

Transprocessing: a proposed neurobiological mechanism of psychotherapeutic processing

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Abstract

How does the human brain absorb information and turn it into skills of its own in psychotherapy? In an attempt to answer this question, the authors will review the intricacies of processing channels in psychotherapy and propose the term transprocessing (as in *transduction* and *processing* combined) for the underlying mechanisms. Through transprocessing the brain processes multimodal memories and creates reparative solutions in the course of psychotherapy. Transprocessing is proposed as a stage-sequenced mechanism of deconstruction of engrained patterns of response. Through psychotherapy, emotional-cognitive reintegration and its consolidation is accomplished. This process is mediated by cellular and neural plasticity changes.

Background

Contemporary research has generated a series of contributions meant to establish a neurobiological framework for human change in psychotherapy.^{1,2} This paper starts from the hypothesis that human survival has as its purpose not only personal but also social viability. Evolutionarily, social viability is as important as personal existence. For this to be accomplished effectively, an initial aim of psychotherapy is to tune down negative affects and strengthen positive ones. Toning down of the panic/anxiety signaling is necessary. Panic limits social affiliation, secure attachments, confidence, and ultimately, procreation and reproduction.

Human healing and change engages a large variety of neurobiological mechanisms that involve the processing of complex memories – multimodal memories (MM), comprised of affective, cognitive and behavioral components. The authors propose the term *transprocessing* (from *transduction* and *processing*) to refer to neurobiological changes induced by environmental influences which are incorporated as new memory functions. Based on previous contributions and on updated functional neuroanatomy, the authors propose that new neural networks occur predominantly in

anatomical areas where implicit emotional and explicit cognitive information intersect. A description of transprocessing along vertical, horizontal and molecular (transduction) neural networks will be proposed. The particular role of the subcortico-cortico midline system (SCMS) in the constitution of the Self, its relationship to primary process emotions or *proto-emotions* will be discussed.³ Even though mental processing like transprocessing and healing are anatomically ubiquitous, there are brain networks that serve special roles as initiators of mental processing, learning and psychological healing.

Unlike natural processing, transprocessing is targeting the reconstruction of complex multimodal memories, developed primarily for defensive purposes, which have become crystallized and thereby associated with chronically dysfunctional behaviors. Mechanisms of processing and repair will be examined both from a bottom-up and top-down perspective (referring to the hierarchy of different brain structures).⁴ We will conclude with the proposal of three phases of transprocessing: i) evaluation; ii) acquisition and self-reference; and iii) re-consolidation.

Socrates: «You declared just now that you yourself cannot even explain what knowing is. How did you learn the verb to know as a child?»

Plato: «Evidently, I assimilated it from hearing it used around me».

Socrates: «Then it was by automatic action that you gained control of it».

Plato: «No... Well, perhaps I see what you mean. I grew accustomed to hearing it in certain contexts, and thus came to be able to use it myself in those contexts, in a more or less automatic fashion».

Socrates: «Much as you use language now – without having to reflect on each word?»

Plato: «Yes, exactly».

An imaginary dialogue between Socrates and Plato by Douglas Hofstadter (2007).⁵

Introduction and terms

Change is a fundamental attribute for the human evolutionary potential. It must include an internalization of the ever-changing living environment and forms of assimilation of experiences, like memory and long-term adaptive changes in behavior. Some contemporary views have touched on all past interactions as permanently encoded human experiences that define one's identity,⁵ thus conferring a new meaning to personal history. Healing in psychotherapy has been the subject of a large body of literature, but less has been written about brain processing in psychotherapy and its relationship to human change. This paper explores the multiple facets

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of brain changes activated by psychotherapy. Neuroanatomical considerations of brain regions where explicit and implicit memory mechanisms intersect, will be reviewed as crucial to the development of new reparative memory constructs. The dimension of *time* as a determining factor in human change will be emphasized. Specifically, time is seen as a bridging element between the reactive, instantaneous functional brain response, and the lasting changes of neural connectivity and functional remapping. Such remapping of the brain mirror lasting experiential change.

The term *psychotherapy* will be used to refer to a psychodynamic, interpretation-based therapeutic interaction that promotes change. The term *transprocessing* (TP) denotes a broad therapeutic event. It includes the roots of *trans* from transduction, the biological term that refers to cellular changes induced by environmental influences, and the term *processing*, common to the brain activities related to incorporation of information. TP as used here will

refer to the changes that occur in psychotherapy: a deconstruction of target memories, which include cognition, affects and behaviors followed by an ensuing adoption of more adaptive constructs. Such a change includes a fundamental learning process (an acquisition and enrichment). Transprocessing is not reconsolidation as described by Nader and Duvarci,⁶ a process of reworking and reinterpretation of memories. Specifically, through reconsolidation, each time a memory is recalled, it is changed according to the context in which it is being recalled. While TP does include elements of reconsolidation, in TP, the newly acquired memory pool and related behaviors override, but do not erase, the old neurotic self. *Multimodal memories* (MM) are complex memories, through which one may hold, experience and/or evoke cognitive, affective and behavioral information concomitantly in mind. Thus through MM, one is able to remember an event, re-experience an emotion and evoke and/or act on one's own behavior, which was previously acquired. MM are highly associative and therefore may activate a variety of brain regions. Traumatic memories are a form of MM that are activated by reminders of past adverse events. Neurotic Symptoms are multimodal memories. The term neurosis has been used interchangeably for the designation of mild psychiatric symptoms of anxiety and depression, for distortions as they transpire in everyday life and for a specific psychological profile for individuals who tend to overreact to environmental stressors. Neurosis is linked to the generation of some psychiatric symptoms. Psychiatric symptoms do not originate in predictable anatomical locations,^{7,8} but genetic and epigenetic factors participate in the development of reactions to environmental stress.⁹ While in this contribution we will not concern ourselves with symptoms *per se*, nevertheless neurosis, psychiatric symptoms and maladaptive reactions have certain autonomous nervous manifestation as a common denominator. This denominator points to the large extent of connectivity between the CNS and the ANS.

Examples of the CNS-ANS anatomic link

The amygdala and the ANS. Through its central nucleus, the amygdala is linked to the dorsal motor nucleus of the vagus in the medulla.¹⁰ By means of tracing studies of neurons, with horseradish peroxidase, the neurons from the amygdala and the dorsomedial medulla were found to extend into the forebrain, the sub-lenticular region of the substantia innominata, under the globus pallidus and internal capsule and into the lateral part of the bed nucleus of the stria terminalis (BNST), forming a continuum and uniting these structures. Thus, areas responsible for somatic symptoms link to neuronal substrate of emotions. Schore pointed to

the right lateralization of the connection between the cortical circuits of social and emotional processing and the autonomic nervous system.¹¹⁻¹⁴ It is noteworthy that an older term for ANS is the *Involuntary Nervous System*, which more precisely denotes its function. The ANS is not autonomous but highly interactive with the CNS.¹⁵ Within the symptomatology of psychiatric disorders, somatic symptoms occur involuntarily, but are linked to mental content (*e.g.*, panic attacks, hyperarousal in PTSD) albeit not at all *autonomous*.

Porges' proposed polyvagal theory views autonomic control as a result of three separate systems:^{16,17} i) the myelinated vagus, which acts under circumstances of low arousal and calm; ii) the sympathetic, which steps in as a second line of response in stress exposure; iii) the unmyelinated vagus, which has a predominant survival function. Therefore, the ANS is highly linked to response patterns of an individual in adverse life circumstances. A dominance of the (*myelinated*) vagus nerve will maintain a high vagal tone, which is associated with increased attention and increased recognition memory, which further influences the cognitive component of anxiety. This high vagal tone is a state that psychotherapy aims to achieve.¹⁸ Autonomic activity is crucial in the body's social engagement mechanisms, as it controls gaze, middle ear musculature (selective sound amplification) and involuntary vocalization.¹⁹ Furthermore, attachment research has also pointed to a transmission from mother to child of fear response and dissociation in attachment of disorganized type.²⁰ Both organized, *e.g.*, secure-autonomous, and insecure, *e.g.*, dismissive, preoccupied and disorganized/disoriented states of mind in parents, with respect to attachment, predicted the same type of attachment in their children.²¹⁻²³

All these constitute accumulating evidence for a multilink evolutionary and adaptive, mechanism of intergenerational transmission of responses to the environment in which the ANS along with implicit memory and language have particularly poignant contributions.²⁴

The neurological model of transprocessing

The idea that mental dysfunction is associated with a miswiring process is not new.²⁵⁻³⁰ Yet, psychological processing, long thought of as part of a healing mechanism, is commonly referred to as understanding and internalizing.³¹ Formed memories of either external events or of internal experiences are split up, reorganized and interpreted within a personal context or an autobiographical narrative. Commonalities in the process of psychological recovery and healing across different schools of thought have been outlined,³² and an integrative function of healing during psychotherapy has been proposed.³³ Given strong social evolutionary pre-programming of humans, multimodal memories that develop interactively, in psychotherapy, carry a heavy weight in defining a changing individual. Such memories are likely to heavily impact an individual's future interpretation of the external world or *Weltanschauung*. Neurologically, transprocessing is a structured form of processing. Processing occurs at the crossing of specialized pathways where signals of different intensity and dimensions intersect. Anatomically these pathways will be described according to vertical, horizontal and cellular brain distribution (Figure 1).

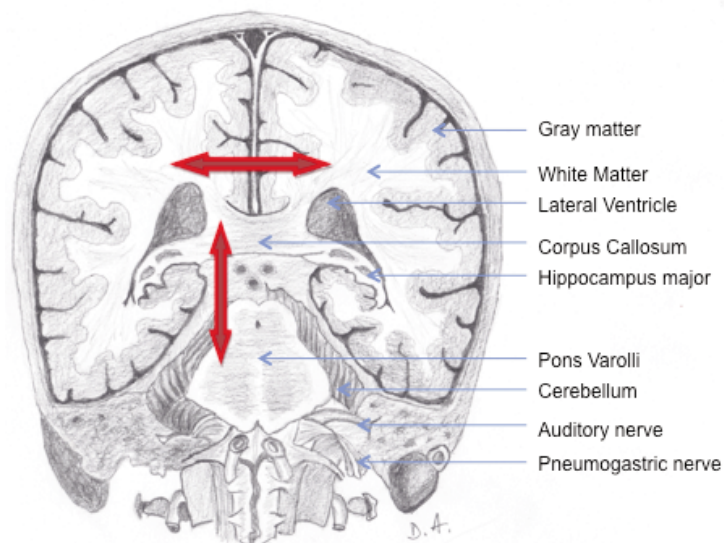


Figure 1. Transverse vertical section of the brain, through the fore part of the foramen magnum, looked at from the front.

Vertical processing systems

Vertical processing system includes: i) self-Related Processing and the Subcortical-Cortical Midline System (SCMS); ii) re-entrance; iii) prefrontal-subcortical circuitry and mood regulation.

The subcortical-cortical midline system and the Self

A large body of literature on the Self and Consciousness has recently emerged.^{7,34} Leonardo da Vinci referred to *senso commune* as the center of all senses including the center of the soul.³⁵ While an in-depth analysis of different schools of thought is beyond our proposed scope, several contributions are noteworthy. Panksepp and Northoff have referred to self-related processing (SRP) as a specific and evolutionary-directed mode of interaction between organism and the environment.³⁶ Through SRP, environmental stimuli are related to organismic needs, and the higher cortical areas are at the basis of epigenetic changes for interactive behaviors necessary for survival. All these are accomplished by a set of midline structures that start in the brain stem, the reticular activating system (RAS) and are interconnected with higher brain structures in the subcortical and cortical areas, referred to as the subcortical-cortical midline system (SCMS). These include the periaqueductal gray (PAG), an extremely rich connected brain structure,³⁷ the superior colliculi (SC), the bed nucleus of the stria terminalis (BNST), ventral tegmental area (VTA), the mesencephalic locomotor regions, preoptic areas, the hypothalamus and the dorsomedial thalamus,^{3,38} which accomplish the integrative bodily functions and the convergence of basic emotional systems to form the proposed *bodily self or proto-self*.^{37,39-46}

Panksepp and Watt suggested that a number of affective states constitute the instinctual building block of basic affective responses necessary for survival.^{3,47} They include: SEEKING (refers to appetitive desires, motivation); FEAR (generates a pure form of trepidation without a specific object which animals can associate with many circumstances and helps the avoidance of danger); RAGE (facilitates the need to protect and defend); LUST (associated with sexual functions); CARE (includes the maternal instinct); PANIC (activated in young mammals when lost accompanied by a crying out for care. The crying out triggers care by the parent); PLAY (exposes young animals to the social systems of their species and provides an initiation of skills by adult animals, necessary to function in the world).

Panksepp's vast contribution and the emergence of Affective Neuroscience points to the primary process emotions that originate in the

lower brain structures.^{43-45,48-51} These structures constitute the lower segment of the neural substrate of the core self and are of a particular significance in providing a bottom-up loop for some basic affective processes with evolutionary significance. The neural basis of the basic emotions has been proposed by Panksepp: SEEKING = nucleus accumbens, VTA, mesolimbic and mesocortical outputs, the lateral hypothalamus, PAG. RAGE = the medial amygdala to BNST, medial hypothalamus to PAG. FEAR = Central to lateral amygdala to medial hypothalamus and dorsal PAG. LUST = Corticomедial amygdala, BNST, preoptic hypothalamus, VHM, PAG. CARE = anterior cingulate, BNST, preoptic area, VTA, PAG. PANIC = anterior cingulate, BNST and preoptic area, dorsomedial thalamus, PAG. Play = dorsomedial diencephalons, parafascial area, PAG.

Northoff *et al.* observed on brain imaging that emotional dimensions and self-relatedness were modulated into opposite directions in the DMPFC and the ventral striatum, while the neural activity in subcortical regions (tectum, right amygdala, hypothalamus) for self-relatedness and emotions was regulated into the same direction.⁵²

All environmental stimuli, through self-related processing (SRP) are being evaluated implicitly or explicitly for their possible value for the survival of the organism.³⁸ This evaluation is accomplished in both as *action* and as *affect* (Figure 2).^{2,3,44,45}

The higher brain structures associated with functions of the Self include the medial prefrontal cortex (MPFC), the dorsomedial pre-

frontal cortex (DMPFC), the supra-genual area of the anterior cingulate, and the precuneus.⁵³

In summary, what Panksepp and Northoff have proposed as the Core-Self,³⁶ refers to a network of midline structures with its lower segment, the reticular activating system (RAS), described above linked to interoceptive states and raw emotions and its higher brain structures, the subcortical-cortical midline structures (SCMS), which provide affective-cognitive integration. Together, these structures of the Core Self make Self Related Processing (SRP) a very specific mode of interaction between organism and environments. From an evolutionary viewpoint, SRP allows for an interaction in which stimuli from the environment are related to organismic needs, and through the higher midline structures, provide the basis for epigenetic emergence of higher forms of selfhood across different individuals within a species. It has been proposed that the SRP and the Core Self are highly evolutionary trans-species domains. In psychotherapy, the operation of the human cortex mirrors and modulates proto-emotions that originate in the PAG. Human socialization can be maintained thanks to cortical inhibition of protoemotions. Neurosis routinely includes a compromising of such modulatory power with both states of unleashing of some and states of blocking of other emotions. Seen from outside, *neurotic* emotions seem idiosyncratic and defensive (*primitive defenses*). As we will propose below, target memories are constructs that interfere with the regulatory effect of higher brain functions. Psychotherapy, by way of transprocess-

Levels of processing and corresponding brain regions

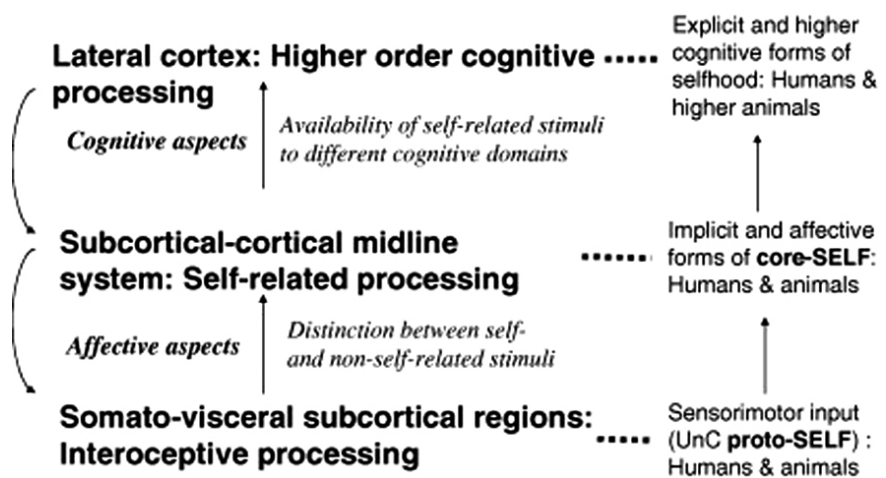


Figure 2. A summary of the different levels of processing of the self in association with possible neural and psychological substrate. (Reproduced with permission: Panksepp & Northoff, 2008).

ing, deconstructs the target memories that dysregulate the cortical modulatory functions. This paradigm shift is often accompanied by a release of emotions that seem unusually intense. As proposed below, in subsequent stages of *evaluation*, *self-reference* and *reconsolidation*, transprocessing constructs proper networks that restore and maintain self-related processing (SRP) necessary for individual survival and affect regulation necessary for group and social survival.³⁶ Of all proto-emotions, PLAY seems particularly significant as access to the know how of early development.⁵⁴

Re-entrance

The term re-entrance is used in the description of the cortico-subcortical parallel re-entrant circuits of the brain, a set of anatomical regions which provide an interactive functional link between cortex and subcortical region. Current knowledge about memory function makes it very obvious that implicit, non-declarative memory shapes and influences explicit, declarative memory, and thus decisions and actions. Re-entrance is a function based on a newer anatomical organization. Lennart Heimer's group reported that the piriform (olfactory) cortex and the neighboring cortex of the amygdaloid complex (together the piriform-amygdaloid cortex) send the majority of their projections to the basal ganglia and terminate in the ventral striatum rather than in the anterior-lateral hypothalamus as was widely accepted previously.⁵⁵⁻⁵⁸ A lesion in the olfactory tubercles would result in a massive degeneration in the substantia innominata, whose precise role in the function of the striatum and the amygdala was believed to be minor. By using the *retrograde lesion technique*, it was demonstrated that these areas and the rest of the hemispheres project into the accumbens and the striatal areas of the basal ganglia of the *forebrain* which projects back to the different areas of the cortex: hence the designation *re-entrant circuits* (Figure 3).

The anatomical areas in question are the basal ganglia (caudate, putamen and globus pallidus), the adjacent, interspersed white matter extrapyramidal structures, as well as the extensions of nearby regions, *e.g.*, the *substantia innominata* and the extended amygdala.

The extended amygdala

Currently, the entire region of the amygdaloid system in the medial temporal lobe is viewed as a network of numerous nuclei with different functions. In its classical description, the amygdala contains two major components: i) the central-medial nuclei, closely connected to the striatum, and ii) the cortical and basal nuclei, which are associated with the cortex. Of this division, the central-medial nuclei

extend projections that reach the bed nucleus of the stria terminalis, a part of the reticular activating system (RAS). In its entirety, the extended amygdala is a ring of neurons that encircle the internal capsule and the basal ganglia. It is subdivided into the central extended amygdala and the medial extended amygdala reaching to the stria terminalis and the bed nucleus of the stria terminalis. These are medially located brain structures.⁵⁵ The extended amygdala is continuous with the shell of the accumbens. Together these two structures form neuronal circuits which connect to the orbito-frontal cortex and the medial temporal lobe.

The striatal-pallidal system

This includes the basal ganglia (caudate, globus pallidum, putamen and the white matter capsules), which form functional units. The ventral striatal pallidal system is especially involved with behavioral functions. Its anterior part, the nucleus accumbens, has a high dopamine neuron content, and thus its importance in reward and motivation. The dorsal striatum and pallidum, and their cortico-subcortical connections, are charged mainly with motor functions.

The substantia innominata

The substantia innominata is a ventral extension of the pallidal complex of the basal

ganglia, which is closely linked to the two major subcortical structures: the striatal pallidal complex and the extended amygdala, which appear like two large diagonally-oriented subcortical bands. The ventral part of the substantia innominata is called subcommissural substantia innominata. The posterior substantia innominata is also referred to as the subnucleus substantia innominata. This latter portion is mainly occupied by elements of the extended amygdala. Heimer *et al.*⁵⁶ pointed to the improper name of this region, *substantia innominata*, which was considered the equivalent of the geographical designation of *terra incognita*, or uncharted territory. However, in this region the basal nucleus of Meynert is a collection of cholinergic and non-cholinergic cells, which are corticopetal and thalamopetal. They stretch from the septum diagonal band to the caudal globus pallidus. Of further importance is the abundance in this area of neurons congregated as the so-called interface (small-celled) island, which are rich in neuro-active substances. They may constitute reserve cells for remodeling and raw material for the adaptive structural reworking of the brain.

There seems to be considerable individual variability of the cortical-subcortical circuits achieved by brain plasticity, *e.g.*, neurogenesis and rapid dendritic spine rewiring, which is sensitive to biochemical changes.⁵⁹ There is also a large variety of neurotransmitter neu-

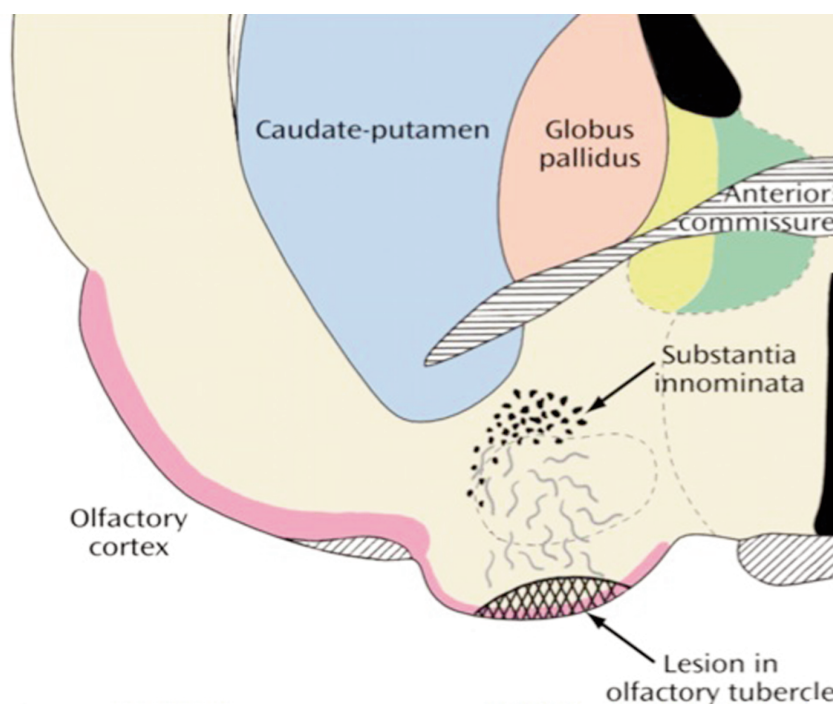


Figure 3. Pattern of degeneration in the Medial Forebrain Bundle in a rat olfactory tubercle and the corresponding terminal degeneration in the substantia innominata, two days later. (Reproduced with permission: Heimer & Wilson, 1975. Copyright Raven Press, New York).

Projections to the hypothalamus and the brain stem. Particularly, the medial network of the OMPFC projects to the hypothalamus and the PAG,⁷⁸⁻⁸³ which mediate visceral reactions to emotional stimuli.^{84,85} Damasio has in fact proposed a *somatic marker hypothesis* referring to somatic/body reactions that accompany emotions as warning signals for situations that ought to be avoided.⁸⁴

The cortico-striato-thalamo-cortical circuits have four different subdivisions which include the medial dorsal thalamic nuclei (MD).⁸⁶ The MD have two segments: the medial segment or medial MD and the lateral segment or the lateral MD. Medial Segment of Medial Dorsal Thalamic Nuclei (Medial MD). The medial MD receive subcortical input from the amygdala, the auditory cortex, and other limbic areas.⁸⁷ However, given the direct cortical projections (the amygdala, the primary olfactory cortex entorhinal, the perirhinal, the parahippocampal cortex and the subiculum of the hippocampus), all send axonal projections to the OMPFC and to the medial MD.^{69,61,88} Non-thalamic input to the cortex from this limbic structure carries more detailed information than the connections that go through the MD nuclei of the thalamus.⁸⁷⁻⁸⁹ Thus, MD receive the limbic system connections which are excitatory (glutamatergic) and inhibitory (GABA-ergic) inputs from the ventral pallidum and rostral globus pallidus,^{90,91} which are part of the larger cortico-striato-pallido-thalamic loop, involving the OMPFC. Behavioral implications: the convergence of opposing neurotransmitter functional systems suggests a modulation of the reciprocal thalamo-cortical interactions between the OMPFC and MD. The limbic inputs are dominant, but there are also ongoing thalamo-cortical and cortico-thalamic interactions allowing for consistent behavior. When pallidal inputs become dominant, ongoing behavior is interrupted promoting a switch to another behavior. In rats lesions of the ventral striatum, pallidum, MD or OMPFC have been shown to cause perseveration, *e.g.*, an inability to switch away from tasks that were previously rewarding and are no longer rewarding.⁹²⁻⁹⁵ Such an inability to switch is likely to have very broad implications in psychotherapy, as it is a component in many dysfunctional manifestations, including the inability of *letting go* of upsetting events, negative moods, depressive thoughts and traumatic events in a large number of psychiatric patients (not just in PTSD).

The lateral segment of the medio-dorsal thalamic nucleus (Lateral MD), receives most of the inputs from the brain stem including the superior colliculus, the vestibular nuclei, as well as the reticular formation.⁸⁷ From the lateral MD they are further relayed to the frontal eye field and related areas in the caudal LPFC. Lateral MD receive GABA-ergic pallidal-like

fibers from the parts reticulara of the substantia nigra.^{96,97} However, brainstem areas do not project directly to the cortex. Lateral MD serve as a relay to the cortex.

Prefrontal projections to the striatum. The OMPFC projects to the rostral, ventromedial part of the striatum.⁹⁸ The subgenual part of the medial prefrontal cortex, also known as area 25, projects to the shell of the nucleus accumbens. The midline intralaminar nuclei of the thalamus, which include the para-ventricular thalamic nuclei (PVT), have a particular role in the response to chronic stress. Behavioral implications: lesions of the PVT block the habituation response to chronic stress in rats. In human brain imaging studies on neuroendocrine stress from chronic hypoglycemia, an activation of the medial prefrontal cortex, the PAG and the midline thalamic nuclei has been observed as well.^{8,99-105}

Circuit-specific neuropsychiatric syndromes have been described.¹⁰⁶⁻¹⁰⁸ For the interested reader, a more comprehensive review of the cortical and fronto-subcortical circuits and their role in neuro-psychiatry can be found in several studies.¹⁰⁸⁻¹¹¹

The horizontal processing systems

Interhemispheric horizontal processing

In inter-hemispheric horizontal processing, the anatomical substrate, the corpus callosum and the anterior commissures represent white matter structures of an extraordinary functional capacity. This is supported by a huge network of fibers. The numbers of fibers comprising the corpus callosum and the anterior commissures are larger than the sum of all fibers ascending to or descending from the cerebral hemispheres.¹¹² It is not the white matter *per se* that accomplishes processing but rather the potential for hemispheric synchrony through the fiber network, which conveys such an important role to the corpus callosum and the commissures. Historically, a developmental right to left shift in hemispheric control and dominance in learning has been recognized.¹¹³ Within the learning process, a dynamic shift from task-naïve to task-experienced recognition,^{114,115} and a change in *locus* of control in hemispheric dominance in the process of cognitive skill development have been identified.¹¹⁶

One prototypical example of horizontal-lateral processing is that of traumatic memories in trauma recovery.

A variety of psychiatric disorders have been linked to trauma exposure, but mood and anxiety disorders are the most common.¹¹⁷ Brain imaging techniques currently also provide a

window into both anatomical and functional connectivity during emotional-cognitive tasks, recall and symptom activation in trauma patients.⁷ Yet neurologically, as explored by neuroimaging, it is not possible to pinpoint to a single neural network characteristic for memories accrued during trauma.⁸

These contributions support a horizontal type of processing. During a traumatic event, the release of high levels of catecholamines (with their memory consolidating properties) leads to a rapid fixation of traumatic memories and characteristic activation of the right hemisphere on brain imaging.¹¹⁸ Traumatic memories have features of right hemispheric manifestations: they are non-verbal memories and are accompanied by somatic symptoms. In an early experiment, patients with traumatic memories showed a right hemispheric dominance and right hemispheric activation during re-experiencing of traumatic memories triggered by means of script driven techniques.¹¹⁹ Following treatment with eye movement desensitization reprocessing (EMDR) psychotherapy, the left anterior cingulate became activated, detecting discrepancies and conflict.^{120,121} In this case, the anterior cingulate may facilitate the resolution of conflict and discrepancies regarding the trauma.^{122,123} By means of the inter-hemispherical (transcallosal) transfer, information reaches the speech center, which exerts its role in awareness formation. Speech, through words designs meaning to objects. It decreases emotional charge by diminishing the *incomprehensible* and unpredictable aspects of the environment. It also provides awareness of place and time, and therefore an understanding that the memories of the traumas are not occurring in the present but are events of the past. This in itself has a *decathecting* and emotionally modulating effect.¹²⁴ As was recognized by Freud,¹²⁵ language has multiple mental modalities (including visual, auditory, kinesthetic, and motor) with complex implications. Loss of any speech function usually affects thought process. For instance, patients with Wernicke's aphasia who have loss of the auditory modality of language may describe an *inability to think*.¹²⁶ On the other hand, psychotherapies focused on language and writing facilitate processing and mastery of the environment, as empirically demonstrated by the writing therapy experience of Pennebaker.¹²⁷⁻¹³⁰

The language brain is closely involved in the processing of new information during psychotherapy. Comprehension of language activates Heschl's gyrus or the bilateral superior temporal gyrus (the primary auditory cortex) for initial phonological processing, the bilateral posterior inferior and middle temporal gyri for semantic processing and the left posterior frontal lobe and the temporoparietal area for mapping sounds into articulatory representa-

tions.^{131,132} Speech produced in accord with the therapist's interpretation would recruit the areas of speech production: the left middle temporal gyrus activates in selection of phrases and lemmata. The left posterior middle temporal gyrus, the posterior superior temporal gyrus activate for phonological code retrieval. The left posterior inferior frontal gyrus is activated for syllabification. The bilateral sensorimotor and supplementary motor areas is activated for articulation. Finally, the bilateral superior temporal gyrus is activated for self-monitoring of speech.¹³³ Over the past years, an extensive literature on lexical tone and pitch has emerged pointing to varied bilateral activations in frontal and temporal areas.¹³⁴⁻¹⁴³ When adding the posterior superior occipital areas activated for visualization and comprehension of writing, *asemi-circle around the brain* is activated by such a complex function as verbal communication. One can observe that speech in an interactional context involves extended bilateral areas that create a *beltway of communication* around the entire brain and not just limited to the classical speech anatomy of Broca and Wernicke. This beltway around the brain further supports the anatomical basis of speech as a main agent of processing and conscious emergence of both new (from exterior) and previously stored (from semantic and even operational memory storage) information. This recontextualization of present and past is the mainstay of transprocessing during psychotherapy.

In the same vein, the split-brain experience has demonstrated that in the absence of adequate inter-hemispheric anatomical pathways, processing is impaired, and awareness for emotions is limited. In alexythymia, a concept introduced by Sifneos for patients that are poor responders to psychoanalytical treatment, and likened to a functional commissurotomy, patients have a poor ability to fantasize, report no or few dreams, present somatization, and have difficulties finding adequate words for the descriptions of feelings.¹⁴⁴

Alexythymia is a concept first introduced by psychoanalysts and later became the subject of interest in general psychiatry and psychosomatic medicine.¹⁴⁵ It has offered a neuroanatomical understanding for poor integration of emotions and somatic expression in some individuals.¹⁴⁵ It was first linked to trauma in veterans with PTSD as a protective mechanisms that helps evade the pain of trauma.^{146,147} This *functional* feature after trauma and its similarities to the split brain makes it an important contribution in the understanding of brain processing of emotions.

The significant role of the inter-hemispheric white matter in facilitating emotional processing and awareness is also suggested by findings related to childhood trauma often associated with a protective block in aware-

ness and a deficit in emotional processing. Such trauma is associated with a *reduction* of the inter-hemispheric white matter as follows: 17% reduction compared to controls, 11% reduction compared to psychiatric patients and 15-18% reduction in the specific segments of the corpus callosum region. Of particular significance is the fact that sexual abuse in girls is the strongest associated with a reduced corpus callosum.^{148,149} Such anatomical reduction may stem from a lack of use of inter-hemispheric white matter from a partial closing of inter-hemispheric connectivity channels during periods of brain development.

Alexythymia has also been associated with limited creativity.¹⁴⁵ Conversely, creativity has been associated with inter-hemispheric synchrony.¹⁵⁰ Trauma may also induce alexythymia in some trauma survivors.¹⁴⁷ On the other hand, transcendental meditation, has been shown to enhance creativity, well-being and access to emotions.^{151,152} Transcendental meditation is also known to induce hemispheric functional symmetry on EEG,¹⁵¹ a state opposite to alexythymia or a split-brain condition. Regarding the split-brain (secondary to commissurotomy), it would be erroneous to assume that repression and alexythymia are due to a malfunctioning of the corpus callosum *per se*.¹⁵³ Instead, it is a lack of hemispheric connectivity from discrepancies in hemispheric signals that lead secondarily to a functional midline split. In this sense, alexythymia, like repression and posttraumatic stress are accompanied by hemispheric dysynchrony and right hemispheric dominance on EEG. In summary, under normal conditions, brain activity is characterized by relative hemispheric synchrony with a slight left dominance, probably due to speech areas activity. States like alexythymia, repression, lack of creative expression and posttraumatic stress disorder are accompanied by right hemispheric dominance. States like, psychotherapy, meditation, EMDR and creative expression states are accompanied by enhanced brain synchrony.

Intrahemispheric, longitudinal horizontal processing

Intrahemispheric horizontal processing occurs within the ventro-dorsal and lateral axes of the same hemisphere and includes a coordination process between multimodal sensory and sensory-motor areas. The brain develops multiple routes of anatomic connectivity that facilitate interactions between the projection areas of the five senses. Large white matter structures like the inferior occipito-frontal fasciculus and the inferior longitudinal fasciculus provide a sizeable *information highway*.

Speech center in emotional and cognitive processing

Given the particular importance of the

speech center in emotional and cognitive processing, one recent experiment demonstrates the involvement of left inferior occipital and longitudinal fasciculi in the facilitation of speech functions. By using intraoperative electrical stimulation in 12 patients who underwent resections for low-grade gliomas under local anesthesia, Mandonnet *et al.*¹⁵⁴ induced semantic paraphasias in seven patients by stimulating the inferior occipito-frontal fascicle and non-semantic paraphasias by stimulating the nearby arcuate fascicle. The resection of a part of the inferior longitudinal fasciculus resulted in transient speech abnormalities only. To clarify, the left subcortical white matter network that subserves language semantics consists of the left inferior occipito-frontal fasciculus, the left inferior longitudinal fasciculus and the uncinat fasciculus, which connects the anterior temporal pole to the fronto-basal area. The author's findings suggest that the semantic ventral stream is constituted by two parallel pathways within the left dominant temporal lobe: a direct pathway, which is crucial in language semantic processing; an indirect pathway, which includes the inferior longitudinal fasciculus, which is not indispensable since its resection results in a speech deficit that is transient. Evolutionarily, such an extended network may suggest extensive functional reserve available in recovery processes.

Catani *et al.*,¹⁵⁵ by using diffusion-tension MRI-obtained tractography of the human brain, point out the discrepancy between the classical description of the inferior longitudinal fasciculus (ILF) (as fibers connecting the occipital and anterior temporal cortex), and results of DT MRI. DT shows that the connections of the two areas are indirect: the occipito-temporal fibers are U-shaped association fibers. ILF includes: i) a major associative connection provided by a fiber bundle which are consistent with the classical ILF, connecting occipital and anterior temporal lobes; ii) ILF is distinct from the optic radiations and from U-shaped fibers connecting adjacent gyri; iii) ILF arises in extrastriate visual association areas; iv) ILF also projects to lateral and medial anterior temporal regions. The latter mediates the fast transfer of visual signals to anterior temporal areas and provides neuromodulatory back-projections from the amygdala to early visual areas.

Seen in the context of the earlier described complexity of language integration over large areas bilaterally within the language *beltway*, the white matter network provides an extensive association between the language brain and the deeper brain structures involved in modulation, including structures of the cortical-subcortical-midline structures (CSMS).

Anterior/motor brain structures

Anterior/motor brain structures have a major

role in emotional processing and control and the constancy of personality, a fact supported by the major affective and personality disruptions in individuals with frontal lobe damage with lesions comparable in size with posterior sensory brain areas.^{3,156-158} Further, animal studies have also shown a direct *cerebellar* input from numerous anatomical structures: the prefrontal cortex, the posterior parietal cortex, the superior temporal cortex, the cingulum, the parahippocampus and the hypothalamus. This implies a significant role of the cerebellum in affect and cognition,¹⁵⁹ which is accomplished through the dense network of white matter fasciculi. Allen *et al.*¹⁶⁰ demonstrated functional connectivity between cerebellar-parietal and cerebellar-prefrontal areas, that is, a coherence between different cerebellar structures and brain regions involved in cognitive/affective processing. In particular, a significant correlation of signals between the dentate nucleus of the cerebellum and frontal and parietal regions, in particular the dorsolateral prefrontal cortex, was found. The authors also demonstrated correlations of signals between the dentate nucleus of the cerebellum and other cerebellar, thalamic, limbic and striatal areas, all participants in emotional processing.

Anatomical variants

White matter diffusion through diffusion-tension imaging, can reveal individual anatomical variants that participate in processing throughout brain development. This is an example of the anatomical principal that *neurons that fire together wire together*.¹⁶¹ In a study by Huang *et al.*¹⁶² the developmental schedule of different white and gray matter structures was studied in a 19-week fetus, at birth and at 5-6 years of age. The authors reported some structures to develop earlier, during fetal development, while others lag behind in development. In the fetal brain, the cerebellar peduncles and the medial lemnisci are smaller, and the descending tracts are larger compared to the brain of the newborn and the brain of the 5/6-year-old child. Major white matter structures, like the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus, are rather undeveloped in the 19-week-old fetus, suggesting a more prominent function in higher cognitive and emotional processing after birth. In the 19-week fetus, the cingulum and the fornix are well developed, while the corpus callosum is developed mainly in the frontal portion, suggesting a progressive development of the corpus callosum from the anterior toward the posterior region.

These preliminary findings confirm a biological principle of economic development that allows for a gradual introduction of gray and white matter structures: a gross neuroendocrine system is significantly developed at birth to sustain the impact of birth stress on

the infant,¹⁶³ early motor functions and emotional interactions, while the massive long-distant white matter structures (like the longitudinal fasciculus) mature later in connection with the development of evolved cognitive emotional processing. The latter may also show greater experience-dependent individual variability.

Neuro-plasticity systems

This refers to experiential remapping of brain projections and pathway rerouting. There is significant experiential learning and memory reworking that occurs during the course of psychotherapy. These are akin to long-term exposure to novel social situations, and the implicated adaptation triggers learning processes.¹⁶⁴ Experiential learning results in the remapping of brain projection.¹⁶⁵ The neural substrate of experiential learning includes: i) dendrite rebranching; ii) hippocampal learning and neurogenesis; iii) synaptic processes.

Dendritic rebranching

Dendritic rebranching is at the base for remapping of brain projections. The dendritic tree has been demonstrated to exhibit rapid and early (within minutes) directional changes as a response to modifications in the immediate biochemical environment. Early dendritic arborization is an elaborate process that occurs during development, which is in part influenced by activity. The specificity of dendritic connections at maturity is determined both early in development, by biochemical laminar cues and by later neuronal activity.¹⁶⁶⁻¹⁷⁰

Hippocampal learning

The hippocampus mediates episodic memory, the retaining of information within a context of time and place. A series of papers have covered the more intimate functioning of different hippocampal regions.¹⁷¹⁻¹⁷⁶ The hip-

poampus is one of the main sites of neurogenesis.

During psychotherapy, specific steps in memory function include the participation of the hippocampal areas CA1 and CA3: auto-association which participates in error correction; cued sequence recall and comparison with information from the cortex; transitive inference, the correct identification of different items based on prior learning. More recently a large body of literature on the difference between memory consolidation and reconsolidation has emerged.^{177,178}

Neurogenesis

Neurogenesis is among the most commonly cited discoveries that have fundamentally changed the understanding of memory and learning.¹⁷⁹⁻¹⁸⁴ Neurogenesis is keenly sensitive to environmental changes (Table 1) and also constitutes an important component of brain plasticity.¹⁸⁵ However, only some experiences have been associated with activation of neurogenesis.¹⁸⁶⁻¹⁸⁹

Psychotherapy creates new multimodal memories through simultaneous activation of cognitive, emotional and behavioral (motivational) experiences. In this regard, psychotherapy resembles early childhood learning when neurogenesis is particularly active. Like in early childhood when learning is interwoven with the pool of early neuron formation leading to a *sculpting* effect of the developing brain,¹⁴⁸ psychotherapy may create a partial reframing of brain connectivity.¹⁹⁰ Such new connectivity may create associations with implicit value similar to memories of early infancy that are not accessible yet continue to implicitly shape actions and personality.¹⁵³ In parallel, they have the potential for neuronal repair.¹⁹¹

Synaptic processes

The synapse provides an extremely wide range of neural activity modulation which participates in learning and implicitly in human change.^{192,193}

Table 1. Adult neurogenesis.

Positive regulators	Negative regulators
Estrogen	Persistent emotional stress
Testosterone	Adrenal steroids like cortisol
A low stress environment	Sleep deprivation
Sleep	Alcohol abuse
Physical activity	Excitatory inputs mediated by N-methyl-D-aspartate (NMDA)
SSRI's	Limited learning opportunities and a relatively deprived environment
Mood stabilizing psychotropics/antiepileptics	Environmental complexity and intellectually enriched environments
Intellectual activity and learning	

Synaptic plasticity

Regarding the messenger system, each synapse contains two type of receptors: inotropic and metabotropic receptors. An inotropic receptor is activated by neurotransmitter molecules which are primary messengers. They open a channel that creates a brief communication between the extracellular and the intracellular environment. Metabotropic receptors secrete enzymes which create the second messengers. Second messengers regulate the activity of the postsynaptic membrane according to functional needs, by either increasing the electrical potential and/or increasing the number of receptors. Thus, a potential of great variability in synaptic response and long-term potential changes is created and provides the plasticity associated with memory and learning.¹⁹⁴

The processes of forming, strengthening and collateral pruning of synapses, further constitutes the basis of associability. Synaptic plasticity provides the ability of neural networks to combine information from new representations, which can later be retrieved.¹⁹⁵ Synaptic plasticity has also been examined in regards to memory traces, drives and defense mechanisms in the context of psychoanalytical growth of an individual and in endurance of long-term memory.¹⁹⁶ Thus, Si *et al.*,¹⁹⁷ summarizing previous contributions,^{198,199} hypothesized that cytoplasmic polyadenylation element binding protein (CPEB), a marker of mRNA activity in the protein synthesis of the neuron, mediates long-term memories. In the absence of CPEB, no memory was formed in the synapse of the aplasia. The amino acid sequence of CPEB includes repetition in glutamine. Its structure provides an unusual resiliency for long-term survival that is necessary for long-term memory functions. Its amino acid sequence was compared to that of a prion,²⁰⁰ hence its ability to survive the long-term variation in the biochemical environment of the brain. Recent contribution further clarify the links between synaptic/molecular processes and aspects of long-term memory.^{172,201}

Long-term potentiation

Memory is initially unstable, and over the course of about 30 minutes it becomes increasingly resistant to interference. This is explained by the fact that long term potentiation (LTP) is accompanied by changes in dendritic spine probably due to cytoskeletal changes. The process is accompanied by the polymerization of the protein actin in spine heads. The new cytoskeletal organization, and thus the new spine morphology, characterizes the initial phase of LTP consolidation. A variety of proteins and signaling cascades modulate LTP.²⁰²

LTP induces protein synthesis, synaptic

reshaping and spine modification in the hippocampus. Patterned electrical stimulation results in postsynaptic depolarization and LTP, which is not automatically induced by the patterns of electrical stimulation through prolongation of NMDA activity.²⁰³ A variety of molecules have been shown to modulate LTP. Ampakines increase excitatory monosynaptic responses in the brain. They improve communication in complex networks and thus facilitate LTP and induce the expression of neurotrophic factors.²⁰⁴ Ampakines elevate BDNF in the rat hippocampus and BDNF promotes long-term potentiation-related cytoskeletal changes in the adult hippocampus.^{205,206}

In conclusion, the adult makes use of an extraordinary network of fibers and synapses, some permanent and parallel, others neuroplastic and experience dependent, which participate in reinterpretation of complex memories, not unlike the systems proposed by Freud and later by Pribram.^{124,207}

Transduction

Transduction refers to a biological process at the cellular level by which external stimuli produce cellular changes which result in a change in the cell's functional output. For instance, if repeated stimulation of a specific cell results in the change of a secreted enzyme, that process is a form of transduction. Most of the time, external events result in a modification of effector genes, which results in changes in protein synthesis, which in turn modifies cell functions. An example here is the manner in which exposure to external stress leads to a signal change in the effector genes of the hypothalamus, which leads to the increased output of CRF, a neurohormone. CRF travels through the hypothalamo-pituitary axis to the pituitary gland and triggers, through positive feedback, the secretion of ACTH. In turn, ACTH will stimulate the adrenal glands into the increased production and release of cortisol, into the bloodstream. Stress and exposure to trauma is transduced into the effector genes of the neurons and could, in the long run, result in sizable changes in metabolism but also in clear bodily changes (obesity, diabetes). By means of transduction, retinal changes in the cones and rod neurons translate their functions into neuronal activity. These are ATP-energy dependent mechanisms.^{208,209} All other senses have similar transduction systems by which the auditory, gustatory, olfactory and tactile environment are transduced into virtual models of the outside world at the cortical level.^{209,210} All long-term cellular changes induced by external events like psychotherapy include transduction. Since psychotherapy includes a further-

ing of individual development,²¹¹ all processes of development and maturation may be activated during psychotherapy: neuropeptide activation (oxytocin, vasopressin, substance P, endogenous opioids), and neurotransmitter activation in bonding and attachment, neuro-mirroring during empathic processes and strong right lateralized representations as in early attachment.^{12,13,212-216}

The transprocessing model and the brain

Humans have the natural ability to interpret and reframe awareness of the present moment in the context of past experiences, while at the same time, retrieved memories, the remembering of the past, is incessantly remodeled in the context of present states of mind. This reworking of memories by means of reconsolidation stays at the foundation of one's capabilities for change. In contrast, the proposed mechanism of *transprocessing* occurs in psychotherapy and thus carries with it, directly guided transformation. Besides the inclusion of reconsolidation, transprocessing contains a controlled processing of the past and a targeted learning process with acquisition of new adaptive abilities and often a new world view. Thus, transprocessing (referring to both processing and transduction) in psychotherapy is part of a universal human biological potential of adaptive change and survival. We are proposing the following stages of transprocessing.

Stage I: the evaluation phase

Through its white matter bundles, information is constantly captured from the periphery and channeled according to each sensory modality or motor functions to specialized areas of the cortex. In the course of a psychotherapy session, the new information signals intersect signals of pre-existing implicit memories. Behavioral patterns and complex memories are multimodal memories. The pre-existing personal behavioral patterns of implicit memories define an individual before the onset of psychotherapy and have their origins in an individual's ontogeny. Simultaneously, from the brain stem, continuously generated activation, representing proto-emotions are produced as a lifeline that maintains a basic drive to live. These proto-emotions are PANIC, FEAR, CARE, PLAY LUST, etc. and are generated in the PAG and other areas of the reticular activation system. Bailey & Davis (1942, 1943) demonstrated that lesions of these areas cause slow death in experimental animals pointing to their vital significance.^{217,218} These neural signals generated as a continuous lifeline reach higher sub-cortical and cortical areas, including areas specialized in different senso-

ry modalities which have direct access to stored implicit memories. Thus, an intersection between the proto-emotions, from the ancient reticular activating system and implicit memories (stemming from prior experiences) occurs. This intersection provides a personal context to the proto-emotions. In this evaluation phase of transprocessing, a conscious comparison at different levels occurs between internally generated signals of proto-emotions perceived as *needs* and the explicit memory pool, including memory about one's own behavioral patterns. Under circumstances of rest, the cortical subcortical midline system (CSMS), associated with functions of the self, is likely to provide a *top down* control over proto-emotions through its known default state of activation seen on brain imaging during rest.³⁶ The top down regulating of proto-emotions has a significant social function, promoting delayed personal gratifications and thus communal cooperation and survival.

Neurotic states, in particular emotional symptoms, may represent in some clinical cases an *escape* of one or several of the proto-emotions that exceed or escape the barrier of emotional regulation provided by the CSMS and probable other subcortical and cortical structures. The uncontrolled release of PANIC combined with blocked CARE/NURTURANCE may dominate in depression and anxiety disorders. Unmodulated SEEKING, LUST and PLAY may dominate, at least in part, manic episodes.

Stage II: the acquisition and self-reference phase

In an awake individual, information from the external world is sent to the thalamic nuclei and the amygdala and is further analyzed for discrepancies by the anterior cingulate. These pathways have been largely elucidated in the study of danger response and trauma.¹⁹³ Neural inputs from the five senses representing external events are initially emotion-neutral but are assigned an emotional valence by the OMPFC.¹⁹³ The assigned valence of threat may determine the degree of amygdala firing in the fight flight response.

During a psychotherapy session, different ego states are evoked: at rest, during free associations, the Benson relaxation response dominates with its hemispheric synchrony.²¹⁹⁻²²¹ At the same time, the language brain is stimulated in its entirety providing a *language beltway* of activation that extends into different segments of the temporo-frontal, parietal and occipital areas, bilaterally (during phonological and semantic stimulation, phonological code retrieval, articulation, self-monitoring of speech, lexical tone, pitch, articulation and concomitant visualization of expressed material).²²² Interactive use of language (like during psychotherapy) creates a bilateral fronto-temporo-occipital shell of activation which may

replace the default activation state of the cortical subcortical midline structures (CSMS) during mental rest. This process may also explain the role of language in mood and behavioral regulation. Contrary to the classical description of the left hemispheric language areas (in right-handedness) recent studies revealed a very extensive brain activation during language use amounting to a *language belt* of brain activation that surrounds the horizontal convexity of the brain.¹³¹⁻¹⁴³

Newly acquired insights are also multimodal memories that can be stored through new dendritic and synaptic modifications as well as reconfiguration of the white matter.¹⁶⁵ Through such neuroplastic changes, associations are expanded. Conversely, the loss of white matter from vascular lesions, visualized on MRI as white matter *hyperintensity*, resulted in loss of mood regulation as seen in syndromes of vascular depression.²²³

The newly formed memories and states of mind may act as extinguishers by overriding older, maladaptive multimodal memories (extinction is not erasing).^{224,225} The old information is still stored and could be reactivated during states of regression, a fact demonstrated by clinical experience.¹⁶³ The emerging self-awareness in psychotherapy, a THIRD person meaning or *observing ego* quality is also stored as a new multi-modal memory. Psychotherapy is not a linear process. The back and forth interactive process may be punctuated by regressive states which routinely release old emotions from time-trapped multimodal memories. With time and repetition, cytoskeletal modifications and transduction at the cellular level eventually consolidate the changes.^{202,209} At the point where one is able to maintain such multimodal memories and their newer meanings within the working memory, one learning cycle has been completed. This is a new memory acquisition, distinct from reconsolidation.¹⁷¹

In this stage, awareness or the *know how* about neurotic experiences is transformed from a third person experiential memory, which is an objectified experience, (*It did happen there to me, this is me*) into a first person experience (*Me*). This is a major transfer process viewed as a change in aspects of consciousness.

The ME experience of *ownership* or self-reference is backed by new midline structure activation.⁵² Through the continuous Me (or first-person) experience in psychotherapy, such structural activations become more routinely accessed. This reinforcement process eventually becomes the main established activation, the basis of a newly acquired aspect of the self. Psychological awareness of new aspects of the self is correlated with language brain activation.¹²³ However, from a neurobiological perspective, perception of *ownership* or self-refer-

ence is likely to include a multi-stage mechanism. It may include the participation of the mirroring system of the patient rather than the therapist, as ownership/self-reference may emulate the developmental stages of the self during infancy. Given that the mirror neurons are a system of specialized cells, psychotherapy like normal self-development, by way of practicing, may lead to further specialization and differentiation of these cells. The intersubjective nature of psychotherapy is a vehicle for ownership/self-reference of one's past Self and the transformation into a new, present Self.

Stage III: the re-consolidation phase

New experiences are reworked through reconsolidation,⁴ but the modified connectivity of the self-related midline structures (the CSMS) become the new global point of reference for future learning and association. New *implicit* memories and their associations may, through re-entrance,¹¹¹ influence explicit memories and the decision-making process. Changes produced by psychotherapy become new skills. Most likely, both new memories and reconsolidation,^{6,171,201} participate in this process. Like many highly practiced skills, as their execution becomes automatic, the brain projections undergo a mutation from occupying initially a larger, predominantly cortical projection, to a limited participation of mainly subcortical and cerebellar structures. Such a shift has been demonstrated in instances where skills were practiced at length.²²⁶ Schore hypothesized over a decade ago about the occurrence of literal anatomical pathway changes throughout the psychotherapeutic process.^{11,13,227} These in turn become backed by intracellular processes referred to here as transduction. Transduction is followed by changes in cellular functions. In the long run, epigenetics may further stabilize the qualitative transformation achieved through long-term psychotherapy. For instance, epigenetic changes secondary to an individual's experience have been reported in prolonged trauma and in the intrafamilial and intergenerational transfer of trauma.^{228,229} *Vice-versa*, in long-term psychotherapy, a reverse process to traumatic changes may be achieved by epigenetics. Ultimately, new, modified cell functions and neural networks are necessary to back long-term behavioral and personality changes characteristic for a modified self through long-term psychotherapy.

Summary and future directions of inquiry

We have reviewed a large body of literature

that suggests the participation of numerous anatomical structures at play in cognitive-affective-behavioral changes achieved in psychotherapy. In the future, research of transprocessing will have to map individual timing of processing and define early (the *functional*) and intermediate stages in new network formation. In the not so far future, the co-administration of very targeted molecules and/or stem cell repopulation of certain circuits (techniques that are already considered in the treatment of some neurological disorders) could create a new *enhanced* neuro-psychotherapeutic technique. This would replace the currently largely non-specific co-administration of psychotherapy and medications. Then, a future classification into professional *Neuropsychotherapy* (or analysis) and *Enhanced Neuropsychotherapy* would cover the treatment of the entire spectrum of psychiatric and psychological afflictions. Such progress could provide psychotherapy a prominent status among developing *brain treatments* in neuroscience.

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