states would be reflected in

improved neural regeneration as demonstrated by an increase in hippocampal size. It is

obvious that the time has come to take MRI s measurements when seriously depressed

and PTSD patients begin long-term psychotherapy and then retest them after a significant

period, such as 300 hours of treatment. Can the effects of psychotherapy lead to the long-

term regeneration of the hippocampus in brain-damaged patients? It is time for all forms

of treatment - ECT , antidepressant medications, psychotherapy, or combinations of them

- to demonstrate that they can consistently produce such physical changes as an increase

in hippocampi volume.

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