Neuroanalysis

A Unifying Theory for the Future of Psychiatry

Abraham Peled M.D.

Second Edition

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INTRODUCTIONS

Author's Preface

As early as 1990, the year I began my residency, it was clear to me that psychiatry has a descriptive diagnostic system (signs and symptoms) because there is no etiology (known causes) of psychiatric disorders. Even though we were taught that mental disorders are disorders of the brain, this idea is not evident in our conceptualization of mental disorders. Terms like "depression" and "anxiety" are not brain-related, as are "encephalitis" and "CVA," terms that include the brain in their taxonomy.

I found it intriguing that the lack of conceptualization of mental-disorders as brain-disorders correlates with the difficulty in discovering their causes. If the causes of mental disorders were known, we could have a brain-based psychiatric diagnosis. My train of thought about this challenge was straightforward, and remains so today. The brain is a physical complex non-linear-system, i.e., composed of billions of units (neurons) interacting in non-linear ways (i.e., there are no one-to-one relationships between their inputs and outputs). As such the brain obeys the laws of nonlinear complex-systems, that of optimization of randomness and orderliness.

This means that psychiatrists should be educated in the physics of complex nonlinear systems, and it also means that mental disorders must reflect disturbances of optimal complex-systems organizations. It is immediately apparent to any clinician in psychiatry that the nature and course of mental disorders obey phase-transition and saturation effects. For example crises-dynamics and trigger-effects are typical nonlinear effects where a small increase in the input (e.g., stress) can generate a large effect in the output (e.g., symptomatic manifestations of crises). Saturation effect is often found in medication-responses when improved reaction to treatment halts even when dosage is increased. In addition, the response to medication can be highly nonlinear as small changes in dosage can result in large abrupt changes in the phenomenology of disorders.

The more I thought of a complex-system approach to mental-disorders; the general notion that came to mind was that symptomless individuals have brains that optimize their functions while mental disorders are the result of disturbances to optimal brain organization. Since different mental disorders show different patterns of phenomenology, they probably reflect different "types" of "breakdowns" of optimal brain organization. The complex system approach also clears some immediate questions about the endogenic versus exogenic origins of mental disorders, as both internal as well as external alterations affect a complex-system interacting with its environment.

The next obvious step on this roadmap is to investigate the brain system in depth, especially its organization level. In the beginning of the 1990s, as is also common today, psychiatrists had the tendency to investigate the brain at the molecular level of genes and neurotransmitters. I was convinced that this is not the correct level of investigation because 1) it did not prove itself, because there was no advancement in understanding how molecules change the mental functions such as mood and consciousness. 2) It seemed to me that there is a large explanatory gap when relating

molecular-levels to mental-levels with no consideration of the billions of neurons at the neuronal network level of the brain. 3) The idea of "Emergent Properties" (the whole is more than the sum of elements) of mental functions that arises from whole-brain organization supported investigating neuronal-network organization of the entire brain. Mental functions important for psychiatry such as personality and mood do not characterize a single neuron, or even millions of neurons, but they do arise from whole brain integration.

At a time when most psychiatrists did not even think of investigating mental-disorders as disturbances to neuronal-network complex-systems using mathematical modeling and physics-related conceptualization, I set out to educate myself in these fields determined to reformulate mental-disorders within the framework of brain-physics of complex-systems.

Whenever I hear the song "Englishman in New York" it reminds me of the days when I was a "Psychiatrist in Computer Engineering". I definitely seemed out of place, the engineering people were intrigued by my presence, as they never had a psychiatrist wandering in their corridors, and my colleagues the psychiatrists were amazed by the computer engineering direction I took which was very odd for them, even threatening, I may say, as any new approach could be.

First, I was lucky to get both the guidance and the collaboration needed to build my first neuronal network models for the phenomenology of mental disorders. The first model involved simulating thought-processes and disorders using a fully connected Hopfield attractor network with dynamic threshold and asymmetric connections (Geva & Peled 2000). The next model involved a layered architecture supervised-learning network, simulating interpretations of Rorschach 3rd blot by schizophrenia patients (Peled & Geva 2000).

Learning to program neuronal network models in those days, using MatLab Version 2 and later going into signal processing of brain-imaging during my post-doc at UC Davis in 1996, really boosted my knowhow in the field of the physical complex brain.

As years went by, the literature in these fields of science multiplied and new terminologies emerged. For example: modeling brain functions is now called "Computational Neuroscience"; the study of the brain at the network-level is now called the "Connectome". Throughout the years, I have followed the literature and periodically would try to relate it to the translation of mental disorders into brain disorders. I have also tried to call the field "Neuroanalysis." This term was coined under the influence of a book by the eminent 19th century Viennese neurologist and psychiatrist, Theodor Meynert. He stated that the term "Psych" is non-scientific and should be avoided, accordingly (Meynert 1884) I have converted the term "Psych" from "Psychoanalysis" substituting it with "Neuro", to become 'Neuroanalysis.' I wrote a book called Neuroanalysis and founded a website dedicated to Neuroanalysis as the theoretical framework for brain-related psychiatric diagnosis (http://neuroanalysis.org.il/). In parallel, the literature of neuronal network modeling expanded and is currently called "Computational Psychiatry", in line with the terminology of Computational Neuroscience.

Despite the advances in this field of investigation, awareness of "Neuroanalysis" or "Computational Psychiatry" among psychiatrists is still lacking. In the effort to introduce such awareness into the clinical practice, a hypothetical-based taxonomy was constructed based on the literature of computational psychiatry and titled "Clinical Brain Profiling." Published in theoretical journals (Peled 1999; 200; 2004; 2005; 2006; 2009; 2010; 2010; 2012; 2013; 2014) and applied to a computerized diagnostic platform (http://www.brainprofiler.com/) Clinical Brain Profiling dares translate mental disorders into brain disorders. This manuscript is a step further in this attempt and a second update improved edition of Neuroanalysis.

Introduction

Psychiatry is facing the major challenge of etiological diagnosis. This is the ultimate challenge because it entails discovering the causes of mental disorders. Currently, because the causes of mental disorders are unknown, psychiatry has to make-do with a descriptive diagnostic approach that relies on symptoms (complaints) and signs (observations) of patients. Even though a majority of clinicians agrees that the brain is the organ of mental disorders, there is not even one disease in psychiatry that includes the brain taxonomically. An etiological diagnosis taxonomically involves a place in the body such as the appendix and the description of its pathology, e.g. appendicitis is the infection (the pathology) of that organ. A descriptive diagnosis has no such definition, "Depression" "Anxiety" do not entail a location in the body and do not define any pathology. Not knowing t the causes of psychiatric disorders has serious consequences on treatment. *You cannot fix a system if you do not know what is wrong with it.* Thus, it is absolutely critical that we psychiatrists discover the causes of mental disorders if we ever want to cure them.

Any discovery begins with a hypothesis; generating a set of testable-predictions about the brain-related pathology of mental disorders is a first necessary step. The second question to ask is, Do we have enough neuroscientific knowledge to formulate a reasonable set of testable hypotheses for brain-related mental disorders? Finally, we ask, is the neuroscientific knowledge accumulated so far, enough for a transformative (and translational) conceptualization of mental disorders into brain-disorders? In other words, is there enough evidence-based scientific literature to generate a preliminary etiological brain-related diagnosis for psychiatry?

An old Chinese adage states that "Wisdom begins by calling things by their correct names" meaning that unless we start reformulating mental-disorders as brain-disorders we shall not be medically wise in psychiatry. This is because today we are locked in a **vicious cycle**, where we do not have brain-related taxonomy for mental disorders because these have not been proven in research, thus we continue to use descriptive non-brain-related taxonomy, that impedes any advancement in discovery because it is not brain-oriented, and so on. To summarize; no testable formulation for discovery, no discovery, and no discovery causes us to stay with descriptive taxonomy, which in turn, does not allow for testable conceptualizations.

In light of these insights, the challenge of reformulating mental-disorders as brain-related disorders becomes critical to the extent that some degree of speculation is tolerated, in the service of breaking loose from the vicious-cycle halting any progress in psychiatry. Even though highly speculative, it is necessary to make the effort and attempt a novel brain conceptualization for psychiatric diagnosis, this should adhere as much as possible to the scientific literature accumulated to date.

Based on computational neuroscience, complex-systems-physics and the science of neuronal networks, an attempt for a preliminary brain-based psychiatry is made in this manuscript. The future diagnosis of mental disorders is presumed to involve neuronal network plasticity. Specifically, mental disorders result from alterations and "breakdown" in the plasticity dynamics

of neuronal network whole brain organization. Disturbances to the optimal (symptomless) brain-organization cause mental disorders; these are detailed in this manuscript and used to generate the future brain-based diagnosis for psychiatry.

BACKGROUND

Networks, synchronization (fast Plasticity) State-space, consciousness,

Neural network models are simplified simulations of biological neural networks spread in the brain. Units in the model are simplified representations of neurons (with input summation and threshold dependent output). The units are richly interconnected to resemble the massive synaptic connectivity found in neural tissue. These models abstract from the complexity of individual neurons and the patterns of connectivity in exchange for analytic tractability. Independent of their use as brain models, they are being investigated as prototypes of new computer architectures. Some of the lessons learned from these models can be applied to the brain and to psychological phenomena (Rumelhart 1986).

One of the relevant models is the class of feed-forward layered network with added feedback connections. In the feed-forward layered network architecture, information is coded as a pattern of activity in an input layer of the model neurons and is transformed by successive layers receiving converging synaptic inputs from preceding layers. Added feedback connections transform the architecture of the network to a fully interconnected structure also named for its inventor, the Hopfield network. In the Hopfield model, 'learning' is achieved by adjusting (strengthening) connections between the units to strengthen certain activation patterns in the model (Hopfield 1982). Strengthening connections simulates synaptic plasticity and the Hebbian algorithm in the model allocates higher activity to the units that are more strongly connected. Input is presented to the model in a form of an initial pattern of unit activation distributed over all of the units. The units in the model are then left to interact with each other. Due to the predetermined strengthening of connections the model "tends" to activate the pattern which is closest in configuration to the input pattern.

The distance between the input pattern and the activated pattern is measured in terms of "hamming distance" which reflects the number of units with different activation values between the two patterns. In this manner, the Hopfield model achieves a computation of content addressable memory activation. The pattern strengthened by connection encodes the memory, just as Hebbian dynamics probably determines learning in actual brains, and the input activates the relevant associated (nearest in hamming distance) memory, just as one memory is associated with its relevant correlated memory. The content addressable computation has been successfully applied to pattern recognition extraction and detection of visual and other stimuli, thus simulating brain perception and perception-dependent memory activation (Rumelhart 1986).

Historically brain activity was formalized using a localised approach of brain centers, defining specific functions for segregated neuronal regions. Later the integrated approach argued against localized functions and evoked a non-localized approach of spread activation and functional connectivity across vast cortical regions.

Today, it is recognized that nervous systems facing complex environments must balance two seemingly opposing requirements. The need to quickly and reliably extract important features from sensory inputs and the need to generate coherent perceptual and cognitive states allowing an organism to respond to objects and events, which present a combination of numerous individual features. The need to quickly and reliably extract important sensory features is accomplished by functionally segregated (specialized) sets of neurons (e.g., those found in different cortical regions), the need to generate coherent perceptual and cognitive states is accomplished by functional integration of the activities of specialized neurons via dynamic interactions (Tononi and Edelman 2000).

The mathematical concept of "neural complexity" (C_N) (Tononi et al. 1994) captures the important interplay between integration (i.e., functional connectivity) and segregation (i.e., functional specialization of distinct neural subsystems). C_N is low for systems whose components are characterized either by total independence or by total dependence. C_N is high for systems whose components show simultaneous evidence of independence in small subsets, and increasing dependence in subsets of increasing size. Different neural groups are functionally segregated if their activities tend to be statistically independent. Conversely, groups are functionally integrated if they show a high degree of statistical dependence.

Functional segregation within a neural system is expressed in terms of the relative statistical independence of small subsets of the system, while functional integration is expressed in terms of significant deviations from this statistical independence (Tononi et al 1994).

One general characteristic of high mental functions is their capacity to flexibly adapt to the necessary information processing mechanisms. For example, working memory tasks involve shifting paradigms, the examined subject is required to choose from a set of stimuli (cards) according to a guiding rule (the color, shape, or a specific number of stimuli). The choice is based on the feedback of "correct" or "incorrect" from the examiner. After a certain number of stimuli is presented to the subject, the examiner shifts categories and the subject is required to change (adapt to) and choose according to the new rule. Adaptive performance is measured as the capacity to flexibly process the changing conditions in the task environment.

For a system to adapt to the environment it must master a degree of flexibility to change according to the demands of the environment (Ditto and Pecora 1993). If the system is rigid and unchangeable, it will not have the ability to modify according to altered environmental conditions. If a certain degree of randomness is introduced to the system, then the system is more susceptible to change and will modify according to the changes in the environment. Once change occurs in the system, it needs to be maintained over time for as long as it serves its adaptive function. If the system is totally random (changes continuously), modifications cannot be maintained for long periods. The system, therefore, needs a certain degree of order that will maintain the acquired change.

It is clear that for optimal adaptability, the system must balance orderliness and randomness in its interaction with the environment. In neuronal terms, randomness involves segregation because segregated neuronal systems will act independently of each other demonstrating non-organized, random activity. Orderliness in neuronal terms involves integration because each neural system constrains the activity of its other related systems via integrative functional connections.

In order to adapt to the shifting paradigms required by high mental functions such as working memory it is likely that brain function requires integrative as well as segregative capabilities. As explained above, the balance between integrative and segregative functions in the brain is achieved when neural complexity is optimal.

As early as 1881, Wernicke regarded the cerebral cortex as constituting, in its anatomical arrangement of fibers and cells, the organ of association (Wernike 1881). Wernike perceived a hierarchy of an even more complex arrangement of reflexes in the brain. With this formulation he preceded later insights of brain organizations achieved by studying sensory and motor brain functions.

According to Fuster (1997) there is a hierarchy of perceptual memories that ranges from the sensorial concrete to the conceptually general (Fuster 1997). Information regarding elementary sensations resides at the bottom of the hierarchy. The abstract concepts that, although originally acquired by sensory experience, have gained independence in cognitive operations are at the top (Fuster 1995). This information process is most likely to develop, at least partially, by self-organization from the bottom up, that is, from sensory cortical areas towards areas of association. Memory networks, therefore, appear to be formed in the cortex by such processes as synchronous convergence and self-organization.

In the higher levels, the topography of information storage becomes obscure because of the wider distribution of memory networks, which link scattered domains of the association cortex, representing separate qualities that however disparate, have been associated by experience. Because these higher memories are more diffuse than simple sensory memories, they are in some respects more robust. Only massive cortical damage leads to the inability to retrieve and use conceptual knowledge, the “loss of abstract attitude” described by Kurt Goldstein (Fuster 1997).

Similar to sensory information, motor information concerning planning and deciding has also been hierarchically described. As first suggested by Hughlings Jackson (1969), the cortex of the frontal lobe computes the highest levels of motor information. The primary motor cortex is at the lowest cortical level and represents and mediates elementary motor performance. The prefrontal cortex, conventionally considered the association cortex of the frontal lobe, represents the highest level of the motor hierarchy (Jackson1969; Feinberg and Guazzelli 1999). This position signifies a role not only in the representation of complex actions (concepts of action, plans and programs) but also in their enactment, including the working memory (Goldman-Rakic 1987).

The prefrontal cortex develops late, both phylogenetically and ontogenetically, and receives fiber connections from numerous subcortical structures, as well as from other areas of the neocortex (Perecman 1987; Weinberger 1987). This extensive connectivity links reciprocally the perceptual and conceptual information networks of the posterior cortex with prefrontal motor networks, thus forming perceptual-motor associations at the highest level (Fuster 1997).

Mesulam (1998) reviewed brain organization leading from sensation to cognition. Unimodal association areas make part of the lower hierarchical organization; they encode basic features of sensation such as color, motion, and form. They process sensory experience such as objects, faces, word forms, spatial locations and sound sequences. More heteromodal areas in the midtemporal cortex, Wernike's area, the hippocampal-entorhinal complex and the posterior parietal cortex provide critical gateways for transforming perception into recognition, word formation into meaning, scenes and events into experiences, and spatial locations into targets for exploration. The transmodal, paralimbic and limbic cortices that bind multiple unimodal and the higher more heteromodal areas into distributed but integrated multimodal representations occupy the highest connectionist levels of the hierarchy. The transmodal systems with their complex functional inter-connectivity actualize (see emergent properties above) the highest mental functions.

Via the various sensory systems, information is continuously sampled from the environment. Simultaneously the environment is subject to continuous manipulations by means of the motor systems. This cycle of continuous sampling and intervention in the environment is governed by the ever more complex circuits which characterize the hierarchical organization of the brain. This hierarchy enables the necessary associative transformations to support cognition that is typical of high mental functions, and that is heavily dependent on neuronal connectivity.

The transmodal connectionist level of brain organization plays an important role in shaping the characteristics of high mental functions. If prior to establishing a connection two neuronal systems could act independently one from another, once their activity is interdependent, the activity of one neural system or network will influence the activity of the other. This might explain the internal consistency we experience in our mental functions, and why reality is perceived as being coordinated audibly, visually and tactically. Planning, thinking and acting also have consistency; thoughts and reactions are goal-directed to the stimuli at hand, and match situational events. Finally, our entire conscious experience seems united in a single, complete, logical and meaningful continuum.

Building on a 'contrastive analysis' that compares conscious versus unconscious processes across numerous experimental domains, Baars (1988) presents an integrative theory of consciousness called the "Global Workspace" (GW) Theory. Baars' theory is founded on the view that the brain is composed of many different parallel "processors**,"** (or modules) each capable of performing some task on the symbolic representations that it receives as input. The modules are flexible in that they can combine to form new processors capable of performing novel tasks, and can decompose into smaller component processors. Baars treats the brain as a large group of separable

"partial processors", very specialized systems that function at unconscious levels much of the time. At least some of these partial processes can take place at the conscious level when they organize to form "global processes." Global processes carry the conscious information and are formed from competing and cooperating partial processors (Baars, 1988).

According to Baars, conscious awareness is subject to "internal consistency." This implies that multiple-constraint-satisfaction characterizes the interacting partial processors when they participate in the global process. This model of the brain is fairly well supported by evidence from brain studies (see above) and studies of patients with brain damage (Roland, 1993). The model also complies with the notion that the brain is composed of interacting elements (i.e., information processors) and is multiply constrained.

To explain the differences between conscious and unconscious processes, Baars turns to the popular models of distributed-processing systems (i.e., neural network models; (Herz et al. 1991)). Baars proposes that a similar structure exists in the human brain, and that it supports conscious experience. The structure, which he terms the global workspace, is accessible to most processors, thus most processors can potentially have their contents occupy the working memory. The global workspace can also "broadcast" its contents globally so that every processor receives or has access to the conscious content. Significant, though, is the idea that only one global process can be conscious at any one given moment. In other words, consciousness is a serial phenomenon even though its unconscious pre-determinants are parallel processes.

Baars' important claim about consciousness is that it has internal consistency, a property not shared by the collection of unconscious processes in the brain. Baars cites as an example of this property the experience of viewing a Necker-cube, an optical illusion which we can consciously see in one of two different orientations. The two views of the cube can "flip" back and forth, but we cannot entertain both of them simultaneously. In other words, our conscious experience of the cube is consistent. A similar situation is found with ambiguous words. People seem to be capable of having but one meaning of a given word in mind at one time. There is evidence, though, that the alternative meanings are represented unconsciously in the brain at the same time as the conscious meaning, in that the other meanings of such words often show priming effects on sentence comprehension (Manschreck 1988; Neely 1991). This indicates that, while conscious processes are consistent, the collection of unconscious processes are not.

To summarize, Baars postulated a theoretical workspace where global processes are formed from the interactions of many partial processes. He postulated that the global formations in the workspace carry the global dominant message of conscious awareness (Baars, 1988). Partial processes are specialized processes, each processing its information in an independent fashion. They function in parallel and if not involved in any global organization, they proceed disconnected from other processes. Partial processes compete, cooperate and interact to gain access to and participate in global organizations. The global formation may be viewed as a complex network of partial processes.

In global formations, there are internal consistencies; consequently multiple constraints are formed between partial processes. When partial processes participate in the organization of a global process they are constrained by the activity patterns of the global formations. Thus, partial processes can no longer function (i.e., process information) regardless of the message. Partial processes are fast, highly specialized and aimed at handling specific types of information. They are, however, limited in the extent of the information they can process and they lack the flexibility and adaptability acquired when many partial processes combine and cooperate. Global formations have the advantage of both the complexity and flexibility necessary for efficient and elaborate information processing.

Combining Baars' theory with notions about hierarchical organization of information (memories) in the brain (see above), it is reasonable to consider that lower level partial processes in the nervous system interact to form higher level neural global organizations. In addition, the idea of internal consistency in global formations captures the basic notion of multiple constraint organization. It is assumed that the dynamic activity of partial processes demonstrate both hierarchical and multiple constraint organizations. For example, once the partial process forms part of the global organization it is interconnected with all the other processes (i.e. is broadcast globally). Thus, it contributes to, or influences, the global organization by virtue of its connections, i.e., by exerting its output through the connections to the rest of the system. On the other hand, because it is a multiple constraint system, many other processes will constrain (through the connections) its activity. One may conclude that from the information processing perspective, the information delivered by partial processes concurrently influences and is influenced by the global message.

Due to internal consistency, if the information structure (i.e., activation pattern) of the partial process "contradicts" (i.e., markedly differs from) the information being represented in the global formation, the partial process will have "difficulty" gaining access to (or fitting with) the global process. This is due to the multiple constraints between the partial process and the global formation, which will not be satisfied in such a situation. As global formations are higher levels of organization (from the hierarchical perspective), by constraining partial processes which are most likely of lower levels, top-down control blocks access of partial processes to global formation (i.e., "repression"). Partial processes compete for access to global formation, creating the bottom-up procedure. Thus, a balance between bottom-up and top-dawn processes becomes crucial for the contents that reach global formations and consciousness.

Tononi and Edelman (2000) combine the above insights with other findings and formulate the concept of the "dynamic core." The dynamic core explains which neural processes underlay conscious experience. Tononi and Edelman conclude that a group of neurons can contribute directly to conscious experience only if it is part of a distributed functional cluster of high millisecond range integration as well as a highly differentiated complexity (i.e., ability to choose from many different states). The dynamic core is a functional cluster of neurons in the sense that the participating neuronal groups are much more strongly interactive among themselves than with

the rest of the brain. In addition, the dynamic core must also have high complexity in that its global activity patterns must be selected within less than a second out of a very large repertoire.

The dynamic core would typically include posterior corticothalamic regions involved in perceptual categorization interacting reentrantly with anterior regions involved in concept formation, value-related memory, and planning. The dynamic core is not restricted to an invariant set of brain regions; it continuously changes composition and patterns.

The formulation of the "dynamic core" as presented by Tononi and Edelman (2000) summarizes many of the ideas about consciousness and brain organization presented thus far. Firstly, it incorporates the idea of global workspace as a globally distributed functional cluster of neuronal groups. Secondly, it refers to brain organization at the edge of chaos (balanced between orderliness and randomness) by introducing the idea of the simultaneous need for integration and differentiation within the dynamic core. Finally, the dynamic core refers to the transmodal connectionist systems at the highest levels of brain hierarchal organization pointing to the relevant formulations regarding memory and mental functions described by Fuster (1997) and Mesulam (1998).

"State-Space" formulation from physics is a useful way to envision the dynamics of the brain system described so far . Imagine a system formed from many elements. The arrangement of the elements in the system represents the "states" of the system. Each distinct arrangement in the system forms a different "state" for the system. If the elements are arranged randomly, all the states in the system are similar to each other. If the elements of the system can form many distinct patterns of arrangements then the system has many possible states. If the system can form only one type of arrangement, then the system is represented by one state only. The **"**space" of a system is represented by all the possible states a system can assume. If the system constantly changes, it is called a "dynamic" system. In this case, the system changes its arrangement from one point in time to the next.

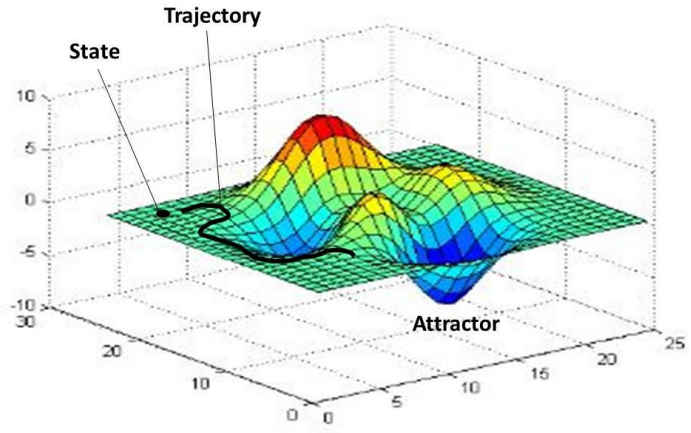
To visualize systems and their dynamics William Hamilton, the well-known physicist, and the mathematician Karl Jacob devised the concept of *state-space* necessary for describing dynamics in physical systems (Ditto and Pecora 1993). A dynamic system is generally defined by a configuration-space consisting of a "topological manifold".

A point on the configuration-space represents the state of the system at a given instant. Each point is a combination pattern in the activity of the elements (i.e., the arrangement of the elements). The configuration-space of the system is determined by all of the possible states that the system is capable of assuming, (i.e., all the possible combinations in the activity of the elements). This configuration-space is sometimes called a "landscape." As the dynamic state of the system changes over time, the combinations in the activity of the elements change (i.e., the points on the space change). The dynamics of the system are described in terms of state-space as 'movement' from one point to the next on the landscape, defining a trajectory, or curve, on the configuration space.

If the system 'prefers' certain states (i.e., arrangements) over other states, it will tend to be 'drawn' or 'attracted' to form these states. Once certain states are preferred by the system, they form "attractors" (basins) in the topological surface (Herz et al. 1991). If a metaphorical ball were rolling on the surface (space) it would be easy to see that peaks represent "repellers" (i.e., those states the system tends to avoid) and basins represent attractors (i.e., those states the system tends to assume).

Using the state-space formulation in relation to Hebbian plasticity (see below) and together with insights from neural networks, a memory embedded in the Hopfield model forms an "attractor" on the space manifold of the model. The attractor represents the dynamic tendency of the system to activate the memory states just as a ball may roll toward a basin of a landscape. Thus, multiple attractor-formations in the space manifold of a system could provide for internal information embedded in that system. In other words, the manifold topography of a dynamic system could well simulate internal representations achieved by that system (Figure 1).

Figure 1



The internal representations in the brain probably follow the general rules of Hebbian plasticity. Since the brain operates on the border of chaos, balanced between orderliness and randomness, the internal representations are probably subject to continuously changing influences. A more complete characterization of the functional connectivity of the brain must therefore relate to the statistical structure of the signals sampled from the environment. Such signals activate specific neural populations and, as a result, synaptic connections between them are strengthened or weakened. In the course of development and experience, the fit or match between the functional connectivity of the brain and the statistical structure of signals sampled from the environment tends to increase progressively through processes of variation and selection mediated at the level of the synapses (Edelman 1987).

To conclude this section of brain systems dynamics, nonlinearity as an inherent character of the brain must be briefly addressed. As mentioned above, nonlinear systems are those where relations between input and output do not have a one-to-one relationship. Nonlinear systems are often described by a sigmoid graph. The initial portion of the graph can be viewed as a "trigger-effect" in which a small increase in input results in a large response in the output. The last portion of the sigmoid graph can be viewed as "saturation-effect" since the increase in input levels does not increase the output further.

In physics, the point at which a system radically changes its behavior or structure, for instance, from solid to liquid, is critical. In standard critical phenomena, there is a control parameter, which an experimenter can vary to obtain this radical change in behavior. In the case of melting, the control parameter is temperature. A self-organized critical phenomenon, by contrast, is exhibited by driven systems that reach a critical state by their intrinsic dynamics, independent of the value of any control parameter. The archetype of a self-organized critical system is a sand pile. Sand is slowly poured onto a surface, forming a pile. As the pile grows, avalanches occur which carry sand from the top to the bottom of the pile. At least in model systems, the slope of the pile becomes independent of the rate at which the system is driven by pouring sand. This is the (self-organized) critical slope.

Self organization systems typically evolve through a set of phase transitions. In non linear systems bifurcation is a typical phenomenon of phase transition. The system driven to a critical optimal condition, when driven further by additional energy becomes unstable and as a consequence forms one of two different organizations each more stable than the prior critical condition. The term "bi (two) furcation" describes this tendency to form one of two organizations.

Generally, we can define criticality as a point where system properties change suddenly, e.g. where a matrix goes from non-percolating (disconnected) to percolating (connected) or vice versa. This is often regarded as a phase change, thus in critically interacting systems we expect step changes in properties and phase transitions in dynamics.

To conclude, criticality may involve both levels as well as patterns of organization in systems. As mentioned above, phase transitions going from one level of organization to another, the system may gain or lose emergent properties as per its transit to higher or lower levels of organization. For example, evolution is generally described as phases transiting from one level to a higher level of organization, thus systems of higher levels have additional properties as compared to the previous level system. Properties of a system can change abruptly according to the changes of organization patterns within the system. Nonlinear systems can react abruptly to small changes (trigger effect) or remain stable in spite of large perturbations (saturation effect).

Instability can occur in all kinds of structures from solids to gases, from animate to inanimate, from organic to inorganic, and from constitution to institution. External and internal disturbances can cause stable systems to become unstable, but this instability does not necessarily occur from

some ordinary perturbation. It depends on the "type and magnitude of the perturbation as well as the susceptibility of the system" (Cambel 1993), which must be considered before the system is rendered unstable. Cambel adds that sometimes it takes more than one kind of disturbance for the system to transform into an unstable state.

Prigogine and Stengers discuss of the "competition between stabilization through communication and instability through fluctuations. The outcome of that competition determines the threshold of stability" (Prigogine and Stengers, 1984). In other words, the conditions must be ripe for upheaval to take place. We could superimpose this theory to many observable situations in areas such as disease, political unrest or family and community dysfunction. In psychiatry it is especially appropriate to conceptualize the idea of acute reaction to stress and adjustment disorders. Cambel used the old adage that it may be the straw that broke the camel's back that finally allows the system to go haywire. This old saying reflects the idea of the trigger effect bringing us back to instability as a 'behavior' inherent to nonlinear systems.

Considering the above introductions we can now begin and try to understand one of our higher mental function consciousness in physical terms. Borrowing from the terminology of state space formulations, let us call all of the possible brain states the "brain space". Since the brain is a dynamic system, as time progresses from one millisecond to the next, the brain state changes. Across time, changing brain states form a trajectory of brain activation, or a "brain trajectory".

If each unit acted independently without any relation to (or regardless of) the activity of other units, the entire brain system would be arbitrary; brain states would appear randomly and the brain trajectory would be random. But we know that this is not true for the brain. Brain architecture involves pathways, synapses and connections among units. In effect the brain is highly connected to the extent that the activity of most units is constrained by (and constrains) the activity of the majority of the other units. Thus, brain states do not appear randomly and brain trajectory is not arbitrary.

Due to connectivity brain units can unite creating many brain states. These brain states can interconnect further creating more dominant brain states from larger, more widespread, ensembles of brain states. The larger the connectivity the more integrated the brain states, to the extent that if all brain units participate in the brain state then that brain state becomes the "global brain state". However it is conceivable that in a very large system not all brain states will be integrated all the time; some brain states will be relatively "independent" from others, in the sense that they will be less influenced (or constrained) by the other brain states. The brain probably balances equilibrium of connectivity where both large-scale integrations form together with smaller scale organizations. Thus connectivity and disconnectivity may be balanced to certain extents in the brain system.

Let us assume that one large-scale integration is always active in the brain and call it the "dominant brain state." Other less dominant organizations will be called "fractional states."

Since dominant brain states involve large scale activity patterns they can be conceptualized as "global processes" similar to those defined by Baars (Baars 1988). Since via connectivity they form dynamics which change in the millisecond range, they also fit the description of the "Dynamic Core" (Tononi and Edelman 2000). Both the global workspace theory and the formulation of the dynamic core relate to consciousness.

This is in accordance with the idea of emergent-properties. Emergent properties arise from large-scale complex (non-linear) integrations (or systems). Thus consciousness can be explained as the emergent property of dominant brain states. Our conscious experience has a streaming motion, we are conscious in time, aware of things as they are from second to second. This supports the idea of a "dominant brain trajectory" where dominant brain states are activated in a continuous sequence, just as our conscious awareness is continuous in time, as represented by consecutive conscious events that occur one after the other.

As mentioned above, not all brain units must participate in the dominant brain state; certain units can create fractional states. Fractional states are unconscious because they do not contribute to the dominant brain state. Their description is in accordance with the idea of 'partial processes' described by Baars (1988). Baars argued that partial processes compete to gain access to global formations, thus unconscious contents of the partial processes become conscious when participating in the global formations. The dominant brain state is a dynamic formation of participating fractional brain states. One can imagine this as a pattern of cars on the highway. Traffic merges and branches out, however the pattern of car flow on the highway is continuously maintained.

This description of the brain system and its dynamic organization is faithful to the model proposed by Freud regarding conscious and unconscious dynamics. Unconscious content can become conscious when fractional brain states integrate into dominant brain states, and vice versa. Conscious content can become unconscious when parts of the dominant state fraction away and are thus no longer part of the dominant organization.

As the interactions that create dominant brain states bind fractional brain states, and as these states are also formed from bindings of brain units, connectivity becomes an important factor determining the formation and nature of dominant brain states. As already mentioned, dominant brain states are not random and they therefore maintain a certain consistency. Consciousness is an ordered consistent experience. This was emphasized by Baars who claimed that consciousness has internal consistency (Baars 1988). Such consistency is attributed to the dominant brain state preserved by the binding of units that result from connectivity in the brain.

The consistent character of conscious experience is related to the connectivity power of the brain system. However our consciousness has many factors that need to be highly flexible; one needs to shift attention according to changing events or occurrences, and to rapidly adapt to new conditions. This requires flexibility from the dominant brain state. Flexibility is obtained if connections can

be loosened and disconnected to allow for changes and new pattern formations. Thus the optimal condition for a dynamic changeable dominant brain state (adaptive flexible awareness) is a balance among a range of connectivity "powers" from overly-connected to disconnected.

Computation of cognitive functions in the brain is achieved by rapid activation and interactions among large groups of neurons. Neuronal networks activate and change from instant to instant in a timescale of millisecond range. The interactions among neurons also termed plasticity, is governed by Hebbian dynamics. Donald Hebb (1949) described connectivity strength as resulting from synchronous activation of neurons, defined by the famous statement "Fire-together Wire - together". Repeated firing of neurons increases the connections among them and the opposite is also true when neurons do not synchronize and fire together, the connections between them are weakened and lost. These dynamics can be fast, dependent on neurotransmitter activity, or slower, dependent on structural cell membrane formations. In any case, faster or slower, they are called Hebbian Dynamics.

The activity of neural-network fast millisecond function is demonstrated when picked-up and detected using sensitive electrophysiological sensors from the scalp. For instance, cognitive functions correlate with electrical activity emerging from activated ensembles of large groups of neurons and is evident in the form of "evoked potentials." These evoked potential are active in the millisecond range after the stimulus to be computed is presented.

The hierarchy of the brain enables higher-level functions to emerge from lower-level processes. Thus, top-down and bottom-up connectivity processes become relevant. The incoming information sampled from the environment "travels" the hierarchy to shape the higher-level organizations, which embed and represent the internal model of the world. At the same time the internal representations control and influence the incoming information sampled from the environment. We all know the set of illusions that are typically created by our past experiences, which can bias and distort our perception. According to Karl Friston's work (Kirchhoff et al., 2018) the brain higher-level organizations constantly generate prediction about the environment and uses a plasticity mechanism, of error correction to update a dynamic internal model of the environmental occurrences. Because the environment is in constant change, this process of error- prediction and correction minimizes the biases and differences that may develop via the changing environment. According to Karl Friston, this is measured by entropy mathematical methods of "Free Energy" which is the reduction of the "Delta" i.e., the mathematical difference between mathematical representations of the environment and those of the internal configuration of the evolving internal model of the world (Friston 2013).

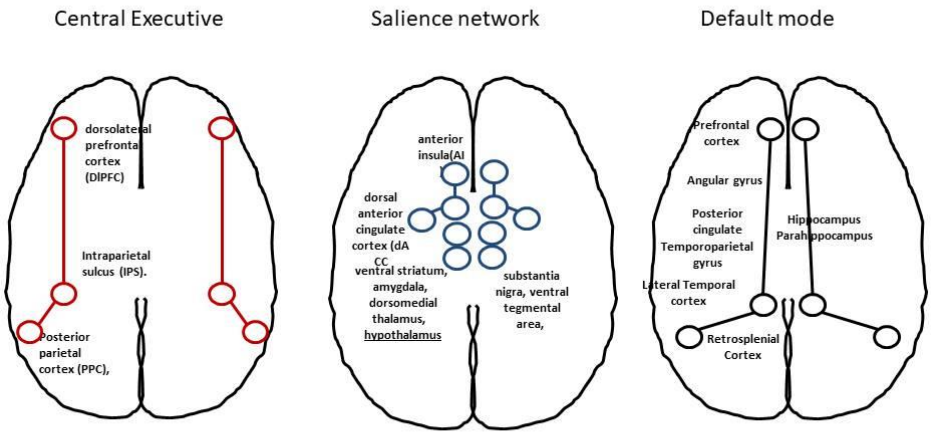
Connectivity in the brain entails small-world-network organization, which is a specific organization of connectivity with dense nearby connections and fewer distant connections formed in a way that "Hubs" integrate multiple clusters of connectivity structures. This lends well to the anatomy of hierarchy where transmodal higher-level organizations require Hub-like integration of many processors.

In recent years it is established that a network with anatomical distribution of hubs in the Dorsolateral Prefrontal Cortex (DLPC) Intraparietal Sulcus (IPS) and Posterior Parietal Cortex (PPC), titled Central Executive Network (CEN) is correlated with fast millisecond-range plasticity integration with the environment and has been found to be activated in High level cognitive functions working memory, problem solving, and decision making executive control tasks and IQ (Culpepper 2015). Thus the CEN can be seen as the network hub organization for fast plasticity conscious cognition and related intelligence functions.

At rest the CEN inactivates and a Default-Mode Network (DMN) is active, this network is composed from Prefrontal cortex, Angular gyrus, Posterior cingulate, Hippocampus Parahippocampus, Temporoparietal gyrus, Lateral Temporal cortex, and Retrosplenial Cortex**.** The DMN has been found to activate in relation to wakeful rest, internal focus daydreaming and mind-wandering. In addition it has been related to Theory of mind Retrieval of social semantic and conceptual knowledge, autobiographical memory and future planning.

The two networks have been described to anticorrelate (Culpepper 2015) when one is active the other is inhibited, the networks switch with flexibility presumed to be modulated by the Salience Network (SN) acting as modulating the switch between the externally directed cognition of the CEN and the internally directed awareness of the DMN. The SN network involves Anterior Insula (AI), Dorsal Anterior Cingulate Cortex (DACC), Ventral striatum, Amygdala, Dorsomedial thalamus, Hypothalamus and also Substantia Nigra (SN), Ventral Tegmental Area (VTA). Anatomically there are known as hub-structures for massive brain connectivity, thus a reasonable anatomical structure for integration of modulation. Figure 2 describes the anatomical distributions of the networks described.

Figure 2



To summarize the fast millisecond range activity in the brain entails connectivity in the form of small-world CEN organization, this connectivity also enables hierarchal formations. The higher-level hierarchal organizations are formed in hubs of brain higher-level organizations such as the DMN. The DMN continually interacting with the CEN via top-down and bottom-up balance of processes, the CEN continually inputs and outputs interactions with the environment. Such hierarchal construct is continually and constantly predicting and error-correcting the environmental occurrences (sensorium) as well as intervening and changing environmental occurrences via action (motor) in the environment.

Optimization, slow plasticity, Hebbian dynamics, learning and memories

Optimization is typically defined as the ability of a system to evolve in such a way as to approach a critical point and then maintain itself at that level. If a particular dynamic structure is optimal for the system, and the current configuration is too static, then the more changeable configuration will be more successful. If the system is currently too erratic, then the more static mutation will be selected. Thus, the system can adapt in both directions to converge on the optimal dynamic characteristics.

Christopher Langdon discussed the "edge of chaos" as the place where systems are at their optimal performance potential (Kauffman 1993). At the edge of chaos, there is a sublime balance between stability and instability. This sublimely balanced formation is the state where the system is at its optimum adaptation where it can naturally approach the more changeable configuration as well as the more static mutation. This balance is important for optimal adaptation to external and internal events as well as for "best solution" configuration toward these events.

The ability of a system to optimize is related to the idea of complexity as well as connectivity. As mentioned above, if the elements of a system are disconnected from each other and act independently, the system will tend toward randomness and thus to the more erratic configurations. If connectivity is dominant and fixed, the more static "freezing" state will prevail. Thus, the connectivity patterns in the system are crucial to the optimization and complexity of the system.

"Multiple constraint satisfaction" is the type of organization that accounts for the interrelations among multiple units in a system. Once the activity of unit A influences the activity of unit B to which it is connected, the activity of unit B is constrained by unit A. This constraint depends on two factors, 1) the activity of unit A and 2) the "strength" of the connection to unit B. The strength of the connection determines to what extent the activity in A constrains the activity in B. If the value of the connection-strength between the units is large, the constraint of the activity in A on the activity in B is large. Conversely, if the strength of the connection is small, then the activity in B will be less constrained by the activity in A. In systems with numerous interconnected units, each unit simultaneously influences (i.e., constrains) several other units, thus the activity of each unit is a result of multiple parallel constraints. When the activity of a unit satisfies all the influences exerted on it by the other connected units it achieves multiple constraint satisfaction. If the activities of all the units in the system achieve multiple constraint satisfactions then the system as a whole optimizes multiple constraint satisfaction.

The relevance of synaptic plasticity to the information processing of the brain was recognized as early as the beginning of the 20th century. Cajal (1952) was one of the first to realize that information could be stored by modifying the connections between communicating nerve cells in order to form associations. Thus, acquisition and representation of information basically entail the modulation of synaptic contacts between nerve cells (Kandel 1991). Information is stored by facilitation and selective elimination of synaptic links between neuronal aggregates that represent discrete aspects of the environment. Memories are hence essentially associative; the information they contain is defined by neuronal relationships.

Hebb (1949) proposed that "two cells or systems that are repeatedly active at the same time will tend to become associated, so that activity in one facilitates activity in the other." This is called "the principle of synchronous convergence" (Fuster, 1997). Through summation of temporally coincident inputs, neurons become associated with one another, such that they can substitute for one another in causing other cells to fire. Furthermore, connections between input and output

neurons are strengthened by recurrent fibers and feedback. By these associative processes, cells become interconnected into functional units of memory, or Hebbian "cell assemblies."

Evidence for synaptic plasticity was presented as early as 1973 when a group of researchers published one of the first detailed reports on artificially induced modification of synaptic strength (Bliss and Gardner 1973). They found that stimulation of certain neuronal fibers with high-frequency electrical pulses caused the synapses of these fibers to become measurably stronger (i.e., their capability to stimulate post synaptic potentials increased) and remain so for many weeks. Their observation, which they called long-term potentiation (LTP), was probably one of the first reports of synaptic plasticity.

One critical component of the induction of synaptic plasticity in virtually all experimental models is a change in post-synaptic (sometimes pre-synaptic) membrane potential, usually a depolarization. There are two other common features. First, Ca^{2+} typically plays an indispensable role in triggering synaptic change. The elevation of Ca^{2+} may arise via flux through membrane channels, release from intracellular stores, or both. Second, plasticity usually comes in two general forms: short-term plasticity which is dependent on post-translation modifications of existing proteins, and long-term plasticity which is dependent on gene expression and *de novo* protein synthesis.

Finally, it is increasingly apparent that for many experimental models a vital bridge between initial induction of plasticity and its maintenance over time is the activation of adenylyl cyclases and protein kinases A. One of the more studied mechanisms of regulating Ca^{2+} flux in synaptic transmission relates to the N-methyl-D-aspartate (NMDA) excitatory amino acid receptor. Over the years it has become apparent that many sub-cellular systems combine in a complicated way to regulate Ca^{2+} flux and levels, for example, the phosphoinositide system, G-protein systems, and the neuronal membrane currents (for detailed explanation of the relevance of these systems to synaptic plasticity see Wickliff and Warren 1997).

In a series of experiments with the marine snail *Aplysia*, Kandel (1989) demonstrated how synaptic connections can be permanently altered and strengthened by regulating learning from the environment. Kandel (1989) found structural changes in neuronal pathways and changes in the number of synapses related to learning processes in the *Aplysia.* Essentially LTP is the mechanism by which *Aplysia* learns from experience at the synaptic level, and the experience-dependent process then translates into structural, 'hard-wire,' alterations (Singer 1995).

In another series of experiments, with monkeys, the map of the hand in the somatosensory cortex was determined by multiple electrode penetrations before and after one of the three nerves that enervate the hand was sectioned (Merzenich and Kaas 1982). Immediately following nerve section most of the cortical territory, which previously could be activated by the region of the hand, enervated by the afferent nerves, became unresponsive to somatic stimulation. In most monkeys, small islands within the unresponsive cortex slowly became responsive to somatic stimulation

from neighboring regions. Over several weeks following the operation, the previously silent regions became responsive and topographically reorganized.

Studies of the primary visual cortex in mammals typically show experience-dependent activity (Kandel 1991; Singer 1995). The blockade of spontaneous retinal discharge prevents the segregation of the afferents from the two eyes into ocular dominance columns; this finding suggests that spontaneous activity may promote axon sorting. Ganglion cells in the developing retina engage in coherent oscillatory activity, which enables the use of synchronous activity as a means for identifying the origin and neighbourhood relations of afferents. However, substantial fractions of neurons in the primary visual cortex, especially those in layers remote from thalamic input, develop feature-specific responses only if visual experience is available. Manipulating visual experience during a critical period of early development can modify visual cortical 'maps' in these layers (Singer 1995).

The descriptions above entail adaptability of information processing as to match internal representations to incoming stimuli. Tononi and colleagues introduced a statistical measure, called "matching complexity" **(**C_M**),** which reflects the change in C_N observed when a neural system receives sensory input (Tononi et al. 1996). Through computer simulations, they showed that when the synaptic connectivity of a simplified cortical area is randomly organized, C_M is low and the functional connectivity does not fit the statistical structure of the sensory input. If, however, the synaptic connectivity is modified and the functional connectivity is altered so that many intrinsic correlations are strongly activated by the input, C_M increases. They also demonstrated that once a repertoire of intrinsic correlations has been selected which adaptively matches the statistical structure of the sensory input, that repertoire becomes critical to the way in which the brain categorizes individual stimuli (i.e., perceives stimuli).

Thus, the internal representations embedded as statistically input-matching patterns are continuously altered by the configuration of external influences. Once altered, the consecutive inputs are "interpreted" by the recently altered internal representations.

According to Karl Friston, the Bayesian Brain acts to reduce Free Energy, the differences (the Delta) between the internal representations and actual external occurrences. This happens hierarchically at each level of neuronal network brain organization and results in a continual 'update" of internal representations using the error-prediction and correction mechanisms underlying what Friston calls Dynamic Causal Modeling (Friston 2012).

Considering the matching low free energy increase, it can be conceptualized that the internal representations are "Optimized" and vice-versa when the environmental occurrences mismatch and the free energy increases; i.e., the delta of the difference between the internal representation and external events increases. Thus, the brain is "De-Optimized," and the dynamics of the brain fluctuate between optimization dynamics and de-optimization dynamics as it evolves to create accurate internal-representations of the ever-changing world.

Negative emotions typically emerge with frustration when something we believe ought to happen (the internal representations) does not happen, i.e., difference between expectation and reality increases. In other words, free energy (delta) increases. The opposite is also true. When an expectation is fulfilled, it is typically accompanied by a satisfactory good feeling. Here the assumption is that "Optimization Dynamics" emerge as mood sensations. In other words, the emergent-property from de-optimization dynamics is a depressed mood and the emergent-property of optimization dynamics is an elated anti-depressive mood.

Elaborating in optimization dynamics, it is evident that de-optimization dynamics will result from two factors (or their combination): 1) that of reduced plasticity of the neuronal network and 2) large fluctuating alternations of the external environmental occurrences. Reduced adaptive plasticity may occur because of neuronal factors such as neurotransmitter alterations, neuro-hormonal factors and any atrophy-inducing biological factors. This will cause the adaptive plasticity to slow-down and relative to the continually changing environment, the free energy will increase De-optimization will occur and depressed mood will emerge. On the other hand adaptive plasticity can also be altered by major alterations in the environment (stresses, i.e., any stress is characterized by alterations in the environment) such alterations that depart from the internal-representations naturally increase the delta between internal representations and external events causing the emergence of depressed mood. It is thus evident that both "reactive depression" and what has been previously called "Endogenic Depression" can be explained by one model of optimization dynamics. Thus, if an elderly patient with brain atrophy and reduced brain plasticity is institutionalized, alerting his environmental habitation of external environment, it is predicted that free-energy will increase both by altering the environment as well as by atrophy and reduced-plasticity explaining why depression is typically characteristic in such cases.

Anatomically the matching dynamics and reduction of Free energy presumably relate to the CEN and the DMN via the action of the SN, The free energy reduction is a result of externally (environmentally) induced fast plasticity of the CEN activity embedded in the internally-represented stable developmental plasticity of the DMN via the 'matching free-energy reducing' activity of the SN.

Internal representation dynamics and psychoanalytic conceptualization.

The ego develops from the id as a result from interaction with reality events. Brain organization is known to emerge through experience-dependent-plasticity. The infant is born with a rudimentary nervous system where connectivity is not effectively established. Thus if any dominant brain trajectory forms it is most likely unstable and fractional. We know that experience-dependent-plasticity defines Hebbian dynamics (see plasticity above) in the sense that consistent environmental stimuli repeatedly activate neuronal ensembles. This repetition strengthens connections in these neuronal ensembles turning them to brain states that represent the relevant environmental stimuli.

If the id refers to a disorganized (random) brain trajectory, the ego refers to a balanced consistent well-organized dominant brain trajectory. The process of development of brain organization through repeated experiences gradually forms evermore complex brain organizations leading from an initially fractional unorganized brain to a highly organized complex brain. The highly organized brain supports the dominant brain trajectory, which enables the appearance of computational ability, reflected by a mature personality cognitively adaptable to the demands of reality.

If we examine the environment into which the infant is born we find that the family and primary caregivers are most relevant. Good enough mother, a term coined by Winnicott refers to the structural consistent care provided by the mother with a schedule of feeding, washing and attending to the infant. From a systems point-of-view it can be concluded that the environmental system is more organized than the brain system of the infant. This organization structures the brain, gradually increasing its organizational level, by the gradually forming input-dependent stimuli-related connectivity. Repeated stimuli continually activate relevant neuronal ensembles which according to Hebbian dynamics, strengthens the connections among the units of the neural ensembles making them functionally structured and organized.

If we consider the idea of interacting systems, i.e. the environmental system and the brain system, and extend it to the entire lifecycle, then as the infant grows his brain system becomes more organized and his environment system becomes less organized. As the child grows he needs to confront new environments kindergarten, and school, moving from the protected structured environment of the family home to the less structured more hazardous social environment outside the home. Thus an inverse graph can be traced where the brain system gradually increases organization levels and the environmental system decreases organization levels. According to this graph, between the ages 18 to 21 there is a critical period with peak vulnerability to brain organization. At that age the brain is approaching a good, but not maximum level of organization, and the environment system is already becoming disorganized as the young adult needs to make his way in the world confronting tasks such as choosing a life style and acquiring a profession. The highly organized brain acts to organize the environment as he creates a stable consistent environment.

From this rough simplistic description of interacting brain-environment organizational levels, during adolescence and young adulthood both are at their lowest levels. Before that age the environmental organization level is high and the brain organizational level is low. After that age the brain organizational level is high and vice versa. This description of system interacting organizations is important to explain why many mental disorders appear in adolescence. This type of systems approach to the vulnerability of the organization of the brain is typically overlooked when searching for the etiology of many mental disturbances that manifest during adolescence.

If the infant grows in a disturbed family where the organizational level of the family environment is low, he/she may suffer mental disturbances. It is not clear exactly how this happens. The interacting brain-environment model can shed light on this question. If an impaired low-organization brain reaches the critical period in an environment with a low organization level, it will be unable to function and achieve an organized life. This impaired brain can have fluctuations in organization levels susceptible to organizational breakdowns, which clinically manifest as symptoms and signs of mental disorders.

Freud, and others who followed him, described the psychological development in phases, each phase allowing for the development of a higher level with new psychological characteristics. This description is faithful to the nature of non-linear dynamic systems. Since the brain is such a system it is not surprising that the psychological descriptions concord with the neurophysiology of the brain. In effect non-linear systems driven by energy to higher levels of organization show a phenomenon of bifurcation, moving in phases each allowing two new patterns of activity. This description accords with the developmental phases described by Eriksson. In each phase success or failure can be achieved (bifurcation), success is associated with development of a new virtue and failure with the acquisition of a certain insufficiency relevant to that phase. Many psychological theories and formulations discuss the importance of stability and good object relationships for a mature personality to develop. These theoreticians describe psychological development starting from rudimental preliminary organization that is typically fragmented and unstable, gradually developing into whole complex intrapsychic structures. For example, Melanie Klein notes the infant's ability to relate only to part objects, Kernberg talks about "islands" of internalized objects around which future structures will be organized, and Kohut talks about the "rudimentary self" un-integrated into the identity of the individual. These authors all agree that good experiences enhance maturation and organization and that bad experiences are split off from the organizing structures and hamper the overall organization. Either as defense or as damaging phenomena, bad experiences destabilize and fragment the intrapsychic structures such as the ego.

As mentioned above the dominant brain states and their trajectories have consistency and coherency due to the connectivity powers of the brain, thus it is conceivable that the brain states that comprise dominant brain organization need to show a certain degree of dependence and constraints among them. If experiences activate neuronal ensembles and similar experiences activate similar patterns of brain states, then activations would maintain dependence and constraints among themselves. However, if experiences differ radically and their correlated brain

activations have patterns that are far removed from each other, dependence and constraints among these patterns may not take place, creating fragmentations of dominant brain states.

Bad early experiences can be viewed as part of instable non-consistent up-bringing where the child's needs are inconsistently met and where experiences can differ largely due to the inconsistencies. Such events activate incoherent brain states, which have difficulty organizing into dominant brain states leaving the individual vulnerable to breakdowns in (and fragmentations of) the dominant brain states and trajectories.

According to Freud, the ego makes use of an unconscious domain of mental activity (the id) into which undesirable drives and ideas are repressed. "Repression" has been described as the mental mechanism that "guards" the conscious awareness from the intrusion of inadequate and intolerable ideas or drives. Freud indicated that the intruding ideas and drives from the unconscious actually threaten ego integrity.

If we adopt formulations about consciousness by Baars (1988), then repression can be re-conceptualised as the dynamics of participating, as well as non-participating processes in the global formations that support conscious phenomena. Partial processes that do not gain access to the global process remain unconscious, (i.e., repressed). In other words those fractional brain states that do not become part of the dominant brain state are unconscious, as long as they do not gain access, i.e., do not become part of the dominant brain state they are repressed. Due to the multiple-constraints that characterize dominant brain states, certain partial fractional brain states may encounter 'difficulty' in accessing the global formations of dominant brain states. This is especially true if the partial processes carry information (i.e., an arrangement pattern) that is entirely removed from, or contradictory to, global messages inherent to dominant brain states. Based on these assumptions it is possible to conceive what type of information will be denied access to the global organization; it will be the contradictory and unfitting messages, i.e., the fractional brain states that activate patterns dissimilar, or removed, from the activated patterns of the dominant brain states. In neuronal terms it will be the partial arrangement that does not satisfy the global constraints. In fact, Freud described the repressed contents as "conflicting" topics or unbearable ideas. Here, "unbearable" stands for the partial process that is removed from (i.e., "unfitting" to) the information pattern presented by the pattern of the global integration.

A fractional brain state that has an activation pattern that is largely removed from the patterns activated by the dominant brain state cannot be incorporated in the general message of that dominant state without damaging its internal consistency and integration and is therefore bound to be excluded. For example, to a mother of a newborn baby the idea of killing her baby is extremely contradictory to the normal loving and "caring state-of-mind" typical to a new mother. If inadequate fractional states somehow gain access to the dominant state of brain organization they are inclined to destabilize or even disrupt it. If many conflicting and disrupting processes gain access to the global dominant brain state, the whole activation pattern of the dominant brain state may be destroyed and the neural systems representing it (i.e., the relevant neural circuits) are bound

to destabilize. Indeed, the types of thoughts which involve killing one's newborn baby often emerge in mentally disturbed patients. It is thus conceivable that in fact certain fractional brain states actually do threaten the integrity of dominant brain formations and the actual stability of the dominant brain state and trajectory. This description conforms to Freud's notion of ego integrity that is being threatened by repressed mental processes of conflicting ideas or drives.

Occasionally, inadequate fractional brain states may gain access to the dominant brain states and are 'transformed' in order to accommodate the global activation pattern of the dominant brain state. For example, immoral ideation is contradictory to the dominating content of a moralistic conscious awareness. Transforming the wish to behave in an immoral way into moralistic ideation may accommodate the prevailing dominant brain state of a "puritanical message." This type of transformation is known in the psychoanalytic literature as "reaction-formation."

Another transformation of unbearable ideation is known as "isolation." Here, ideation is not excluded from awareness; only certain relevant parts of it are "neutralized." These are the parts that are incompatible with the rest of the conscious message, i.e., the global activation pattern of the dominant brain state. The fractional brain state is included in the conscious awareness emerging from the dominant brain state, only to the extent (i.e., it is isolated) that it is removed from certain contents of the conscious awareness. If isolation is not enough to satisfy the message of the global integration then "dissociation" might occur and certain contents of awareness would be ignored or experienced as independent and unrelated (i.e., split off).

The "transformations" described above are necessary to "protect" the global formation of dominant brain states from being disrupted by contradicting fractional brain states. Therefore, it is conceivable that these transformations justify the term "defence mechanism." They protect the global formation of dominant brain states and prevent its destabilization. From the biological point of reference, this may translate into destabilization of the interrelations between groups of neurons, which presumably have direct neuro-pathological outcomes on transmitter-receptor activity.

Freud affirmed that defence mechanisms reduce anxiety. The conflicting information in the form of constraint frustrations within global dominant activation patterns of the brain states, results in the emergent property of anxious sensations. Thus it is imaginable that defence mechanisms actually reduce such constraint frustrations by allowing only transformed activation patterns of fractional states to participate in the dominant brain state.

We can assume that if defence mechanisms are insufficient, there will be repeated perturbations to the constraint formations and that continuous constraint frustration may eventually push the brain dynamics toward deoptimization shifts. This may explain why anxiety and depression typically manifest together in many patients (i.e., deoptimization results in depressed mood, see above).

We have seen that the extensive psychological literature on "object relations" relates to internal representations of the real world embedded in the brain. It is evident that object relations psychologists concentrated on the study of the dynamics of internal presentations and their

relevance to personality and personality disorders. Internal representations on the neural network level of brain tissue can be explained using the knowledge relevant to information storage in the brain, that of brain plasticity and Hebbian neuronal ensembles. Using the state-space formulation in relation to Hebbian plasticity together with insights from neural networks, a memory embedded in neuronal tissue (similar to a Hopfield model) forms an "attractor" on the space manifolds of the brain. The attractor represents the dynamic tendency of the brain to activate the memory states. Thus, multiple attractor-formations in the dominant space manifold of a brain could provide for internal information embedded in that brain, i.e., the internal object relations. In other words, the manifold attractor-related topography of a dynamic brain system embodies the internal representations of object relations.

Since object relations psychology is relevant for the nature of personality and is useful for treating personality disorders let us examine personality in relation to internal representations. Personality traits are enduring patterns of perceiving, relating to, and thinking about the environment and oneself. They are exhibited in a wide range of social and personal contexts (Sadock 1989). Specific configurations of internal representations have first-hand impact on personality traits. For example, internal representations regarding hygiene, punctuality and precision, are more pronounced for some individuals, while for other individuals other representations are prominent; e.g., vanity and pride. The first example is typical of individuals who give special importance to order and strive to achieve perfection. These individuals are often referred to as having "obsessive" personality traits. The second example is more typical of individuals who regard themselves as special and important. They are often referred to as having "narcissistic" personality traits.

But what shapes these internal representations and how do they mature in the developing brain? From the brief preliminary overview of the psychology related to object relations it is strongly suggested that early experiences shape critical first internal representations. Later on experience keeps shaping the way we view ourselves as well as others in the world around us, thus interaction with the environment is the shaping force that determines our internal object relations. This is in concert with modern knowledge about the brain; 'experience-dependent-plasticity' and is actually a neuroscience explanation for such transmutations. Hebbian processes can now explain internal contexts and information built into neuronal circuitry.

Psychologists have described the gradual, repetitive processes of internalizations that take place during the development of internal representations, for example Kohut talks about transmuting internalizations via "non-traumatic failures" that eventually result in a mature "self" integrated into the personality and identity structure. Neuroscientists have described the processes of "matching complexity" in which stimuli gradually alter connectivity patterns (i.e., Hebbian plasticity) to match input-related (outer-world correspondent) activation patterns in the brain. If we accept the previously described idea, in which internal representations are expressed by attractor formations created by altered connectivity patterns of Hebbian plasticity, then we have the neuroscientific assumption that may explain how the brain forms internal object relations.

Personality assessment equals the assessment of internal representations. Unfolding the subjective experience of the patient and his/her perception of the world, especially of interpersonal experiences, allows for the reconstruction of his/her "internal map" of organismic evaluation. Once reconstructed this internal map of representations (object relations) is a powerful predictor of the modes of reactions and interactions that the patient will actualize. One could easily predict what the patient with predominant internal representations of orderliness and hygiene will experience when confronted with filth and dirt. Personality traits (i.e., emotional responses) emerging from internal configurations of object relations play an important role in the interplay between internal configurations and their optimization dynamics triggered by external events.

A mismatch between the internal configuration and the statistical structure of an input set that is coming from a psychosocial event in the environment can deoptimize the relevant set of internal configurations. Thus, an individual reared to appreciate hygiene and perfectionism will deoptimize these representations when presented with a situation carrying the information of disarray and filth. It is proposed that the combination of certain internal configurations (or sensitivities of personality traits) with certain specifically significant situations (or stimuli) may create frustration of constraints, deoptimization shifts that could trigger anxious depressive reactions (i.e., emergent properties). In effect, certain types of depression (e.g., dysthymia, mixed anxiety and depression) have been typically related to personality disorders in clinical experience.

In addition to the '"structure," "features" and "content" of internal representations, the levels of their development also warrant assessment. We have seen from the descriptions of object relation theoreticians that internal object relations develop gradually from initially primitive unorganized constructs that can be rudimentary, split and incomplete. Such internal representations of context or reference allow for partial and opposing representations to “split” awareness and experiences. For example, partial development of internal representations can induce "all-or-nothing" experiences (black and white attitudes) impeding complex realistic experiences (variations of grey spectrum attitudes). This mode of experiencing reality is non adaptive due to the large discrepancy (mismatch) between what is perceived and what is real. In effect the most serious personality disorders have undeveloped, rudimentary and partial internal representations, meaning that they have non-organized primordial attractor-landscapes within the brain space. This emphasizes the importance of assessing not only the content or configurational map of brain organization but also to the level of development of these internal organizations.

Lower organization levels of internal representations result in psychological attitudes and complaints, which have been called "borderline personality organization". Higher organization levels of internal representations show representational content-relevant attitudes and complaints. Various levels of organizations on a spectrum of personality disturbances can be described.

Authors such as Kernberg and Kohut excelled in describing the consequences of rudimentary partial immature object relations on the behavior of severe personality disorders. If the internal representations cannot distinguish between representations of self in relation to others, then

experiencing attitudes toward others and self become fused with intense self-object dependency, i.e., dependence of self-experience on experience toward others. For example if the person in the relationship is devaluated then worthlessness and self belittlement is experienced. Split incomplete representations limit experience to the split representations causing the individual to be blind to a whole integrated reality, and cause the individual to experience only partial extreme aspects of it (i.e., all-or-nothing, idealization-or-devaluation). This inability to integrate experience toward oneself and others is reflected in extreme unstable behaviours and attitudes, oscillating between idealization of others (and self) and devaluating others and feeling worthless.

These unstable oscillating attitudes translate to unstable relationships in work settings and family frameworks causing incapacity to hold a job or career and maintain family or social relationships. These dynamics constantly cause frustration in the constraints among activated brain states and deoptimization shifts in the dominant brain trajectory, accompanied by continuous experience (emergent properties) of anxiety and depression (i.e., dysthimia mixed anxiety and depression according to the DSM [Diagnostic and Statistical Manual of Mental Disorders] diagnostic system for psychiatry).

PSYCHPATHOLOGY

Connectivity dynamics, disorganized psychosis negative signs and schizophrenia

As mentioned in the introduction, Meynert believed that the associations of an adult ego could be temporarily or permanently weakened. He thought that certain conditions in the brain can produce ego weakness resulting in psychotic states.

Meynert also mentioned that certain toxic conditions also weaken associations, i.e., ego or brain-state organizations. An example is delirium that arises in demented patients from neuronal damage with instability of brain connectivity. This is also evident in toxic conditions caused by psychoactive drugs that interfere with brain neuronal connectivity and neurotransmitter activity. For example LSD creates psychotic experiences by altering neurotransmitter activity.

Although the causes of schizophrenia psychosis are not clear, there is evidence pointing to the assumption that schizophrenia is also a disorder of brain neuronal connectivity, or a 'disconnection syndrome' as described by Friston (1995). Some of the early findings supporting a disconnection syndrome for schizophrenia psychosis are: (1) Principal component analysis of PET data suggests that the normal inverse relationship between frontal and temporal activation on a verbal fluency task is disturbed (they show weak positive correlation). This finding may suggest disintegration between the two areas in schizophrenia patients (Frith et al. 1991). (2) Studies with Functional MRI replicate these findings (Yurgelun-Todd et al. 1995). (3) Subjects imagining another person talking activate left inferior and left temporal cortices (McGuire et al. 1995). Schizophrenia patients not suffering from hallucinations have the same activation pattern as normal subjects. Schizophrenia patients suffering from hallucinations show a reduction in activity of the left temporal cortex, despite normal activation of the left inferior frontal region (McGuire et al. 1993). (4) Phencyclidine (PCP) is a psychomimetic drug that induces schizophrenia-like symptoms (Allen and Young 1978). PCP is a potent inhibitor of N-methyl-D-aspartate (NMDA) glutamate receptors. Glutamate neurotransmission is the mainstay of the excitatory cortico-cortical interactions (Friston and Frith 1995). (5) Reduced EEG coherency between frontal and temporal electrodes are highly correlated with reality distortion symptoms in schizophrenia, suggesting disruption of fronto-temporal connectivity (Norman et al. 1997).

More recent findings that support the disconnection hypothesis involve EEG coherence task-locked to the delay-response epochs of a working memory test. Schizophrenia patients showed less coherent activity during the delay period of the working memory task (Peled et al. 1999). Previous work with gamma-complexity also showed loosened cooperation in the anterior brain regions of schizophrenic patients (Saito et al. 1998) and in acute neuroleptic-naive first-episode schizophrenia patients. Dissociated complexity levels partially regressed, similar to premature brains at an earlier, age were found in schizophrenia patients during a study of the neurodevelopmental hypothesis of schizophrenia (Koukkou et al. 2000).

These findings started to indicate that may psychosis result, or is an emergent property, from global disintegration of the dominant brain organization, as this neuro-system disconnection fragments conscious experience. The specific clinical patterns of psychosis relate to the different neuronal subsystems which are affected.

As consciousness is a result of global brain connectivity organizations, It is thus conceivable that disturbances to connectivity in the brain will fragment the higher-level conscious experience with sensations and concepts disconnected and statistically independent from each other. Thus, thoughts organized as interdependent neuronal activations will become disconnected and unconstrained, causing the individual to suffer from loosening of associations. Since logic is built on semantic integrated network concepts, logical thinking becomes impaired, causing biased erroneous ideas to form (delusions). With the spread of disconnection dynamics loosening of associations in the form of disordered speech is evident and biased erroneous conclusions form. The hierarchal top-down processes may become overly active and constrain information via top-down shifts and thus maintain and increase erroneous conceptualizations (delusions) by damage to the error-prediction and correction processes.

Disconnection-dynamics spreading in the cortex, causes more macro-network disintegration that my cause entire neuronal systems to disconnect from whole brain organization. For example, the auditory cortex with its speech-related adjacent cortical network can become disconnected from the brain with the emergent property of experiencing talking voices emerging from the disconnected brain systems while there is no real auditory input to the brain and regardless of other brain systems such as the visual one. The experience of the patient in such a case will be that of auditory complex hallucinations as is typical in schizophrenia.

The above description indicates how positive symptoms of functional psychosis are explained by disconnection dynamics both in general as well as hierarchal in the brain. This description is supported by many papers in the literature that discuss disconnection and small-world disturbances in psychotic and schizophrenic patients (Guye et al., 2010). In addition, neuronal network models simulating psychosis and schizophrenia-like phenomenon support this notion (Peled & Geva, 2000; Geva & Peled, 2000).

There is less literature about the probable opposing dynamics of Over-Connectivity in the brain. It is well known that increase of connection-strengths in a network model causes the dynamic activity of that model to constrain and even stop. This is typical of a fully connected Hopfield Network (1982) that shows local minima dynamics of restricted activity halting at the attractor local-minima. Other work showed (Geva & Peled, 2000) that increasing connectivity dynamics in network models constrain their activity to few attractors in space state and also shows tendency to repeat and get “stuck” in attractors. This is metaphorically similar to the reduced thought process of negative-signs schizophrenic deficient patients with their tendency to perseverate, which is actually the activation of the few repeated activations in the model. Thus, the poverty of thought and presentations are naturally simulated by over-connectivity dynamics in the brain models.

Another possible aspect of Over-connectivity relates to hierarchy because with fixated connections the bottom-up brain hierarchal organization is hampered. Higher-level construct cannot be formed and this curtails higher-level hierarchal organizations in the brain also resulting in Avolition, loss of motivation, which is one of the more debilitating manifestations of negative-signs schizophrenia. In all, the Over-connectivity dynamics in the brain can begin to explain the negative and deficient signs and symptoms of schizophrenia.

In a more recent review by O'Neill et al (2018) they provide substantial evidence of widespread resting-state functional connectivity abnormalities of the DMN, SN, and CEN in early psychosis; particularly implicating DMN and SN disconnectivity as a core deficit underlying the psychopathology of psychosis.

Schizophrenia is probably an "oscillating disorder" starting with positive symptoms and progressing over-time to deficiency, negative signs and symptoms. Thus from the point of connectivity conceptualizations, patients' brains oscillate between disconnection and over-connection dynamics. As the disease progresses the connectivity organization is progressively damaged, with progression of negative-symptoms increasing over-time. In a very general manner, the spectrum of schizophrenia phenomenology manifestations can be re-conceptualized as disorders of brain-connectivity organization broken down to disconnection over-connection and hierarchical top-down and bottom-up disturbances.

Networks stability perturbations, anxiety and phobia

In order to analyze the emergent phenomena of anxiety we go back to refer to the idea of constraints among brain units (and states) caused by connectivity and mentioned above. In a system, "connection" signifies constraint and the fact that different parts are not independent. The knowledge of one part allows the determination of features of the other parts. A gas where the position of any gas molecule is completely independent of the position of the other molecules is an example of disconnection leading to disorder and chaos. An example of connection leading to fixed order is a perfect crystal, where the position of a molecule is determined by the positions of the neighboring molecules to which it is bound.

"Multiple constraint satisfaction" accounts for the interrelations among multiple units in a system. If the value of the connection-strength between the brain units is substantial, then the constraint of the activity in one brain unit on the activity in the other brain unit is substantial. Conversely, if the strength of the connection is small, then the activity in a brain unit will be less constrained by the activity in the relevant brain unit. In the brain with numerous interconnected brain units, each brain unit simultaneously influences (i.e., constrains) several other brain units, thus the activity of each brain unit is a result of multiple parallel constraints.

When the activity of a brain unit satisfies the input exerted on it by the other connected brain units it, it achieves multiple constraint satisfaction. If the activities of all the units in the system achieve

multiple constraint satisfactions then the system as a whole optimizes multiple constraint satisfaction.

Whenever constraint satisfaction in the brain tends to be disturbed, "frustration" of the connection between the elements in the brain occurs. Frustration indicates that connections are only slightly unsatisfied and implies that the elements of the system act barely in 'disagreement' with the multiple connections among them. The elements in such a system will change their states (i.e., values) in an attempt to reach full satisfaction of the constraints, and continue to change as long as frustration of constraints characterizes the system.

Since the brain is a dynamic system (Globus 1992), once connections are satisfied, the system has already changed and a new set of constraints needs satisfaction. As such, a certain degree of ongoing frustration is typical to the system of the dominant dynamic state. If the frustration of the constraints increases, the dynamic process of constraint-satisfaction increases, causing the elements to change their states more abruptly. If the frustration of constraint increases even more, surpassing the dynamic ability of the elements to change their states, a "danger" of breakdown threatens the connections.

Since the dynamic dominant brain trajectory results from a massive connectivity structure, multiple constraint frustrations can "spread" over many connections in the brain system, and to some extent be "absorbed" by the interconnected structure of the entire system. This process of absorbing the frustrations of the constraints maintains the stability of the global integration within the dominant brain state.

It is suggested that whenever the degree of frustrations applied to the multiple connectivity of the system exceeds the level at which it can be absorbed, the system is "destabilized," and the risk of rupture to the connections becomes imminent. At this level of disturbance, elements in the system change rapidly in a "desperate" attempt to satisfy their connections. It is suggested that anxiety is the emergent property from this type of instability in the neural systems especially in those neural systems that are involved in global formations such as transmodal processing systems of the dynamic dominant brain state.

This model can explain possible relations between conflicting ideas, actions or motivations and anxiety. Let us assume that a population of neurons processes certain information assuming an activation pattern relevant to that information. During the information processing constraints among neuronal ensembles become satisfied toward the relevant information-dependent pattern of activity. Now imagine that another set of information is applied simultaneously to the system. However, the new information contradicts the original information pushing the system to an opposing configuration in comparison to the original information patterns. The result is that units in the system are simultaneously constrained to "comply" with opposing patterns of activity. Opposing patterns of activated units disturb the process of constraint satisfaction that takes place

in the system and causes augmented frustration to the constraint satisfaction processes among units in the system.

Assuming that anxiety is an emergent property of constraint frustration in the system, it is comprehensible that conflicting information processing increases the sensation of anxiety. Conflicting information processing involves experiencing opposing stimuli and confronting opposing actions in decision-making. In effect, our environment as well as our brain system is dynamically changing to provide continuous frustration of constraints in our brain system, thus allowing for a continuous physiological life-long level of anxiety to characterize our psychic awareness.

From the above we can learn that neuronal networks in constant flux of activation inhibition and reconfiguration are constantly changing and are thus unstable. Stability is perturbed by the stimulated activity from the environment and by the "computational load" that characterize neuronal networks activities. These are stabilized by the slightly longer plasticity, the "Reactive Plasticity", which is responsible for maintaining the constraints among working networks and their elements. Frustration of constraints implies that the elements of the system act minimally when in "disagreement" with the multiple connections among them. The elements in such a system will change their states (i.e., values) in an attempt to reach full satisfaction of the constraints, and will continue to change as long as frustration of constraints characterizes the system.

Since the brain is a dynamic system (Globus, 1992), once connections are satisfied, the system has already changed and a new set of constraints requires satisfaction. As such, a certain degree of ongoing frustration is typical to the system of the dynamic core. If the frustration of the constraints increases, the dynamic process of constraint-satisfaction increases, causing the elements to change their states more abruptly. If the frustration of constraint increases even more, surpassing the dynamic ability of the elements to change their states, a 'danger' of breakdown threatens the connections. Since the dynamic core has a massive connectivity structure, multiple constraint frustrations can "spread" over many connections in the cluster system and to some extent be "absorbed" by the interconnected structure of the system. This process of absorbing the frustrations of the constraints maintains the stability of the global integration within the dynamic core.

Whenever the degree of frustrations applied to the multiple connectivity of the system exceeds the level where it can be absorbed, the system is "destabilized," and the risk of rupture to the connections becomes prominent. At this level of disturbance, elements in the system change rapidly in a "desperate" attempt to satisfy their connections. Anxiety is the emergent property of this type of instability in the neural systems, especially in those neural systems that are involved in global formations such as transmodal processing systems of the dynamic core.

The fact that Reactive Plasticity when perturbed generates anxiety supports the fact that a load of cognitive demands and prolonged cognitive efforts are typically accompanied by sensations of anxiety.

The networks that are stabilizing brain connectivity typically those of slower plasticity, i/e/, the DN and the DMN are typically perturbed more than usual when anxiety occurs, this has been recently confirmed by a review made by Van Oort (2017) he found that the acute stress response is consistently associated with both increased activity and connectivity in the salience network (SN) and also with increased activity in the default mode network (DMN), These results confirm earlier findings of an essential, coordinating role of the SN in the acute stress response and indicate a dynamic role of the DMN and are in line with the Neuroanalytic theory.

Optimization dynamics of internal configurations and mood

We have already described that adaptation is related to "optimization" in dynamic systems. Optimization is typically defined as the ability of a system to evolve until it approaches a critical point and then maintain itself at that point. If a particular dynamic structure is optimal for the system, and the current configuration is too static, then the more changeable configuration will be more successful. If the system is currently too changeable, then the more static mutation will be selected. Thus, the system can adapt in both directions to converge on the optimal dynamic characteristics.

In complex systems the dynamics of constraint satisfaction among the units is in continuous flux and can proceed in two directions; 1) optimization, when more constraints become satisfied over time; and 2) deoptimization, when fewer constraints are satisfied over time.

Previously, we assumed that the emergent property of anxiety results from constraint frustrations; now let us assume that depression is the emergent property whenever brain state dynamics is subjected to deoptimization.

Deoptimization shifts in the brain system could be triggered by the alterations of the neural substrate itself (i.e., neurohormonal and neurotransmitter activity). Probably the hormone or neurotransmitter directly alter the transfer functions of the neurons, or their connectivity patterns, and directly alter the space-state topology of the internal configurations. In this manner, configurations that were “normally” optimized could now be deoptimized triggering a deoptimization shift that induces a depressed mood.

To support the idea of neural network alterations in mood disorders there is growing evidence in recent studies that anti-depression treatment is actually related to plasticity and connectivity of neurons in hippocampal and prefrontal brain regions (Laifenfeld et al; 2002; Manji et al. 2003; Coyle and Duman 2003). Recent research into depression has focused on the involvement of long-term intracellular processes, leading to abnormal neuronal plasticity in brains of depressed patients, and reversed by antidepressant treatment (Laifenfeld et al. 2002). There is growing evidence from neuroimaging and postmortem studies that severe mood disorders, which have traditionally been conceptualized as neurochemical disorders, are associated with impairments of structural plasticity and cellular resilience (Manji et al 2003). Postmortem and brain imaging

studies have revealed structural changes and cell loss in cortico-limbic regions of the brain in bipolar disorder and major depression (Coyle and Duman 2003).

In extremely stressful events, such as grief, or calamity, the external constellation of life events changes dramatically. The change typically involves "loss" (certain regular patterns of incoming stimulations are lost) these are the information patterns that represent the lost person or the lost factor. In other words, a loss of a significant figure or factor in one's life leaves the individual without the "regular" usual environmental inputs which that person or factor had generated. Certain configurations that were normally optimized by usual environmental inputs will now suffer the loss of the optimization dynamics and will be deoptimized. This deoptimization can be enhanced by loss of connecting spines and marked pruning of dendrite arbores. Widespread deoptimization of many internal representations could shift the dynamics of the dominant system trajectory toward deoptimization and trigger the emergent property of a depressed mood.

The optimization dynamics can also be described as "Adaptive Plasticity." While fast plasticity continually shape the internal memories the slower adaptive plasticity makes them become permanent. The fast Hebbian dynamics caused by calcium flux and synchronized electrical ion-channels activation potentials, with repeated experiences, training, and skill acquisitions depend on longer processes of Hebbian dynamics, that of actual structural plasticity with generation of new synapse pathways and even neurons. These processes take place in time-scales of days to weeks and act as adaptation mechanisms to the changing fluctuating environmental occurrences. The actual experience embedded as memories forms internal representations of the active external world.

As already mentioned above, Tononi and colleagues introduced a statistical measure, called "Matching Complexity," which reflects the change in connectivity observed when a neural system receives sensory input (Tononi et al., 1996). Through computer simulations, they showed that when the synaptic connectivity of a simplified cortical area is randomly organized, Matching Complexity is low and the functional connectivity does not fit the statistical structure of the sensory input. If, however, the synaptic connectivity is modified and the functional connectivity is altered so that many intrinsic correlations are strongly activated by the input, Matching Complexity increases. They also demonstrated that once a repertoire of intrinsic correlations has been selected which adaptively matches the statistical structure of the sensory input, that repertoire becomes critical to the way in which the brain categorizes individual stimuli (i.e., perceives stimuli).

Thus, the internal representations embedded as statistically input-matching patterns are continuously altered by the configuration of external influences. Once altered, the consecutive inputs are "interpreted" by the recently altered internal representations (see Rogers, "organismic evaluation below).

Recently the fact that adaptive plasticity involves the interactions of the SN and the DMN have been confirmed by a review from Mulders et al 2015 where they find increased connectivity within the anterior default mode network, increased connectivity between the salience network and the anterior default mode network and changed connectivity between the anterior and posterior default mode network. All indicating connectivity formations in the DMN related to the SN activity just as predicted by the neuroanalysis approach.

Psychoanalytic formulations internal configurations, representations and personality disorders

The emergent property of consciousness is relevant to many insights including psychoanalytic insights generated by Freud and later some of his followers.

Combining Baars' theory with notions about hierarchical organization of information (memories) in the brain, it is reasonable to consider that lower level partial processes in the nervous system interact to form higher level neural global organizations. In addition, the idea of internal consistency in global formations captures the basic notion of multiple constraint organization. It is assumed that the dynamic activity of partial processes demonstrate both hierarchical and multiple constraint organizations. For example, once the partial process forms part of the global organization it is interconnected with all the other processes (i.e. is broadcast globally). Thus, it contributes to, or influences, the global organization by virtue of its connections, i.e., by exerting its output through the connections to the rest of the system. On the other hand, because it is a multiple constraint system, many other processes will constrain its activity (through the connections). It can be concluded that from the information processing perspective, the information delivered by partial processes concurrently influences and is influenced by the global message.

Due to internal consistency, if the information structure (i.e., activation pattern) of the partial process "contradicts" (i.e., markedly differs from) the information being represented in the global formation, the partial process will have "difficulty" gaining access to (or fitting with) the global process. This is due to the multiple constraints between the partial process and the global formation, which will not be satisfied in such a situation. Global formations are higher levels of organization (from the hierarchical perspective). Thus, by constraining partial processes that are most likely of lower levels, top-down control blocks access of partial processes to global formation (i.e., "repression"). Partial processes compete for access to global formation, creating the bottom-up procedure. A balance between bottom-up and top-dawn processes then becomes crucial for the contents that reach global formations and consciousness.

The first concepts introduced by Freud in his topographic model were related to the levels of consciousness. We now have the tools to define his description of conscious, unconscious, and subconscious as levels of integration that partial processes achieve to form global organizations. Conscious awareness is the property of global formations. Unconscious information is presented

as partial processes that do not contribute to the global organizations. The subconscious is characterized by those processes that are about to contribute to, or drop out of, the global formations. In the structural model, psychic "compartments" such as the ego and id were conceived. The ego is described as developing from what was initially the id in the infant. The id is described as a disorganized system where concepts are disconnected or dissociated in every "strange" possible way. Freud named this form of inconsistency "primary thought process." From the system point of view described so far, primary thinking can be conceptualized as a feature of a system without internal consistency, or, in other words, where multiple constraints are not satisfied. This enables conflicting ideations to coexist and concept formations that do not make any sense to predominate. Biological evidence shows that in infants, synaptic connectivity is just beginning to develop. Thus, the biological neural correlate at this phase of development cannot support the needed multiple constraints organization that forms the basis of ordered mental activity. Ego development involves the formation of a secondary thought process. This process is described by Freud as the normal thinking that characterizes each one of us. In other words, secondary thinking emerges from multiple constraint satisfaction organization of the neural system; and in fact, synaptic connectivity fully matures from infancy to adulthood. By introducing the concept of superego, Freud suggested what were later to be developed as internal representations of social and interpersonal norms. This line of thinking gave the ego (i.e., its superego portion) not only the scope of organizing the disordered id processes, but also the entire responsibility of representing, and adapting to, psychosocial reality. Introduction of the dynamic model added the interplay among the psychic compartments of Freud's model. "Defense mechanisms" are probably the most described dynamic factors in this model. According to Freud, the ego makes use of an unconscious domain of mental activity (also referred to as id) into which undesirable drives and ideas are repressed. "Repression" has been described as the mental mechanism that "guards" the conscious awareness from the intrusion of inadequate and intolerable ideas or drives. Repression keeps them unconscious. Freud indicated that the intruding ideas and drives from the unconscious actually threaten ego integrity.

Based on the formulation described so far, repression can be re-conceptualized as the dynamics of participating, as well as nonparticipating, processes in the global formations that support conscious phenomena. Partial processes that do not gain access to the global process remain unconscious (i.e., repressed). Because of the multiple constraints that characterize global organizations, certain partial processes may encounter difficulties in accessing the global formations. This is especially true if the partial processes carry information that is entirely removed from, or contradictory to, global messages. Based on these assumptions it is possible to conceive that information comprised of contradictory and unfitting messages (i.e., partial patterns that do not satisfy the constraints of global patterns) will be denied access to the global organization. In fact, Freud described repressed contents as conflicting topics or unbearable ideas. Here, "unbearable" refers to information (of the partial process) that is removed from (i.e., unfitting with) the information presented by the global formation. The unbearable partial process cannot be incorporated into the general message without damaging its internal consistency (i.e., its multiple constraint satisfaction organization) and

therefore it is bound to be excluded. For example, to a mother of a newborn baby, the idea of killing her baby extremely contradicts the normal loving and caring state of mind typical of a new mother. If inadequate partial processes somehow gain access to the global organization, they are inclined to destabilize or even disrupt it. If many conflicting and disrupting processes gain access to the global formation, the entire global message may be destroyed and the neural system representing it is bound to destabilize. Indeed, the types of thoughts that involve killing one's newborn baby often emerge in mentally disturbed patients. It is thus conceived threatening to the integrity of global organizations and the actual stability of neural systems. This description conforms to Freud's notion of ego integrity being threatened by repressed mental processes of conflicting ideas or drives. Occasionally, inadequate partial processes may gain access to the global organizations and be "transformed" in order to accommodate the global pattern. For example, immoral ideation is contradictory to the dominating content of a moralistic conscious awareness. Transforming the wish to behave in an immoral way into moralistic ideation may accommodate the dominating global organization of a puritanical message. This type of transformation is known in the psychoanalytic literature as "reaction formation." Another transformation of unbearable ideation is known as "isolation." Here the ideation is not excluded from awareness, but certain relevant parts of it are "neutralized." These parts are incompatible with the rest of the conscious message. The partial process is included in the conscious awareness only to the extent that it is removed from certain contents of the conscious awareness (i.e., isolated). If isolation is not enough to satisfy the constraints of global formations, then *dissociation* might occur, and certain contents of awareness will thus be ignored or experienced as independent and unrelated. The transformations described above are needed in order to protect the global formation from being disrupted by contradicting partial processes.

Therefore, it is conceivable that these transformations justify the term "defense mechanism." They protect the global formations and prevent destabilization of multiple constraint activity in the neural system. From the biological point of reference, this may translate into destabilization of the interrelations between groups of neurons, which presumably has direct neuropathological outcomes on transmitter-receptor activity.

The psychologist Carl Rogers (1965) suggested that the best vantage point for understanding behavior is from an "internal frame of reference" of the individual himself. He called this frame of reference the "experiential field," and it encompasses the private world of the individual.

Neuroscience teaches us that experience dependent plasticity creates internal "maps" to represent information. One of the more famous examples is the homunculus of sensory and motor representations spread over the cortex. Just as the homunculus is probably formed from the strengthening of synaptic pathways (i.e., Hebbian dynamics), the experiential field probably results from experience-dependent plasticity in the brain. In terms of space-state formulation (see above), the experiential field can be conceptualized as a configuration of attractor systems in the brain.

According to Rogers, "organismic evaluation" is the mechanism by which a "map" (i.e., an internal configuration) of the experiential field perceives the psychological events of everyday life. Using the formulation of state-space for internal representations, organismic evaluation can be re-conceptualized as convergence into, or activation of, relevant experience-dependent attractor configurations of the internal map. If the incoming experience is identical to the previous internal representation of that experience, no change will occur and the map of internal representation will activate familiar past experiences. On the other hand, if the new experience is slightly different from the previous experience, this will be enough to "reshape" the topological map and add attractor systems to the internal configuration. Activation of the internal map organizes the incoming stimuli into a meaningful perception. The newly perceived experience is meaningful when it relates to the previous experience already embedded in this map. This is a circular process in which the map of internal representation simultaneously influences, and is influenced by the incoming stimuli. In other words, the brain sustains a map of internal representations that is continuously updated through interactions with the environment.

This type of interaction between internal representations and perception of environmental stimuli has been referred to as context-sensitive processes (Tononi et al 1994). Owing to this interaction, internal representations can be viewed as approximated models of reality. It is reasonable to assume that a "good match" between internal representations (of the psychosocial world) and external psychosocial situations will enable efficient adaptive interpersonal relationships. On the other hand, a "mismatch" between the psychosocial events of the real world and their internal representation may "deform" both the perception and the behavioral responses of the individual. The concept of matching complexity (see above), further indicates that mismatch will be related to reduced neural complexity in the relevant neural systems and thus will be responsible for more adaptation problems on the neuro-computational level.

The process of creating the specific maps of attractor configuration in different individuals depends heavily on the background experiences of the individual. The developmental experience-dependent processes responsible for the formation of internal representations of context may involve deviations from the "normal itinerary" of internal representations needed for "regular" psychosocial function. These deviations may form internal representations that are greatly removed from psychosocial realities. A large mismatch between internal representations and environmental reality is likely to provoke distortions that lead to disturbances in perceiving and reacting to the environment (such as personality disorders).

To a certain extent, incoming information from environmental stimuli maybe conceptualized as partial processes competing to gain access to global organizations of conscious awareness. A large mismatch between the internal map of representation and the pattern of environmental stimuli is likely to create the same difficulties that conflicting partial processes may encounter when trying to gain access to global organizations of conscious awareness (see above). This mismatch may distort the incoming information similar to the way unfitting partial processes that attempt to

access the global workspace are distorted; they have to be transformed before they can participate in the dominant message of conscious awareness.

A good example of this distortion is seen in the phenomenon of "transference." Transference is regarded as an attitude toward an event or individual that is based on previous experience with similar events or people that is not congruent with the current situation. Thus, the incoming stimuli from the psychosocial event are distorted to "fit" the internal representation of similar events already dominating the global processes in conscious awareness. Since incoming information is "evaluated" by internal representations, and since these are formed by experience, it is only natural that many of the perceptions we have are related to past-experiences. When a set of stimuli of a new psychosocial event enters the system and causes it to converge to a set of attractors that represents similar past experiences, that set of attractors activates the past-experience in the global organization, bringing it to a conscious level. The conscious awareness regarding the individual or event that provoked this process will be perceived in many connotations as being the past-experience. If there is a substantial mismatch between the internal representations and the actual psychological event, the transference (i.e., the perception as past-experience) may distort the perception of that psychological event.

Matching complexity may be the future mathematical tool that will predict to what extent transference is likely to determine one's behavior. Sometimes the set of environmental stimuli is so removed from any context of internal representation that it is totally unperceived by the individual. This is defined in psychodynamic terms as "denial."

Considering the above, we can redefine the process of developing personality traits and maturation as a life-long process of Adaptive Plasticity, which gradually incorporates the experiences of an individual (i.e., experience-dependent-plasticity) to create memories-dependent internal representations. Such internal representations incorporated by Hebbian dynamics can be also defined as internal objects. They represent not only the physical environment but also complex presentations of peoples' attitudes and behaviors, our self-representations (self-objects) and the relationships formed among others and ourselves. This past psychosocial experience once internalized in the form of internal-maps becomes the point of reference for our understanding and familiarity, and thus serves as an evaluation-map ("organismic map" according to Rogers (1965)). Our psychosocial experience will determine how we perceive and react psychosocially, and will determine our personality styles.

Distortions, immaturity and biases in developmental plasticity will cause maladaptive constant predictable pervasive behavioral problems typical to those suffering from personality disorders. In short, personality disorders are disorders to developmental plasticity networks.

BRAIN PROFILING

"Brain Profiling:" Translating phenomology to brain etiology

Brain Profiling is the diagnostic process based on neuroanalysis. Brain Profiling is the etiological diagnostic formulation for mental-disorders making the daunting conceptual leap of defining mental disorders as brain disorders. Even-though theoretical, Brain Profiling is a reasonable estimation of genuineness based on the fact that it was developed built on empirical peer-review literature, and more than two decades of associating neurocomputational conceptualization with that of neuroscience and clinical literature.

Based on the previous chapters, Neuroanalytic theory for psychiatry is rather straightforward. It is based on the assumption that mental disorders are "emergent properties" from the disturbed brain network dynamics.

Emergent properties are typically defined by the statement that the "whole is more than the sum of its parts". This is true for systems characterized by non-linear interacting elements. The emergent properties evolving from the complexity of the brain are phenomena such as consciousness, mood and personality. One neuron, or even a large group of neurons, do not show characteristics such as consciousness, mood and personality. However the whole brain integrative activity does. Thus, in disturbances to consciousness, mood and personality, we assume that whole brain organization will be influenced. Different phenomenological manifestations of mental disorders are caused by different types of neuronal network "breakdown" patterns.

To recapitulate and condense the Neuroanalytic process for Brain Profiling diagnosis of mental disorders in this chapter we shall translate the phenomenology of psychiatric disorders as follows:

1) Psychosis and schizophrenia
2) Negative signs and deficiency
3) Mood and Anxiety
4) Personality disorders

Into the three major brain-organizational disturbances:

1) Brain arrhythmias (network connectivity hierarchy and topological configurations),
2) Brain Dynamics (plasticity timescales),
3) Brain Anatomy (networks hubs)

But first we shall give a brief description of the healthy optimal brain.

The optimal brain.

However before we discuss the altered deficient and perturbed brain we shall briefly describe the optimal (healthy) brain. Anatomically the optimal brain is organized as vast neuronal network spread in the brain and each instant the brain assumes a highly hierarchical whole-brain optimal configuration. The brain is very dynamic and the major organizational configuration takes the form of the Central Executive Network (CEN) the Salience Network (SN) and the Default-Mode Network (DMN) with their relevant hubs acting as the organizational "anchors" where the peak activity is optimized.

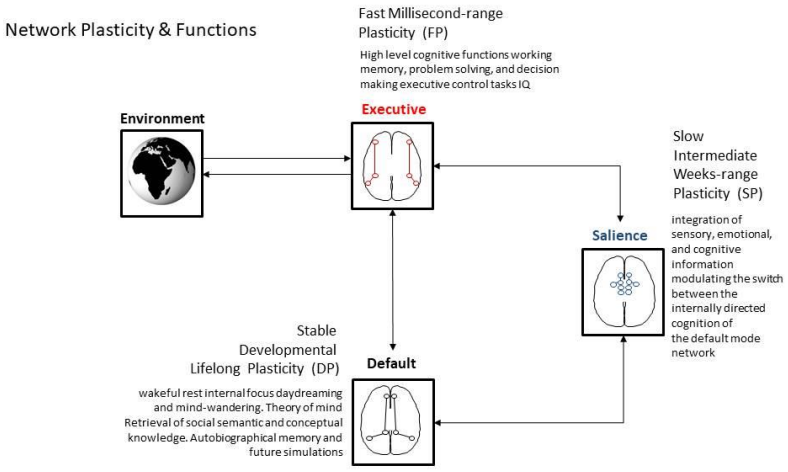
All networks obey the nonlinear, hierarchal connectivity and Hebbian small-world connectivity ensembles these can be seen as the brain normal rhythmic (comparison with the optimal cardiac rhythmic activity) which can be later compared to pathology of brain arrhythmia (equivalent to cardiac arrhythmia causing cardiac illness).

Networks connect (synchronize activity) too compute cognition, use hierarchy to achieve abstraction and predictions, and change structures for permanent stable configurations.

The millisecond range interactions of synchronized neuronal network activity are the fast plasticity interactions, typically activated within the CEN. The adaptive optimization of error-prediction and adaptation to the changing environmental stimuli is on a longer time-scale that of days and weeks, it is relevant to the activity of the SN that orients externally-relevant events of the CEN, to the internally oriented configurations of the DMN.

Finally the continually repeated experiences coded by the CEN are embedded by Hebbian dynamics into the configuration of the DMN creating a lifelong plasticity process which embeds experiences into attractor –formations, thus creating the internal models of experience, or as object relationship psychologists call it, the "Object Relationships." Such representations can be seen as internal "maps" (e.g., the homunculus) used to represent the environments as maps for optimally acting upon those environments. Good match of internal models to their corresponding realities offers an optimal good action within those environments, one which is beneficial for good optimal brain function. Figure 3 schematizes the optimal brain networks anatomy, plasticity and function.

Figure 3



These network systems and their dynamics evolve gradually with neuronal and psychological maturation. The DMN matures by evolving into a well-organized small-world network organization (Meng L, Xiang 2016). The organizing forces probably emerge from stabilization of networks as to specialize in optimal coping and interaction with the dynamic environments.

The environment of the normal child is relatively stable as the family organization and upbringing carries stability and repeatability of life-events and consistent education. The structured environmental stimuli offer the basis for proper Hebbian dynamics which allows the organization of the DMN and its stabilizing effects on the CEN via the action of an effective SN.

As is evident from disturbance to developmental processes (personality disorder below) if networks do not mature into stable dynamic small-word optimal organizations the entire brain optimization may collapse creating various patterns of disorganization making the individual prone to various manifestations of mental disorders.

Networks can also become perturbed and malfunctioning due to multiple reasons, starting from structural neuronal malfunctions, via functional organizational neuronal discoordination (i.e., arrhythmias) up to perturbating stimuli from harsh environmental occurrences. The combination of these are relevant and often the rule, especially when occurring during developmental processes.

Here we describe each major type of disturbance and relating to the 1) brain arrhythmias, 2) dynamics and 3) anatomy

Psychosis and Schizophrenia

As evident from the studies cited above disconnection is the hallmark of psychosis dating back to Theodor Meynert's writing in 18 hundred. In modern terms disconnection would be altered small-world organization as to create changes in clustering coefficient and long-pathway with reduced hub connectivity altogether causing the network organization to disintegrate with emergence of fragmented conscious manifestations. Disconnecting the auditory cortex from visual and other brain systems causes auditory hallucinations. Disintegrated conceptual semantic networks result in loosening of associations. Behavior is erratic and disorganized, abstraction is lost logic (which is based on conceptual association) is disturbed, in total the phenomenology of functional psychosis arises from the disconnection dynamics.

Disconnection applies also to interactions among networks with altered higher level organization of concepts at the DMN. Hierarchy disconnectivity may bias incoming experiences via possible top-down distortion, this will cause delusions which can be of different level of organization, from systemized delusions to fragmented delusions. In all, it is presumed that the entire spectrum of functional psychotic manifestations can be explained by disconnection dynamics, general and hierarchal.

Since the psychotic manifestation afflicts conscious cognitive processes which act in the realm of the millisecond range they involve the fast millisecond range plasticity that anatomically relates to the CEN. Thus one can conclude that psychosis is a result of CEN disconnection and fragmentation in the fast (millisecond range) plasticity. In other words the brain arrhythmia is the "Disconnection", brain dynamics is the fast plasticity and brain anatomy is the CEN and its connection to other network organizations.

Negative signs and deficiency

When elements in a system over-connect they constrain each-others activity limiting the entire dynamics of a system. Reactivating each other via increase connectivity dynamics the system becomes repetitive and tends to freeze assuming local minima attractor states. The space of the system limits into few attractor-states reducing all possible states that the system can assume (see above state-space dynamics).

This description is typically relevant to the description of negative signs in schizophrenia. The patients become perseverative repeating the same concepts over and over again; the thought is constricted to few concepts with emergence of poverty of thought and speech.

Such Overconnectivity hampers hierarchical organization as higher-level formations are damaged, and also connections to other higher-level networks can become hampered. Hierarchical insufficiency ensues with disturbances to the emergent-properties of motivation and volition thought to arise from the highest hierarchal formations of the brain.

Thus 'Overconnectivity Dynamics' and 'Hierarchal Insufficiency' are responsible for the negative signs of schizophrenia. Plasticity wise, they also occur in the fast plasticity range of the CEN thus

when formulated as brain arrhythmias, dynamics and anatomy they involve, Overconnectivity, Fast-Plasticity and the CEN correspondently.

Mood and Anxiety

The environmental interactions and experiences computed by the activity of the CEN are continually embedded into the configurational experience-dependent developmental-plasticity of the DMN. This is achieved via the adaptive plasticity processes (weeks-range plasticity) of the SN (Figure 3). This process of adaptive plasticity is described by the Free-energy (Delta reduction) theory of Karl Friston (Almgren et al 2018) where the brain acts as error reduction machine, in the sense that it continually predicts and assesses-errors between internal configuration and environmental occurrences and acts to minimize the errors, thus acting as free-energy, or delta (differences) reduction. Such process has also been described (above) as matching complexity explaining how internal representations are formed by experience- dependent Hebbian dynamics.

The process of error, free energy reduction and matching-complexity all optimize internal configurations, and give raise to the emergent property of satisfaction, mood elation and antidepressant sensations. If mismatch between occurrences in the environment and the internal configurations occurs, then free energy increases and deoptimization dynamics becomes dominant with the emergent property of depressed mood.

Elaborating in optimization dynamics, it is evident that de-optimization dynamics will result from two factors (or their combination): 1) that of reduced plasticity of the neuronal network and 2) large fluctuating alternations of the external environmental occurrences. Reduced adaptive plasticity may occur because of neuronal factors such as neurotransmitter alterations, neuro-hormonal factors and any atrophy-inducing biological factors. This will cause the adaptive plasticity to slow-down and relative to the continually changing environment, the free energy will increase De-optimization will occur and depressed mood will emerge.

On the other hand adaptive plasticity can also be altered by major alterations in the environment (stresses, i.e., any stress is characterized by alterations in the environment) such alterations that depart from the internal-representations naturally increase the delta between internal representations and external events causing the emergence of depressed mood.

It is thus evident that both “reactive depression” and what has been previously called “Endogenic Depression” can be explained by one model of optimization dynamics. Thus for example, if an elderly patient with brain atrophy and reduced brain plasticity is institutionalized, alerting his environmental habitation of external environment, it is predicted that free-energy will increase both by altering the environment as well as by atrophy and reduced-plasticity explaining why depression is typically characteristic in such cases.

With such description it is not surprising that alterations of the SN and the DMN were found to be involved in depression (Mulders et al 2015). Using the brain arrhythmias, dynamics and anatomy formulations mood is related to matching (reduction of free-energy dynamics), plasticity that is in the adaptive slow (days to weeks) range of the SN and the DMN.

As already mentioned above neuronal networks in constant flux of activation inhibition and reconfiguration are constantly changing and are thus unstable. Stability is perturbed by the stimulated activity from the environment and by the "computational load" that characterize neuronal networks activities. These are stabilized by the slightly longer plasticity, the "Reactive Plasticity", which is responsible for maintaining the constraints among working networks and their elements. Frustration of constraints implies that the elements of the system act minimally when in "disagreement" with the multiple connections among them. The elements in such a system will change their states (i.e., values) in an attempt to reach full satisfaction of the constraints, and will continue to change as long as frustration of constraints characterizes the system.

As already mentioned above, since the brain is a dynamic system (Globus, 1992), once connections are satisfied, the system has already changed and a new set of constraints requires satisfaction. As such, a certain degree of ongoing frustration is typical to the system of the dynamic core. If the frustration of the constraints increases, the dynamic process of constraint-satisfaction increases, causing the elements to change their states more abruptly. If the frustration of constraint increases even more, surpassing the dynamic ability of the elements to change their states, a 'danger' of breakdown threatens the connections. Since the dynamic core has a massive connectivity structure, multiple constraint frustrations can "spread" over many connections in the cluster system and to some extent be "absorbed" by the interconnected structure of the system. This process of absorbing the frustrations of the constraints maintains the stability of the global integration within the dynamic core.

Whenever the degree of frustrations applied to the multiple connectivity of the system exceeds the level where it can be absorbed, the system is "destabilized," and the risk of rupture to the connections becomes prominent. At this level of disturbance, elements in the system change rapidly in a "desperate" attempt to satisfy their connections. Anxiety is the emergent property of this type of instability in the neural systems, especially in those neural systems that are involved in global formations such as transmodal processing systems of the dynamic core.

The fact that Reactive Plasticity when perturbed generates anxiety supports the fact that a load of cognitive demands and prolonged cognitive efforts are typically accompanied by sensations of anxiety. Using the brain arrhythmias, dynamics and anatomy formulations anxiety is related to fast reactive plasticity that involves the activity of all networks CEN, SN and the DMN.

Personality disorders

As mentioned above, the process of adaptive plasticity acts to embed the experiences picked-up by the fast-plasticity of the CEN, into stable memories and internal representations of experience which later, once formed, act as navigators (internal maps) of action and behaviors acting in the world's complicated environmental manifestations. The time scale of personality is that of a lifetime. Actually the personality styles of each individual result from the total experiences that shaped the way he perceives and react to the environments and their psychosocial manifestations.

If upbringing is disturbed and the individual grows in unstable erratic reality, (this is typically broken turmoil homes), Hebbian assemblies do not form, internal representations are deficient partly-matured and unstable, the entire internal-configuration of the DMN cannot develop properly. Such maturation of the DMN and its internal presentations is a source of whole-brain instability. First the alterations of the internal repetitions frequently fail to adapt to the environmental occurrences with the emergence of depression due to deoptimization dynamics. Second, the instability distributed in the networks can result in anxious mood. Finally if instability is extreme, it can fragment networks causing the emergence of psychotic symptoms. In fact, the clinical manifestations of those defined as suffering from personality disorders are anxiety, depression and brief transient psychosis.

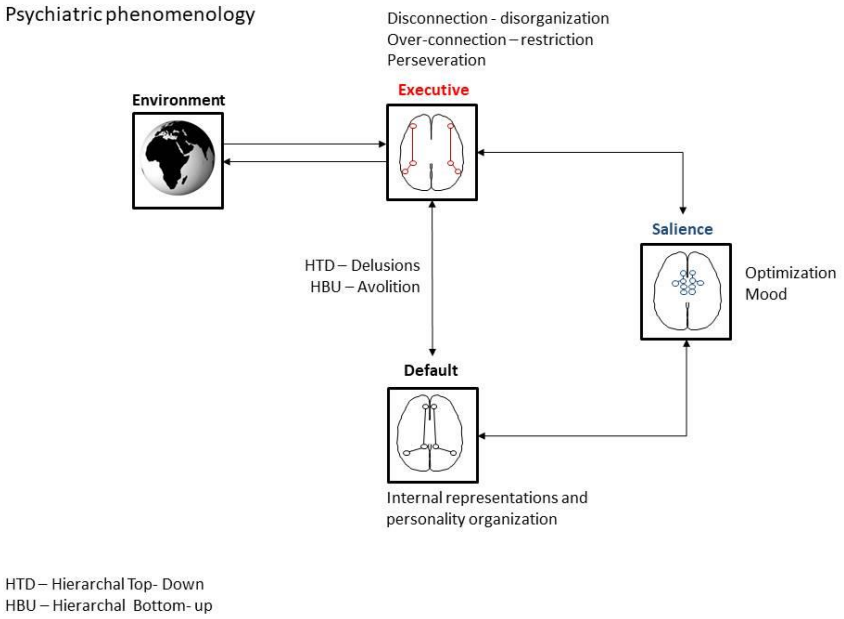
The interplay between activity of CEN fast-plasticity cognition and consciousness, and DMN developmental slow stable plasticity with its internal-representations, has been detailed above, and related to psychoanalytic conceptualizations of defense mechanisms and object-relationship psychology. These indicate that the psychology-biology divide is not real and that experience-dependent therapies such ag psychotherapeutic interventions are not less biological than any other intervention in the brain, e.g., medications.

To reformulate personality disorders in the concise conceptual framework of brain arrhythmias, dynamics and anatomy, we can assume that they result from immature, unstable attractor-configurations as the fundamental arrhythmia, which afflicts the life-long developmental plasticity, and is located in the distributed DMN of the brain.

Table 1 summarizes the brain arrhythmias, dynamics and anatomy of the various mental disorders.

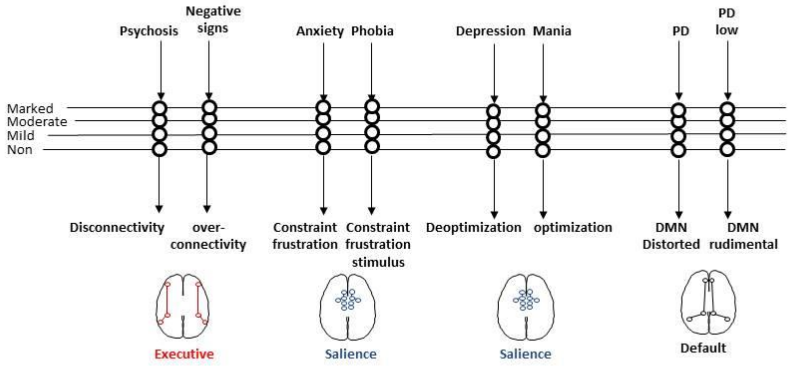
	Brain arrhythmias	Brain Dynamics	Brain Anatomy
Psychosis and schizophrenia	Disconnection dynamics general and hierarchal	Fast millisecond-range plasticity	CEN
Negative signs and deficiency	Over-connection dynamics general and hierarchal	Fast millisecond-range plasticity	CEN
Anxiety	Instability of connections (constraints frustration)	Fast minutes-range plasticity	CEN SN DMN
Mood	Optimization of matching and Free-energy alterations	Slow days, weeks-range plasticity	SN DMN
Personality disorders	Attractor internal configurations and maturation	Lifelong developmental plasticity	DMN

Figure 4 schematizes the networks and the related psychopathology.



The brain profiling diagnostic framework for psychiatry can be formulated as translational schema that can act also as a documentation form or computer program (figure 6).

Figure 6



The patient is diagnosed with the regular descriptive DSM-like rating scales (upper part of figure 5). Degree estimation is a roughly ‘Mild,’ ‘Moderate’ and ‘Marked,’ scale, which them outputs brain disturbances specific for each phenomenological symptomatic rating (lower part of figure 5). Thus in the end, a personalized diagnostic profile of the patients involves both the descriptive regular diagnosis as well as the presumed testable predicted profile of brain disturbance.

NEUROANALYTIC TREATMENTS

The brain profiling diagnostic framework specifies new approaches to psychiatric treatment (i.e., the 'Neuroanalytic Treatment'). The uniqueness of the Neuroanalytic Treatment approach is a combined technology-based intervention which can be implemented when the e brain-profiling framework is utilized. Thus, the brain-profiling framework opens up a novel rationale for an innovative approach to the treatment of mental disorders.

Within the brain-profiling framework, old and new treatment options can be combined, new interventions can now have a guiding -rationale. Novel combinations of typical treatments and new interventions not previously attempted will inevitably require research validation.

Combined interventions should be tailored to the normal activity of the brain. The brain combines tissue-related capabilities that interact with the environment, thus interventions should combine 1) direct therapeutic manipulation of the brain's neural networks plasticity, and 2) therapeutic modulations of experiences, in other words beneficial experience- dependent- plasticity interventions. Currently the regimen of medications in psychiatry is directed to the molecular (neurotransmitter) level of brain tissue where plasticity induction of SSRI in depression currently seems to be one of the more effective treatments in psychiatry. Even though there is growing realization of the neuronal-network level in the etiology of mental disorders, only a few therapeutic interventions have been conceptualized to intervene at that network level (e.g. transcranial magnetic and current stimulations). Finally, therapeutic modulations of experiences, known as 'Psychotherapy' are interpersonal relationships between patient and therapist in psychotherapy sessions, which use corrective experiences to modulate internal representations resulting in symptom-reduction and empowerment. Various psychotherapies target different levels of symptomatic manifestations. For example CBT (cognitive behavioral therapy) targets a more forward cognitive process of emotions to modulate and treat depression. Recently, VR (virtual reality) technology has exhibited potential for powerful experience modulation, currently for treatment of phobias and post-traumatic stress disorder (PTSD)..

The proposed comprehensive Neuroanalytic Treatment can be implemented when the clinical brain profile diagnostic framework is utilized. , Direct brain interventions (medication molecular interventions and 'brain-pacing' network interventions, combined with experience-dependent indirect external modulations can be used to treat connectivity alterations in the fast plasticity of the Central Executive Network, the instability and altered optimization of the slow plasticity which inflicts Salient Newton dynamics, and finally the altered life-long developmental Default Mode Network.

Treating Connectivity & Schizophrenia

Antipsychotic medications are direct brain interventions on the molecular level, that treat connectivity alterations in the fast plasticity of the Central Executive Network. . It is not clear how dopaminergic blocking exerts the antipsychotic affect. The dopaminergic synapses exert both an excitatory (direct) effect on the pyramidal cells of the IV layer of prefrontal cortex, as well as an inhibitory effect (via excitation of inhibitory interneurons) on the same pyramidal neurons. Thus, it is possible to conceive a dual excitatory and inhibitory outcome as a regulatory modulating effect on the pyramidal neurons. Since these neurons receive massive inputs from large cortical regions and out-puts that are distributed efferents to similarly large cortical areas, it can be presumed that these neurons act as connectivity hubs of whole-brain wide spread cortical network connectivity control. Even though antipsychotic agents seem to work on such a modulating network circuit, clinically, once patients suffering from psychosis respond to the medications, they often develop negative symptoms, which indicates that the intervention was not regulatory but rather a phase - transition from psychosis of positive symptoms to deficiency expressed in negative signs, i.e., the modulation does not really optimize connectivity to achieve a pre-morbid healthy state and elimination of symptoms.

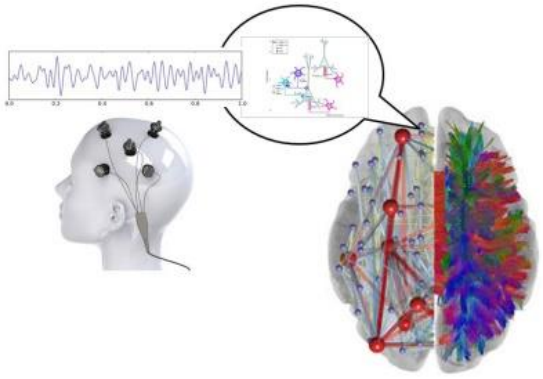
Thus, it is suggested that antipsychotics should be administered at minimal dosages while introducing an additional novel, currently available, direct network-regulating intervention, e.g. 'brain-pacing' transcranial alternating current stimulation (tACS).

Transcranial current stimulation is a non-invasive brain stimulation technique. Low intensity transcranial electrical stimulation (TES) in humans, encompassing transcranial direct current (tDCS), transcranial alternating current (tACS), and transcranial random noise (tRNS) stimulation or their combinations, appears to be safe. No serious adverse events have been reported in over 18,000 sessions administered to healthy subjects, neurological and psychiatric patients (Antal et al 2017). Specifically, tACS seems likely to open a new era in the field of non-invasive electrical stimulation of the human brain by directly interfering with cortical rhythms (Andrea and Walter, 2012). tACS is hypothesized to influence endogenous brain oscillations. If applied for a long enough period ot time, it may cause neuroplastic effects as tACS can be tuned to local neuronal network dynamics entrenching these oscillation dynamics (Cottone et al 2017). In the theta range (4-10Hz) it may improve cognition, gamma stimulation (30-100 Hz) and gamma intrusion can possibly enhance or interfere with attention respectively. Frontal theta-tACS generates benefits on multitasking performance accompanied by widespread neuronal oscillatory changes (Hsu et al 2017). Active tACS improved learning ability, but at the same time interfered with applying the rule to optimize behavior (Wischnewski and Schutter 2017). Phase synchrony of tACS is thought to entrain and enhance neural network oscillations, however, antiphase stimulation desynchronized theta phase coupling and impaired adaptive behavior in one study (Reinhart 2017). Thus, tACS when desynchronized, can also attenuate neuronal oscillations and event-related oscillatory activity can be inhibited using a rhythm slightly below the stimulation frequency.

Clayton et al 2018 found that alpha-tACS appeared to exert a consistently stabilizing effect on visual attention. They suggested that these results are most consistent with the view that alpha oscillations facilitate processes of top-down control and attentional stability. Luft et al., (2018) found that right temporal alpha oscillations may support creativity by acting as a neural mechanism for active inhibition of obvious semantic associations, thus creating in some sense, loosening of associations to offer place for creativity of non-obvious associations. This supports the assumption that increase in alpha dissociates and disconnects the system. In another study Prefrontal IAF-tACS (Berntsen et al 2018), led to significant improvement in motor sequence reproduction. In a previous study using transcranial alternating current stimulation (tACS), van Schouwenburg et al (2017) found preliminary evidence that phase coherence in the alpha band (8-12 Hz) within the fronto-parietal network may critically support top-down control of spatial attention. In a new study van Schouwenburg et al (2017) found no spatially selective effects of stimulation on behavior or coherence in either stimulation protocol compared to sham. This is explained by the fact that in their study, subjects were not stimulated at their individual alpha frequency; everyone was stimulated at the same frequency (10 Hz). Differences in the size of the stimulation electrodes caused the stimulation to be lower intensity; 0.11 mA/cm^2 instead of 0.32 mA/cm^2. Clinical improvement of auditory hallucinations correlated with enhancement of alpha oscillations (Ahn et al 2018). Together, their findings suggest that tACS has potential as a network-level approach to modulate reduced neural oscillations related to clinical symptoms in patients with schizophrenia. Micheli et al (2018) mentioned abnormal gamma oscillations, measured by electroencephalography, that were associated with chronic psychotic disorders and White and Siegel (2018) addressed evidence indicating that there is increased resting-state gamma power in schizophrenia

These recently accumulated research insights support attempts to regulate oscillatory neuronal activity for therapeutic purposes. Combining the knowledge presented thus far, it is possible to attempt control over connectivity dynamics in the brain by manipulating prefrontal cortex (PFC) hub neurons with tACS.

Figure 7



Assuming that increased gamma activity is related to positive symptoms and relevant to an increased threshold and disconnection dynamics in computational models of psychosis, then interference or slightly lower gamma rhythm tACS may reduce gamma oscillations resetting the PFC hub neuronal activity offering over-connection dynamics to rebalance disconnection disturbance and to reconnect networks activity. Contrary to such intervention in patients with negative signs schizophrenia where over-connectivity is the predicted pathology, an increase of gamma activity (increasing threshold) and disconnecting the overly-connected network could be the beneficial therapeutic intervention.

To understand in-depth how tACS is directed toward regulating an important brain hub it is important to take an example and dwell on the neuronal structure and the tACS structure-related intervention. For this example, let us concentrate on the prefrontal cortex networks and gamma oscillations taking into consideration calcium-binding protein of parvalbumin interneurons and their role in severe mental disorders;

The prefrontal cortex (PFC) is involved in many mental disorders (Arnstein 2010) and especially in severe disturbances such as positive and negative signs schizophrenia. The involvement of PFC in disturbances to higher mental functions is relevant to its neuroscientific characteristic as a major 'Network Hub' in the brain, receiving multiple afferent pathways and radiating numerous efferent pathways to distant brain regions (Liau et al 2013). As a brain network hub, the PFC has the potential to alter and regulate distributed neuronal network dynamics in the brain, responsible for global brain organizations underlying higher mental functions such as consciousness, attention, executive foundations, mood and feelings.

Brain dynamic organization of neuronal network activity is presumed to correlate with electrical oscillations measured over the scalp, propagating from the brain neuronal activity. Gamma oscillations (30-100 Hz) have been repeatedly correlated with distributed neuronal network activation over distant brain regions and are also involved in performing higher-mental functions

of attention and executive functions (Fortenbaugh et al 2017). In addition, BOLD signals measured by fMRI correlate strongly with the power of local gamma oscillations (Niessing et al 2005) further supporting the relevance of Gamma activity to brain network activations.

Calcium-binding protein parvalbumin (PV) interneurons are clearly involved in gamma oscillations, and found to be both necessary and sufficient for explaining these oscillations (Sohal 2012). Gamma oscillations may be generated by networks of inhibitory interneurons which fire and inhibit each other, until inhibition decays and they fire again, initiating the next cycle of the oscillation i.e., interneuron gamma, "ING,". Alternatively, gamma oscillations may result from interactions between excitatory and inhibitory neurons, in which excitatory neurons fire, triggering interneuron firing, which, after a delay, suppresses excitatory neuron firing i.e., "pyramidal-interneuron gamma", PING (Sohal 2012).

In the prefrontal cortex PV interneurons may have a 'hub-related control' over wide-spread neuronal networks in the brain. This is by virtue of their ability to regulate the hub-related pyramidal neurons which receive connectivity pathways from multiple spread-out brain systems and regions.

In severe mental disorders such as schizophrenia and autism, PV interneuron dysfunction is thought to contribute to deficient gamma oscillations and cognitive deficits (Sohal 2012). Several groups have found alterations in PV interneurons, particularly in the PFC, in post-mortem brain tissue from patients with schizophrenia (Hashimoto et al 2003; Woo et al 1998; Pierri et al 1999; Volk et al 2001, 2002).

But how can hub-related control and activity of prefrontal cortex PV interneurons explain brain-related disturbances in severe mental disorders such as schizophrenia and autism? A computational neuronal network model (Geva & Peled 2000) used dynamic thresholds that act in a similar way to gamma oscillations. In this model clustered memories simulate spread activation that is hypothesized for semantic networks in the brain. By altering the parameters of the dynamic thresholds i.e., hypothesized alterations of gamma oscillations, a large range of disturbances can be generated in the model. These disturbances showed metaphorical resemblance to certain general clinical descriptions of mental disturbances found in psychiatric patients suffering from severe mental disorders such as schizophrenia (Geva & Peled 2000).

This theory correlates with many studies summarized by Sohal (2012) that found that patients with schizophrenia exhibit reduced power or synchrony of gamma oscillations during responses to sensory stimulation or cognitive tasks (Spencer et al 2004; Gallinat et al 2004; Symond et al 2005; Wyinn 2005; Ford et al 2007, 2008 Cho 2006). Although patients with schizophrenia typically exhibit decreased power or synchrony of gamma oscillations (especially those evoked by sensory stimuli or cognitive tasks), within this clinical population, auditory hallucinations seem to be associated with increased power or synchrony of beta and gamma oscillations (Lee et al 2006;

Spencer 2009; Malert 2010). This suggests that in some cases, increased beta or gamma oscillations may contribute to positive symptoms.

The fact that increased power or synchrony of gamma oscillations could relate to positive symptoms is in line with computational psychiatry assumptions (Peled 2013) that simulated increased threshold activity to the prefrontal lobe may disconnect the brain dynamic neuronal network organization and reduction of threshold activity may 'over-connect' the same neuronal network organizations. Increase of gamma may thus relate to positive signs and reduction or suppression of gamma may relate to the emergence of negative signs in schizophrenia. This is relevant if we reconceptualize schizophrenia in terms of brain network disturbances to the functional connectivity in brain systems.

In summary, increased personalized gamma for negative symptoms schizophrenia and reduced desynchronized personal gamma tACS for positive symptoms schizophrenia is a reasonable therapeutic approach using personalized feedback loop tACS

As explained above the direct interventions molecular, or network related, are best when combined with the indirect (experience dependent plasticity) modulation. In the case of psychosis and negative signs schizophrenia we are interested in inducing brain networks to act in synchrony, thus tasks of concentration and working memory are warranted. New technology can best deliver such challenging task experiences.

Such experience control optimally includes currently emerging computer technology of virtual reality (VR) that provides for interactive control over the senses and enables the creation of controlled environments and two-way interplay. VR is a set of computer technologies which when combined; provide an interactive interface to a computer-generated world. Virtual reality technology (VRT) combines real-time computer graphics, body tracking devices, visual displays, and other sensory input devices to immerse a participant in a computer-generated virtual environment. He then can see, hear and navigate in a dynamically changing scenario in which he participates as an active player modifying the environment via his interventions. This technology provides such a convincing interface that the user often believes he is actually in the three-dimensional computer-generated environment. The term "presence" was coined by the experts of VRT to describe this conviction.

The field in which VRT is currently most intensively investigated in psychiatry is that of exposure therapy for treating anxiety disorders such as phobias and PTSD (Glantz and Lewis 1997; Vincelli et al. 2001; Pertaub et al. 2001; Jo et al. 2001; Rothbaum et al. 2000). In traditional exposure-therapy, the subject is exposed to anxiety producing stimuli while allowing the anxiety to attenuate with the aid of various relaxation techniques. VRT enables low cost (flight phobia treatment without really flying), time saving (from therapist's office) and controlled (the phobic stimulus can be designed and controlled) virtual phobic environmental exposures.

VRT has an excellent potential both for neuropsychological assessment as well as for cognitive rehabilitation. There are already a few research groups experimenting with VRT for cognitive rehabilitation (Christiansen et al.1998). Traditional neuropsychological testing methods are limited to measurements of specific theoretically predetermined functions such as short-term memory or spatial orientation. Given the need to administer these tests in controlled environments, they are often highly contrived and lack ecological validity, or any direct translation to everyday functioning (Rizzo and Buckwalter 1997).

VR technology enables subjects to be immersed in complex environments that simulate real world events and challenge mental functions more ecologically. While existing neuropsychological tests obviously measure some brain mediated behavior related to the ability to perform in an "everyday" functional environment, VR could enable cognition to be tested in situations that are ecologically valid. While quantification of results in traditional testing is restricted to predetermined cognitive dimensions, with VR technology, many more aspects of the subjects' responses could be quantified. Information on latency, solution strategy, visual field preferences, etc. could be quantified. VR can immerse subjects in situations where complex responses are required and the responses can then be measured (Rizzo and Buckwalter 1997).

These capabilities may potentially act upon diagnosed brain deficiencies. For example, performing within virtual environments that require intensive activation of working memory would enhance the integration of higher-level contextual systems. If additional multimodal integration is required to perform within that environment, then additional multimodal integration would be enhanced.

Virtual environments could also target delusional ideation and attempt to correct it by providing opposing or "correctional" occurrences tailored to counteract the specific false ideation. The correctional situations provide additional possible interpretations of the situation thus increasing the number of possible interpretations and increasing differentiation in the representational contextual system. Performance within complex social situations that require theory-of-mind capabilities would enhance the higher-level brain integration needed to represent and perform within socially cued situations.

In sum, VRT in diagnosis and rehabilitation of mental disorders could have a significant role both for increasing integration as well as differentiation by exposing the patient to complex challenging expressly designed interactive virtual environments.

Drawing upon the theory of experience-dependent plasticity, it is presumed that many sessions with the pre-designed virtual experience will eventually "reconnect" and re-associate the neuronal network circuitry required to re-establish consistent and coherent everyday experiences for the patient. Thus, if there are no speaking figures in the immediate experience, hallucinatory voices should disappear. It is predicted that once experience control sessions are stopped and speaking figures disappear the voices will also vanish. The newly formed consistency in the system will inhibit the activation of voices without their counterparts of experience (i.e., will not enable

inconsistencies of experience). The end result could be reduction of hallucinations providing symptomatic relief for the patient.

Delusions could be treated by repeated sets of virtual experiences where delusional thinking contrasts the virtual events. For example, the patient who is convinced of being persecuted by the FBI might be virtually introduced to the FBI headquarters where he experiences warm and caring acceptance, with no evidence of persecution. Gradually, this type of a repeated "corrective-experience" "improving experience" might alter his delusion, reducing its threatening content. One may argue that delusions are unshakable beliefs and thus could never be altered. Nevertheless, clinical experience shows us that beliefs may come in various degrees from normal and overvalued ideas to real delusions. Intensive and repeated virtual experiences delivered in an "aggressive" and "focused" manner to the specific delusional system of the patient may turn delusions to overvalued ideas or even to normal thinking.

Specifically, for inducing neuronal network organization during gamma stimulation with tACS it is proposed that targeting the cognitive functions of the frontal cortex is advisable. While there are some studies of the use of VR in dementia and ADHD there is no strong evidence that the VR as standalone is meaningfully effective. As for the use of VR technology to improve schizophrenia, also here results are not very strong. In a review article by Brun et al (2018), standalone computer-assisted therapy, video games and **virtual reality** efficacy in schizophrenia patients has been found to be premature because of the recent and preliminary character of most studies. This is relevant if we consider a combined stimulation with direct medication and tACS stimulations. In contrast, Adrei et al (2018) found that 10 sessions of Multimodal Adaptive Social Intervention in **Virtual Reality resulted in the** reduction in overall clinical symptoms, especially negative symptoms. **Sohn et al (2018) found that a virtual reality**-based vocational rehabilitation **training** program improved general psychosocial function and memory, in patients with **schizophrenia**. Thus, the potential of VR cognitive intervention exists as a standalone and is predicted to become relevant in combined direct and indirect interventions as mentioned above. Regarding non-invasive brain **stimulation** combined with rehabilitation strategies have demonstrated some success for speech and motor rehabilitation in stroke patients (Sathappan et al 2019).

Treating Network instability, Optimization & Mood

Direct brain interventions at the medication molecular level for the treatment of mood and anxiety are probably the most effective treatments in psychiatry, because they target plasticity inducing neuro and synaptic-genesis. They also teach us about the importance of plasticity-induction which is probably a necessary direction for future development.

As already mentioned, to date the most effective medications are synaptogenetic antidepressants. Based on the above chapters it is conceivable that synaptogenetic medications are effective, because they help the adaptive plasticity processes reduce free energy and increase brain optimization. This line of action can also be relevant to help corrective experiences treat personality disorders. Imagine medications that when given may take the brain back to early-stages

of development as if the patient was a 3 or 7 year-old child, with 3 to 7 year-old brain plasticity. Imagine how much could be corrected and developed resulting in improved maturation of the DMN and cure, especially when concurrent with psychotherapeutic and other experience dependent interventions.

Certain neurohormones and growth factors generate new cells in the brain, for example, fibroblast growth factor (FGF) injected subcutaneously in rats successfully passes the blood brain barrier (BBB) and increases cell and synaptic growth (Xian and Gottlieb, 2001). However, evidence suggests that in humans FGF might induce brain tumours (Berking et al. 2001) making this factor inappropriate for treatment.

A better candidate for inducing neurogenesis in the human brain could involve neurotransmitter agonists and antagonists. The activity of serotonin and norepinephrine has been found to participate in cell growth. Chronic antidepressant treatment has been found to increase neurogenesis of hippocampal granule cells via post-receptor increase of AMP (Thompson et al. 2000). Agonists of serotonin for 5HT1A and other receptors, have also been mentioned as important neurogenetic factors (Lotto et al. 1999). In effect, serotonin depletion during synaptogenesis leads to decreased synaptic density and learning deficits in the adult rat (Mazer et al. 1997). Tianeptine a 5HT1A agonist blocks stress-induced atrophy of CA3 pyramidal neurons (Magarinos et al. 1999). Intrathecal treatment with quipazine (another serotonin agonist) has improved locomotion deficit induced by ventral and ventrolateral spinal neural injury (T13) in two cats. Both cats recovered quadrupedal voluntary locomotion and maintained regular steeping with this treatment (Brustein and Rossignol 1999). Sumatriptan (CPP) is a 5HT agonist (5HT2C, 5HT1D and 5HT1A agonist) typically used in treatment of migraine headaches, chronic administration of sumatriptan has been found to slightly improve OCD patients (Hwang and Dun 1999).

Additional findings relevant to neurogenesis involve electroconvulsive seizures (ECS), chronic ECS administration induced sprouting of granule cells in the hippocampus (Kondratyev et al. 2001; Lamont et al. 2001). This effect is dependent on repeated ECS treatment and is long lasting (observed up to at least 6 months after the last ECS treatment). Excitotoxin and kindling-induced sprouting are thought to be, at least in part, an adaptation in response to the death of target neurons. In contrast, there is no evidence of cell loss or dying neurons in response to chronic ECS (Gombos et al. 1999).

In recent years attention has been directed toward N-Methyl-D-aspartic acid (NMDA) receptor and alpha-amino-3-hydroxy-5-methyl1-4-isoxasole propionic acid (AMPA) receptors because of their probable role of regulating neural plasticity. The L-quinoxalin-6-ylcarbonyl piperadine (CX516) AMPA modulator have the potential to control certain neuronal plasticity processes (Lynch and Gall 2006).

CX516 was tested as a sole agent in a double-blind placebo-controlled design in a small series of patients with schizophrenia (n=6) who were partially refractory to treatment with traditional neuroleptics. The study entailed weekly increments in doses of CX516, from 300 mg tid for week 1 up to 900 mg tid at week four. Patients were followed with clinical ratings, neuropsychological testing, and were monitored for adverse events. Four patients received 2 to 4 weeks of CX516, two received placebo and two withdrew during the placebo phase. Adverse events associated with drug administration were transient and included leukopenia in one patient and elevation in liver enzymes in another. No clear improvement in psychosis or in cognition was observed over the course of the study. CX516 at the doses tested did not appear to yield dramatic effects as a sole agent, but inference from this study is limited (Marenco et al 2002).

CX516 was also added to clozapine in 4-week, placebo-controlled, dose-finding (N = 6) and fixed-dose (N = 13) trials. CX516 was tolerated well and was associated with moderate to large, between-group effect sizes compared with placebo, representing improvement in measures of attention and memory. These preliminary results suggest that CX516 and other "ampakines" hold promise for the treatment of schizophrenia (Goff et al. 2001).

Current stimulation has also been shown to induce plasticity. According to Kenny et al (2018), tDCS showed evidence of promising therapeutic applications for depression in adults. Transcranial non-invasive brain stimulation has plasticity-like effects because of their common mechanisms of synaptic plasticity in physiology, pharmacology and behavior response (He et al 2018). A review by Kim et al (2018) strongly supported electrophysiological sensitivity to reflect plastic brain changes and the associated symptomatic improvement following tDCS. A recent review by Gomes-Osman et al (2018) found that repetitive tDCS can be used to modulate neuronal excitability and enhance cortical function, and thus offer a potential means to slow or reverse cognitive decline.

Linking plasticity to the underlying mechanisms of mood disorders should also link brain current stimulation to the effects on these disorders i.e., that electric current stimulation will have effect on anxiety and depression. In a recent review, Vicario et al (2018) found preliminary evidence that both, excitatory stimulation of the left prefrontal cortex and inhibitory stimulation of the right prefrontal cortex could reduce symptom severity in anxiety disorders. According to Brunoni et al (2018), the most promising results of noninvasive brain stimulation techniques, such as transcranial direct current stimulation have been obtained for depression. D'Urso et al (2018), in their review, found reports that highlight the importance of combining tDCS with different procedures, including computerized tasks and behavioral paradigms. In conclusion, even in its infancy, the use of tDCS for the treatment of anxiety disorders does show promise and deserves extensive research efforts.

As mentioned above combining direct brain interventions as mentioned so far, with indirect experience mediation can a synergistic effect. Indirect experience inducing interventions for anxiety can be provided from the vast digital technology related to relaxation and meditation

therapies. According to Meister & Becker (2018) there is preliminary evidence that meditation-based yoga interventions may be helpful for depression, and anxiety (2018). As for distress related to cancer, Yoga, hypnosis, relaxation, and imagery, which harness the power of the mind focus on training in mindfulness meditation show (Carlson 2017) their role in alleviating distress regarding cancer diagnosis. Bonadonna (2003) argued that living mindfully with chronic illness is a fruitful area for research, and it can be predicted that evidence will grow to support the role of consciousness in the human experience of disease. Attention Training Technique and Mindful Self-Compassion training showed significant reductions in symptoms of anxiety and depression accompanied by significant increases in mindfulness, self-compassion, and attention flexibility in a study by Haukaas et al (2018). Van der Riet et al, (2018) reviewed the topic of mindfulness meditation and found that it has positive impact on nurses' and nursing students' stress, anxiety, depression, burnout, sense of well-being and empathy. However, the majority of the papers described small scale localized studies which limits generalizability of the findings. With VR technology such interventions can be more effectively delivered. It has been found that VR may facilitate mindfulness practice. Normal participants in a pilot study (avarro-Haro et al 2017) reported increases/improvements in state of mindfulness, and reductions in negative emotional states, significantly less sadness, anger, and anxiety, they also reported being significantly more relaxed.

Treating internal configurations & Personality

Psychotherapy is an experience-dependent-plasticity therapy, as it becomes a continual repetitive experience that the patient is experiencing in his life. Individuals often seek psychotherapeutic treatment out of distress that originated from interpersonal relationships. Initially the relations with the therapist will repeat the same patterns of interpersonal relations that caused the distress. The skilled therapist identifies these malfunctioning interpersonal patterns and during therapy behaves in a manner that gradually changes the attitudes of the client so that he/she will be able to respond more appropriately to similar situations in the future. This therapeutic intervention is called a "correcting experience." Better coping in psychosocial situations reduces suffering and enables relief from symptoms. Psychodynamic therapy involves overcoming resistance, offering appropriate interpretations and increasing insight to relevant aspects of interpersonal relations (Freud 1953; Michael 1986).

According to the approach of constraint-organization in the brain, the psychotherapeutic process can be described as a physical change that takes place in the brain of the client. Initially, the relations between the internal map of reference of the individual (i.e., internal representations) and some aspects of the psychosocial situations he encounters are incongruous. This incompatibility reaches the extent where perception and reaction to those psychosocial situations are distorted and interfere with the psychosocial functioning of the individual. The psychosocial dysfunction is generally accompanied by distress, which is typically expressed by symptoms of anxiety and depression.

The goal of the therapy is to reshape the internal representations to include the appropriate internal configurations for coping with the psychosocial situations at hand. Initially, the client perceives the therapist as a person from his past. This is because the client activates the attractor systems, which represent the person from the past. Since the therapist is not the same as the activated representation, a distorted perception of the therapist emerges. Due to this distortion an inappropriate behavioural reaction to the therapist (transference) occurs. Most probably, this distortion occurs with other interpersonal situations outside the therapeutic sessions. This indicates that there is substantial mismatch between the internal representation and the psychosocial reality.

The therapist strives to enlarge the repertoire of representations of the individual to match many more different psychosocial situations. In other words, the psychotherapeutic process increases the neural complexity (C_N) in the brain of the client. When the therapist reacts to the client in a novel manner, Hebbian mechanisms of plasticity will gradually create the new attractor systems necessary for the additional internal representations. In this manner, the therapist "shapes" the space-state topology of the brain to form new internal representations. The process probably involves actual changes in the functional connectivity of the neural systems involved, and as such it is a physical process in the brain.

The process described thus far is actually much more complex than the above description suggests. For example, due to a lack of representational systems, many times the interpretations offered by the therapist are denied and do not gain access to the global formation of dominant brain states s (denial). These interpretations will never reach conscious levels (resistance in psychoanalytic terminology). The set of inputs from the interpretation of the therapist simply do not satisfy the constraints of the global configuration (i.e., dominant brain state), thereby conflicting with the message in the global dominant brain state. Thus, it has been correctly indicated that for an interpretation to succeed it must be delivered at the right time (i.e., when the individual is ready for it; (Michael 1986)). There must be a certain constellation of the global dominant brain state (i.e., organization), which is favourable for including the new patterns of information proposed by the interpretation. The therapist first prepares the patient by repeated clarifications, confrontations and other interpretations. This process changes the global formation of dominant brain states, "moving it slightly" toward the pattern that will be favourable for accepting the critical interpretation (i.e., the one that will induce the change).

Freud indicated the importance of overcoming resistance in psychotherapy (Freud 1953). By gradually changing the global formation of dominant brain states to a favourable configuration, the therapy enables the incorporation of an interpretation and the therapist overcomes the resistance to that interpretation.

Repeating this process over and over again will eventually "reshape" the state-space of the brain and increase the complexity of internal representations and thus the psychological repertoire of the individual. These changes transpire and are maintained by the experience-dependent plastic processes of the brain. It is probably the increase in neural complexity that improves psychosocial

adaptability. In turn, psychosocial adaptability reduces the suffering that originates from conflicts of interpersonal relations.

The outcome of psychotherapy is relief of distress in interpersonal situations. It is achieved via the reduction of specific sensitivities of personality traits and the increase of flexibility and adaptability to changing psychosocial situations. Increase of flexibility and adaptability reduces constraint frustration and deoptimizations of dominant brain states thus reducing the experience (emergent properties) of anxiety and depression.

Considering that psychotherapy is a plasticity-related intervention it is acceptable to speculate that medications that increase plasticity can become relevant in augmenting psychotherapeutic effects. An extreme scenario would be if it were possible to take an adult brain and induce it to possess the plasticity capabilities of a 3 year-old child. What potential could that offer for psychotherapy? Consider that children are responsive to fast-learning and and easily manage educational interventions which can foster character changes and correct biased developmental styles. Thus, plasticity induction combined with psychotherapy can become a powerful therapeutic tool. This brings to mind the use of SSRIs and electrical stimulations in concomitant and during psychotherapy treatments.

As experience-dependent- therapy, psychotherapy can also use experience-control-technology to improve the delivery of the therapy. Psychotherapeutic corrective-experience can be enhanced using VR, a technology that potentiates experience control over the patient- user.

The use of virtual reality traditionally began with treating anxiety specific phobia and PTSD (Grös & Antony 2006; Mitrousia et al 2016). Also, social phobia was treated with a virtual classroom (Rizzo et al 2006).

According to Frith et al (2018)

> There is now substantial clinical research demonstrating the efficacy of internet-delivered cognitive behavioral therapy in the treatment of anxiety. However, the ability of these interventions for engaging patients in "real-world" settings is unclear. Recently, smartphone apps for anxiety have presented a more popular and ubiquitous method of intervention delivery, although the evidence base supporting these newer approaches drastically falls behind the extensive marketing and commercialization efforts currently driving their development. Meanwhile, the increasing availability of novel technologies, such as "virtual reality" (VR), introduces further potential of e-health treatments for generalized anxiety and anxiety-related disorders such as phobias and obsessive-compulsive disorder, while also creating additional challenges for research. Although still in its infancy, e-health research is already presenting several promising avenues for

> delivering effective and scalable treatments for anxiety. Nonetheless, several important steps must be taken in order for academic research to keep pace with continued technological advances.Rizzo & Koenig (2017)_review of the theoretical underpinnings and research findings to date leads to the prediction that clinical VR will have a significant impact on future research and practice. Pragmatic issues that can influence adoption across many areas of psychology also appear favorable.

As for using VR for psychiatric diagnosis van Bennekom et al (2017) argued

> to date, a diagnosis in psychiatry is largely based on a clinical interview and questionnaires. The retrospective and subjective nature of these methods leads to recall and interviewer biases. Therefore, there is a clear need for more objective and standardized assessment methods to support the diagnostic process.

They reviewed a total of 39 studies and concluded

> nearly all VR environments studied were able to simultaneously provoke and measure psychiatric symptoms. Furthermore, in 14 studies, significant correlations were found between VR measures and traditional diagnostic measures. Relatively small clinical sample sizes were used, impeding definite conclusions. Based on this review, the innovative technique of VR shows potential to contribute to objectivity and reliability in the psychiatric diagnostic process.

A systematic review of empirical studies was conducted by Freeman et al (2017)). “In all, 285 studies were identified, with 86 concerning assessment, 45 theory development, and 154 treatment. The main disorders researched were anxiety (n = 192), schizophrenia (n = 44), substance-related disorders (n = 22) and eating disorders (n = 18).” They conclude that VR has the potential to transform the assessment, understanding and treatment of mental health problems.

In psychiatric diagnosis, history-taking involves asking the patient about his feelings and behavior in relevant situations of his life. With VR life-like situations can be constructed virtually and the patient’s behavior and reactions can be monitored by placing him in these reconstructed virtual situations. This type of monitoring patient’s reaction and behavior is more objective and accurate then history-taking, that relies on memories which can be biased.

The diagnostic virtual environments can elicit a set of reactions which can become diagnostic. These can range from simple gaming virtual situations to measuring cognitive capacity and disorders. Vr can reach much more complicated evolutions such as those of personality styles and disorders. For example, a specific social condition can be tailored and by placing the patient in that condition his personality will dictate his reaction. A person with narcissistic personality style will

feel good in a virtual party where he is center of attention, thus he will prefer staying longer in such an environment in contrast to a person with schizoid introvert personality traits.

Novel and futuristic interventions

In recent years there has been growing interest in 'brain pacing' technologies that promise to control brain activity and thus may act as therapeutic agents for mental and neurological disorders. Some of these technologies are Invasive (DBS, Optogenetics) but others already mentioned, are non-invasive and work transcranially, these are the TMS (Transcranial Magnetic Stimulation) and the various transcranial electrical current stimulations (tECSs).

Of the invasive methods, deep brain stimulation (DBS) now plays an important role in the treatment of Parkinson's disease, tremor, and dystonia. DBS may also have a role in the treatment of other disorders such as obsessive-compulsive disorder, Tourette's syndrome, and depression (Okun et al 2007). The effects of DBS on cognition and clinical psychiatric symptoms are just beginning to be researched. Page et al (2007) examined the effects of deep brain stimulation of the subthalamic nucleus on tests of set-shifting and dual task performance in patients with Parkinson disease. All patients revealed a clinical benefit from DBS of the subthalamic nucleus (STN).

Among the invasive technologies, optogenetics is a new technology that offers control over neuronal activity by turning on and off distinct neuronal populations using cell-type specific, optically sensitive, molecular neuronal activity "switches." These "switches" are microbial, light-sensitive ion conductance-regulating proteins, e.g., channelrhodopsin-2 (ChR2) and halorhodopsin (NpHR). They are genetically engineered to become part of the cellular machinery and introduced individually to target neurons relevant for activating or inhibiting pre-chosen neuronal circuits (Berdyyeva & Reynolds 2009).

Recently Focused Ultrasound (FUS) technology has been developed and was found useful for both ablating small brain targets and for stimulating deep brain networks (Tyler et al 2008).

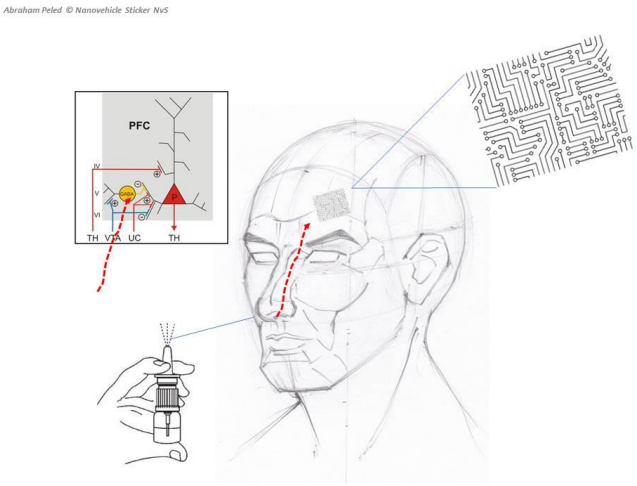
Ultrasound is a term used for the sound waves, which are propagated higher than audible range of human hearing. Recently, MRI imaging is used to guide high intensity focused ultrasound through tissues for ablation treatment. In 2008, Tyler and his colleagues discovered that low intensity focused ultrasound (LIFU) can stimulate membrane ion channels and synaptic transmissions (Tyler et al., 2008). Later on, neuromodulatory properties of LIFU stimulation was represented by electrophysiological recordings (Bystritsky et al., 2011). LIFU activates voltage-gated sodium and calcium channels, thereby eliciting action potentials and synaptic transmission (Bachtold, Rinaldi, Jones, Reines, & Price, 1998; Boland & Drzewiecki, 2008; Morris & Juranka, 2007; Rinaldi, Jones, Reines, & Price, 1991; Sachs, 2010; Sukharev & Corey, 2004; Tyler et al., 2008). LIFU seems to be safe, studies have reported (Hameroff et al., 2013, Legon et al., 2014) no sign of heat or cavitation by histological examination both within regions of interest (RIOs) or surrounding tissues. It seems that LIFU provides the possibility of precisely modulating corticothalamic,

corticocortical, and thalamocortical pathways. LIFU stimulation on prefrontal areas of 2 macaque rhesus monkeys showed that ultrasound significantly modulated anti-saccade task latencies as a sample of high-level cognitive behavior (Deffieux et al., 2013). In a study on pain, in human subjects, Hameroff targeted scalp over posterior frontal cortex, contralateral to maximal pain, for 15 seconds in a double-blind crossover study. They found improvement in subjective mood 10 minutes and 40 minutes after ultrasound stimulation (Hameroff et al., 2013). Another study, on human subjects, probed the influence of LIFU on the primary somatosensory cortex (Legon et al., 2014). The stimulation volume size was 4.9 mm in depth and 18 mm in diameter which could significantly attenuate the amplitudes of somatosensory evoked potentials from median nerve stimulation (Legon et al., 2014).

The future of brain pacing probably lays in more subtle and sophisticated technology such as complex functional interfaces with biological circuits (Anikeeva et al2018). For example, alternating magnetic fields cause magnetic nanoparticles to dissipate heat while leaving surrounding tissue unharmed, a mechanism that serves as the basis for a variety of emerging biomedical technologies (Christiansen et al 2017). Other magnetic handles on cellular or molecular function could be mutant iron storage ferritin proteins that improved magnetism in part from increased iron oxide nucleation efficiency (Matsumoto et al 2015). Molecular-level iron loading in engineered iron storage ferritin enables detection of individual particles inside cells and facilitates creation of ferritin-based intracellular magnetic devices

Looking beyond the horizon of current science, it is predicted that brain-pacing technology will involve miniaturization of devices and nano-level brain interface. In fact, one can envision a “Sticker-device” carrying a sensing, organizing, feedback loop apparatus placed on the forehead, acting remotely and non-invasively on nasally-pre-inhaled bio-nano-particles positioned on prefrontal cortical interneurons.

See Figure 8



Patients would place two stickers bilaterally on the sides of their forehead, and then (nasally) inhale specially designed nanoparticles. These can be Dynamic Viral Capsids DNA Nanorobots, or inorganic fabricates hybrid system interfaces with relevant neurons (Alivisatos et al 2013). These would be guided into position traveling upward toward the prefrontal cortex, traversing through nasal epithelia and relevant tissues. Guided by magnetic or other sticker-related mechanisms they would settle on prefrontal cortical interneurons and act to control channel receptors, thus indirectly controlling layer IV pyramidal neurons considered to be central to prefrontal hub regulation for large-scale brain connectivity and organization (Arnsten et al 2010).

Once in place the sticker "sensing arm" (EEG analysis) will evaluate global-brain organization. It will then use a self-organizing optimization device to calculate a "Delta" between actual and desired brain optimization. The desired simulated optimization and "Delta" statistics will be used to generate a relevant controlled-energy feedback to act on the channel-ligated-nano-particles regulating prefrontal interneurons to reinstitute brain optimization.

In summary, future brain-pacing technology to cure mental disorders will probably require a sticker device carrying a miniature sensing-acting feedback-loop device that can calculate and correct brain optimization; such a device will feedback "corrective signals" by acting remotely and non-invasively upon neuronal-related nanoparticles, nanoparticles previously nasally-inhaled into position. In sum the device will detect and sample disturbances to brain optimization related to psychiatric illness, and correct them, thus optimizing brain organization via network prefrontal hub control, eliminating related psychiatric phenomenology and curing the patient.

This plan poses a huge challenge, and offers multiple obstacles to overcome on the road for its realization. For example: how to sample whole-brain organization using two localized stickers? How to analyze and calculate desired brain optimization? How to deliver "corrective" signals, and how to make them relevant translating into biological neuronal activity? How to reduce all this onto a sticker device? How to power it and shield it from external energy noises? How to insert and maintain nanoparticles in action without triggering harmful tissue reaction, and inducing unwanted strains on neuronal activity? Actually every step in this plan is an obstacle to be surmounted.

Roughly the obstacles can be divided into three: "site of action," "mode of action" and the "Pacing Sticker" integrating explanations of the device and its biological action on the brain.

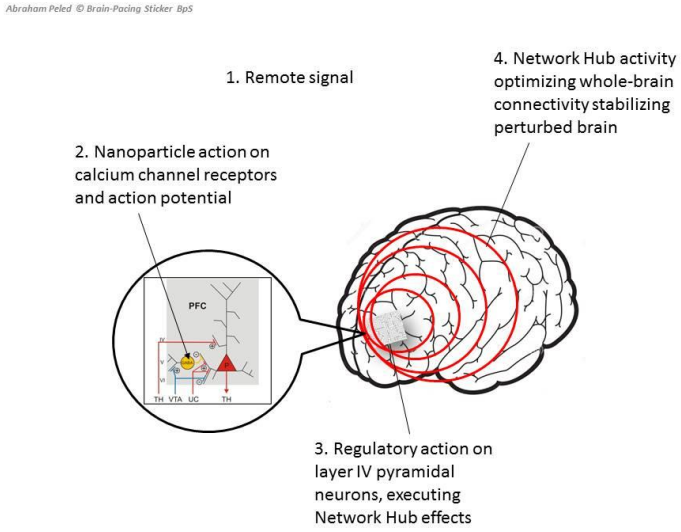
Site of action: The site of action is the IV-layer structure of the prefrontal cortex (PFC) considered relevant to brain hub networks involved in all higher mental functions, those relevant to psychiatric illness (Stam 2014). The hub network activity has a network organizing effect and is thus in a position to regulate whole-brain organization, presumably executing its mental effects via global brain organizing capabilities (Sohal et al 2009). There are other such hub systems in the brain, e.g., medial temporal structures such as the hippocampus, and subcortical systems such as the basal ganglia. However, the PFC is the only cortical structure that can be in proximity of a brain-pacing sticker which in this case is placed on the forehead.

As previously mentioned, this PFC cortical structure is chosen because it has already been demonstrated that by manipulating "relay" activity of pyramidal neurons in layer IV of that cortical region, whole brain organization can be influenced, e.g., generate EEG gamma waves presumably related to long distance connectivity (Sohal et al 2009). The manipulation of layer IV pyramidal neurons of that PFC is achieved by targeting the interneurons acting upon these pyramidal neurons.

Mode of action: Targeting the interneurons acting upon these pyramidal neurons will be achieved by nanoparticles attached to the calcium channel receptors of these neurons capable of opening and closing these channels by some Nanoparticle-Receptor-Bioaction (NRB) remotely controlled from a distance (i.e., extracranial). Thus, a chain of controlled action is formed as follows:

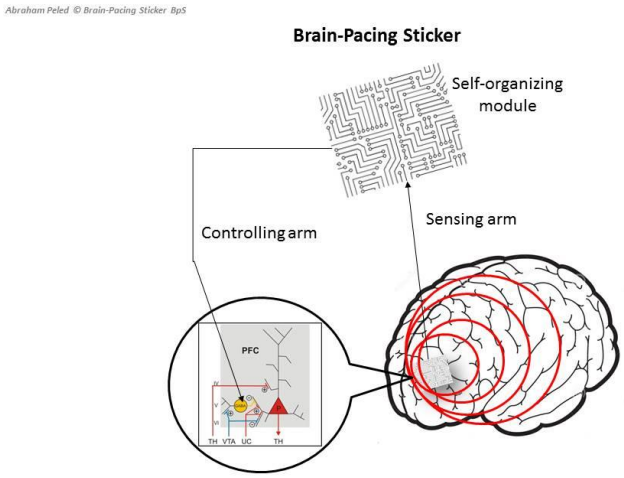
1. Remote signal
2. Nanoparticle action on calcium channel receptors and action potential
3. Regulatory action on layer IV pyramidal neurons, executing Network Hub effects.
4. Network Hub activity optimizing whole-brain connectivity stabilizing perturbed brain.

Figure 9 illustrates this regulatory effect:



The Pacing Sticker: The Brain-pacing Sticker has a sensing arm of input; a controlling arm of output and a self-organizing module see Figure 10:

Figure 10

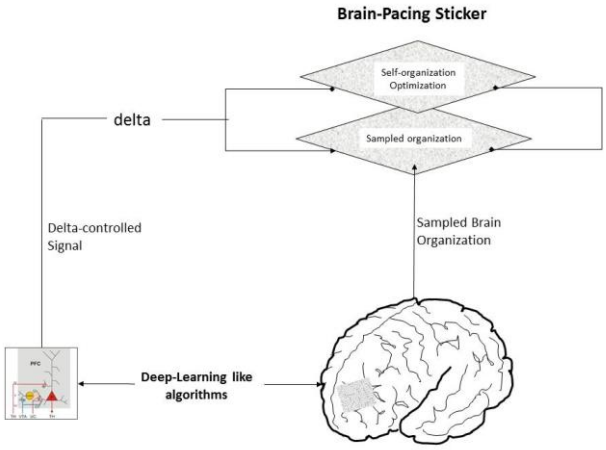


The sensing arm collects the EEG signals from the prefrontal cortical regions located underneath the sticker. Regular EEG will probably not suffice and some more accurate imaging technology will be needed, this may include "quantum dots" "optical sensing-like' devices, probably Ca^{+} imaging but such that will have negligible adverse interactions with surrounding neural tissue in order to offer longevity sampling activity (Alivistos et al 2013). It must then calculate whole-brain organization sensing using signal processing methods that can extract whole-brain activity from

localized PFC activity. The sensing input arm must convey whole-brain organization to a "self-organizing" module in the sticker, in a manner that allows for that module to simulate both the actual brain-organization and an optimal brain-organization. The optimal brain organization is the one that will be conveyed by controlled signal via the controlling-output arm. A "Delta" calculated between actual brain-organization and desired optimal brain-organization (e.g., hamming distance measuring apparatus) monitors the online feedback-loop of this brain-pacing system. Gradient-descent dynamics between actual and desired brain-optimization characterizes a well-functioning brain-pacing device.

A major challenge for this feedback apparatus is discovering the relationship between the remote signal and the activity of the nanoparticles-regulated ion-channel activity. What will be the algorithm of controlled ion-channels activation that will translate to relevant global network optimizations thus optimizing global brain activity? This link will probably require deep-learning-like algorithms with reduced Delta as learning coefficient.

Figure 11 schematizes the Brain pacing Sticker activity



NEUROANALYTIC ALGORITHMS

Neuroanalytic diagnosis: Psychiatric phenomology translated to brain-disturbances based on literature from computational neuroscience and psychiatry

PHENOMENOLOY	BRAIN
Positive Signs Incoherent thoughts. Loosening of associations, excitement delimits attention, and affects personal functions such as eating and sleeping Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements.	Disturbance to connectivity (disconnection) millisecond-range integration of brain organizations, specifically the Central Executive Networks. Disconnection syndrome with neuronal subsystems acting statistically-independent from each other. The normal small-world-organization of brain networks is disturbed with clustering of subnetworks loosing connection and Hubs suffering from reduced "degrees" (afferent efferent connections). Small-world-organization causes brain instability and fragmented activity, as a consequence of this disconnection spread in the brain, multimodal brain integration becomes disjointed and likewise conscious experience becomes fragmented and behavior becomes uncontrolled. The state-space dynamics of higher-level transmodal networks destabilizes and states organization is disturbed disrupting state-trajectory dynamics, this is responsible for the loosening of associations in the train of thoughts.
Positive Signs Delusions and / or hallucinations.	Disturbance to hierarchal connectivity (disconnection) millisecond-range integration of brain organizations specifically the Central Executive Networks.. Normally the brain achieves an hierarchal top-down bottom-up processing balance where; 1) bottom-up incoming processes travel up the hierarchy to form higher-level transmodal organizations embedding higher-level schemata's of concept neurons, and 2) top-down control meaningfully integrating lower-level incoming experiences to higher level internal expectations, memories and representations. Top-down and bottom-up processes are balanced by a continuum of error-prediction and error- corrections processes traveling the hierarchy. Top-down hierarchical shift causes mismatch between ideas and thought-schemes, and the actual incoming environmental occurrences, such biases and mismatches humper logical reference creating delusions and hallucinations.
Negative Signs Restriction. Thinking is rigid and repetitious limited to only two or three dominating topics. Concrete mode, Lack of spontaneity and openness, replying to questions with only one or two brief sentences. Conversation lacks free flow halting.	Disturbance to connectivity (over-connection) millisecond-range integration of brain organizations specifically, the Central Executive Networks. Over connection syndrome with neuronal subsystems acting statistically-overly-dependent on each other; the normal interdependent constraints are excessively strengthened. The normal small-world-organization of brain networks

	is disturbed with increased clustering and Hubs suffering from "degrees" proliferation (i.e., increase of afferent efferent connections). Disturbed Small-world-organization causes brain fixation reduced dynamic activity, as a consequence of this over-connection spread in the brain, multimodal brain integration becomes overly constrain and "crystalized" and likewise conscious experience becomes fixated and behavioral repertoire is reduced . The state-space dynamics of higher-level transmodal networks is restricted and state-trajectory dynamics is caught in local minima repeatedly activating limited states only (perseverations and poverty of thought/speech).
Negative Signs Avolition. Disturbance of volition interferes in thinking as well as behavior. No interest or initiative. Tendency to avoid eye or face contact.	Disturbance to hierarchal connectivity millisecond-range integration of brain organizations, specifically the Central Executive Networks.. Normally bottom-up processes form higher-level constructs; here this process is hampered with deficiency of the formation of higher level brain organization. Higher-level integration of sensations with actions are deficient causing disturbance the emergent property of 'motivation" and 'volition."
Anxiety (Generalized) Fear tension, fatigue, irritability startle response, worries, anticipation of the worst, fearful anticipation, feelings of restlessness, inability to relax. Difficulty in falling asleep, broken sleep, fatigue on waking, nightmares, night terrors. Somatic symptoms trembling, palpitations, suffocation, dizziness tingling.	Disturbance in the longer minute range activity more specifically in the Salient Networks of the brain. Stress and intense network computational activity perturbs brain network stability resulting in "Constraint Frustration" among neurons and network systems. A connection is considered "frustrated" when the weighted value of connectivity is in discrepancy with the value of neuronal activation. In other words within neuronal ensembles when the value of connection weights are incompatible with that of values of neuronal activation. The emergent property of that condition manifests as anxious sensation. Any increase of computational demand on the neuronal network can cause frustration to constraints,
Reactive Anxiety Phobia: Same as generalized anxiety but stress or phobic stimulus bound	As above, in reaction to abrupt intense environmental changes
Depression, (more in the morning), frequent crying, possible nihilistic delusions, and/or possible suicidal thoughts or action. Somatic symptoms, psychomotor retardation, impaired concentration, social disinterest, self-neglect, Ideas of guilt, hopelessness, worthlessness, blame. Motor	Disturbance to "Adaptive Plasticity" slower time-scales, those that span hours to weeks and are responsible for reducing free energy the differences between internal representations (emergent constructs) and external environmental occurrences, these involver more specifically the Salient Networks of the brain. Deoptimization takes place when free energy increases and mismatch between internal representations and

speech retardation, early insomnia, loss of appetite weight loss.	external events becomes larger. Deopitmization dynamics caused by reduced neuronal plasticity, emerging (Emergent Property) as depressed mood. Normally the brain continually updates internal representations (error-prediction and correction); these are internal representations of the world of our experiences built from memories of past familiarities. The experience continually updates the internal formations to match what is transpiring, this process of update reduces inconsistencies (Free Energy) and is called "optimization," because it optimizes internal representations to match real life events and occurrences, when neural plasticity is hampered the optimization process is disturbed and De-optimization dynamics takes over. Mismatch between internal configurations and actual occurrences transpire, with depressed mood as a consequent emergent property.
Mania. Elated expansive mood Euphoric; inappropriate laughter; singing. Pressured, uninterruptible, continuous speech. Content grandiose, superiority, amazing ability, wealth knowledge, fame, power, and/or moral stature, can be paranoid. Motor excitement; continuous hyperactivity (cannot be calmed). Overt sexual acts. Hostile, uncooperative; Denies need for sleep, interview impossible	Disturbance to "Adaptive Plasticity" but in the hyper-plasticity and optimization creating a fast optimization shift resulting in fast reduction of free energy with the emergence (property of) elevated mood. These also involve more specifically the Salient Networks of the brain.
Moderate personality disorders. Predictable behaviors egocentricity, dependence, obsessions rigid.	Disturbance to "Developmental plasticity " that of lifetime long organization the Default-Mode Networks . Experience dependent plasticity lifelong processes of neuronal activations and Hebbian ensembles encode environmental occurrences creating an internal model of the world and its psychosocial environment. These internal representations of the world include others and self-representations, and the social interacting patterns and emotions. Thus the personality style depends on these representations. The level of disturbance to the "maturity" of this developmental organization determines the adaptability, functionality and stability
Sever personality disorders. Unstable emotionally Easy frustration, impulsive splitting, brief psychosis risk behaviors intense transference low-self-esteem and sensitivity to criticism.	Disturbance to "Developmental plasticity " that of lifetime long organization the Default-Mode Networks. Early internal representations are not properly formed, generating unstable, disinhibited, chaotic, split experiences. Individualization is not achieved and experiences are undistinguished from internal identity.

Schizophrenia alternations of positive and negative signs over time with advanced severity of negative signs intensifying over time.	Possibly once connectivity balance is disrupted the brain connectivity dynamics starts oscillating. Once disconnection happens (positive signs) it triggers an reconnection dynamics that over-shoots to become over-connectivity (negative signs). 'Struggling' to achieve optimal connectivity again, over-connectivity 'tries' to 'disconnect,' 'pushing' brain dynamics to disconnection states again, and vice versa.
Bipolar alternations between depression and mania	Systems try to optimize balance, thus once deoptimized the brain may 'try' to optimize creating an hyper-optimization dynamics, oscillations between deoptimization and hyper-optimization can push the system to oscillatory behavior expressed as mood swings known phenomologically as bipolar disturbance.
Combined disturbances Anxiety. Anxiety typically accompanies (comorbid) many mental disorders	Any disturbances mentioned above, be it connectivity or plasticity, perturbs the global brain network stability thus creating spread out of disturbance to constrain frustration of the neuronal network in action. Thus such destabilization emerges (property) as anxious feeling which will accompany the relevant brain disturbance
Combined disturbances Personality	When internal configurations of developmental plasticity are impaired the entire brain neuronal network construct is weak and unstable submitting the entire brain organizations to plasticity and connectivity imbalances and disturbances, this can explain first, why depression and anxiety are the hallmark phenomology of personality disorders and secondly, how come brief psychosis can arise, that is from even more instability reaching levels of connectivity disruptions.

How to validate Neuroanalytic assumptions:

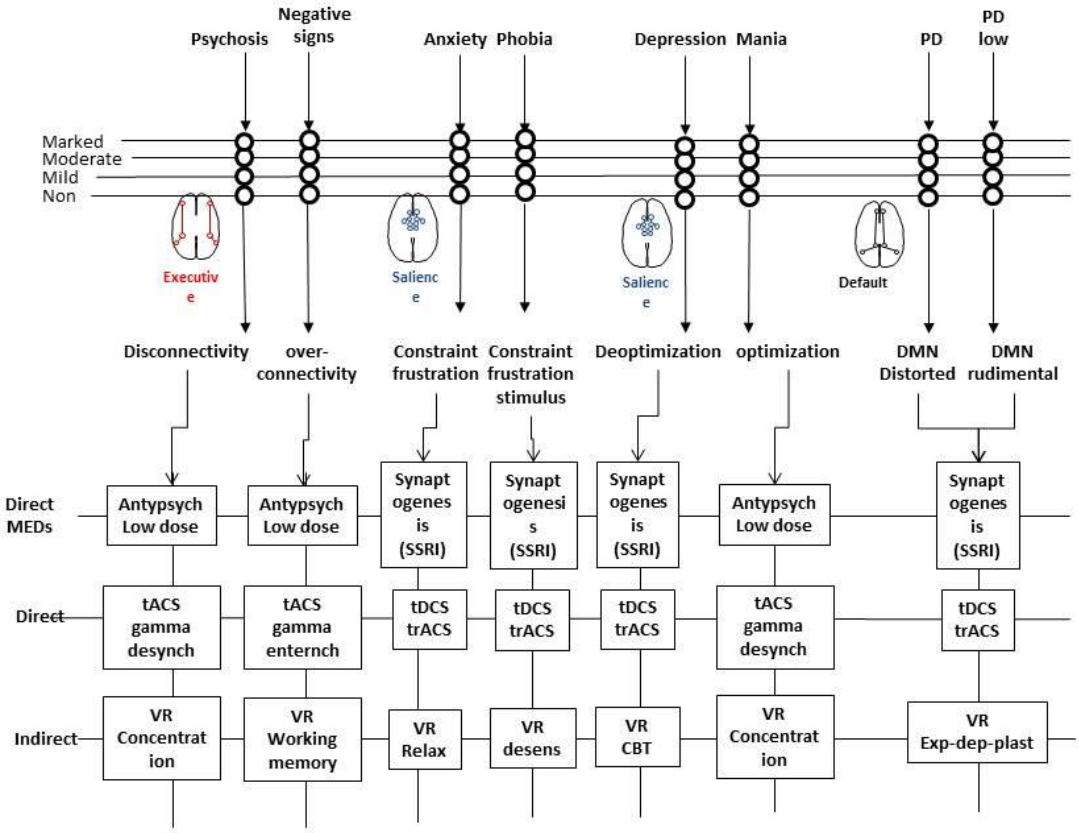
In the case of psychosis and disconnection dynamics, brain-imaging is expected to find reduced correlation-matrixes, disconnection in graph-analysis (e.g., small world), the opposite is expected for over-connectivity dynamics, and these are expected to happen in the millisecond range timescale, and affect the Central Executive Networks. Increase error predictions in Dynamic-Causal-Modeling are expected to characterize delusions resulting from hierarchical brain imbalances also relevant to the Central Executive Networks. Increase and decreased entropy-measurements (of Free Energy) are expected in Depression and Mania respectively these will be evident at larger timescales of months and weeks and affect the salience networks. Resting-state-networks (Default Mode) are lifelong (timescale) developmental brain organizations they are expected to be altered in cases of personality disorders. In these cases small-world alterations are expected.

Neuroanalytic treatment

PHENOMENOLOY BRAIN	Treatment
Positive Signs Incoherent thoughts. Loosening of associations, excitement delimits attention, and affects personal functions such as eating and sleeping Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements. Disturbance to connectivity (disconnection) millisecond-range integration of brain organizations, specifically the Central Executive Networks. Positive Signs Delusions and / or hallucinations. Disturbance to hierarchal connectivity (disconnection) millisecond-range integration of brain organizations specifically the Central Executive Networks.	Direct intervention low dose antipsychotic combined with reduced desynchronized personal gamma tACS sessions. Indirect intervention using VR cognitive training for attention and working memory
Negative Signs Restriction. Thinking is rigid and repetitious limited to only two or three dominating topics. Concrete mode, Lack of spontaneity and openness, replying to questions with only one or two brief sentences. Conversation lacks free flow halting. Disturbance to connectivity (over-connection) millisecond-range integration of brain organizations specifically, the Central Executive Networks. Over connection syndrome with neuronal subsystems acting statistically-overly-dependent on each other; the normal interdependent constraints are excessively strengthened. The normal small-world-organization of brain networks is disturbed with increased clustering and Hubs suffering from “degrees” proliferation (i.e., increase of afferent efferent connections). Negative Signs Avolition. Disturbance of volition interferes in thinking as well as behavior. No interest or initiative. Tendency to avoid eye or face contact. Disturbance to hierarchal connectivity millisecond-range integration of brain organizations, specifically the Central Executive Networks.. Normally bottom-up processes form higher-level constructs; here this process is hampered with deficiency of the formation of higher level brain organization.	Direct intervention low dose antipsychotic combined with Increased personalized gamma with synchronized entrenchment of personal gamma tACS Indirect intervention using VR cognitive training primarily for working memory
Anxiety (Generalized) Fear tension, fatigue, irritability startle response, worries, anticipation of the worst, fearful anticipation, feelings of restlessness, inability to relax. Difficulty in falling asleep, broken sleep, fatigue on waking, nightmares, night terrors. Somatic symptoms trembling, palpitations, suffocation, dizziness tingling. Disturbance in the longer minute range activity more specifically in the Salient Networks of the brain.	Direct plasticity induction to reduce constraint frustration with 1) synaptogenetic medications and tDCS or/and random distributed tACS Indirect intervention of meditation mindfulness VR relaxation scenarios.

Stress and intense network computational activity perturbs brain network stability resulting in "Constraint Frustration" among neurons and network systems.	
Reactive Anxiety Phobia: Same as generalized anxiety but stress or phobic stimulus boun. Brain disturbances as above, in reaction to abrupt intense environmental changes	Direct plasticity induction to reduce constraint frustration with 1) synaptogenetic medications and tDCS or/and random distributed tACS Indirect intervention of relaxation during gradual VR exposure personalized to the specific fear-stimulus.
Depression, (more in the morning), frequent crying, possible nihilistic delusions, and/or possible suicidal thoughts or action. Somatic symptoms, psychomotor retardation, impaired concentration, social disinterest, self-neglect, Ideas of guilt, hopelessness, worthlessness, blame. Motor speech retardation, early insomnia, loss of appetite weight loss. Disturbance to "Adaptive Plasticity" slower time-scales, those that span hours to weeks and are responsible for reducing free energy the differences between internal representations (emergent constructs) and external environmental occurrences, these involver more specifically the Salient Networks of the brain.	Direct plasticity induction to reduce "Free Energy" with 1) synaptogenetic medications and tDCS or/and random distributed tACS Indirect intervention CBT-level psychotherapy, with VR technology.
Mania. Elated expansive mood Euphoric; inappropriate laughter; singing. Pressured, uninterruptible, continuous speech. Content grandiose, superiority, amazing ability, wealth knowledge, fame, power, and/or moral stature, can be paranoid. Motor excitement; continuous hyperactivity (cannot be calmed). Overt sexual acts. Hostile, uncooperative; Denies need for sleep, interview impossible Disturbance to "Adaptive Plasticity" but in the hyper-plasticity and optimization creating a fast optimization shift resulting in fast reduction of free energy with the emergence (property of) elevated mood. These also involve more specifically the Salient Networks of the brain.	Direct intervention should take a direction of transient periodic inhibition on plasticity mechanisms, thus increasing free energy lowering mood elevation. Having resemblance to psychosis should induce psychosis-like interventions, both direct and indirect.
Moderate personality disorders. Predictable behaviors egocentricity, dependence, obsessions rigid Disturbance to "Developmental plasticity" that of lifetime long organization the Default-Mode Networks . Experience dependent plasticity lifelong processes of neuronal activations and Hebbian ensembles encode environmental occurrences creating an internal model of the world and its psychosocial environment. These internal representations of the world include others and self-representations, and the social interacting patterns and emotions.. Sever personality disorders. Unstable emotionally Easy frustration, impulsive	Primarily treatment of biased internal-representations is that of corrective experience dependent plasticity which can be effectively delivered if psychotherapy process is optimally exercised. Thus the indirect intervention is the primary one in the case of personality disorders. However if the brain could become highly plastic like the brain of a 3-year old child, then it can be predicted that the

splitting, brief psychosis risk behaviors intense transference low-self-esteem and sensitivity to criticism. Disturbance to "Developmental plasticity" that of lifetime long organization the Default-Mode Networks. Early internal representations are not properly formed, generating unstable, disinhibited, chaotic, split experiences. Individualization is not achieved and experiences are undistinguished from internal identity.	psychotherapeutic process could advance faster and more effectively. Thus the direct intervention can take the form of that for depression but for longer periods, such as years, according to the progress of the treatment. VR controls the experience more effectively than regular psychotherapy thus can be used to diagnose and treat more effectively. VR scenarios can be designed to elicit specific personality-related behaviors in patients, the behavior becomes diagnostic and the scenario-related behavior can them be used for therapy altered to become a "corrective" experience / scenario.



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