Plasticity and Brain Profiler

A Unifying Theory for Psychiatric Diagnosis

Abraham Peled M.D.

Self-Publication

Content

Author 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, the 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 to 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-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" of mental functions that arises from whole-brain organization supported investigating neuronal-network organization of the entire brain.

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 were amazed by the direction I took which was very odd for them, even threatening to some extent, 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 "Connectom". Throughout the years, I have followed the literature and periodically would try to relate it to the translation of mental disorders to brain disorders. I have also tried to call the field "Neuroanalysis." This term was coined under the influence of a book by the eminent 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.

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.

Plasticity-Brain Profiler Theory in a Nutshell

The plasticity theory for psychiatry is rather straightforward. It is based on two assumptions 1) Emergent properties from the brain, and 2) 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.

As for the second assumption, that of brain network dynamics, the hypothesis is that mental disorders are disturbances to the optimal whole brain organizations. Different phenomenological manifestations of mental disorders are caused by different types of neuronal network "breakdown" patterns. These can be conceptualized in terms of disturbances to plasticity dynamics.

Plasticity is the term reserved for interactions taking place between, and among, neuronal network systems in the brain (neurogenesis and synaptic activity), these are typically interactive with external environments via sensation (sensory systems) and actions (motor activity).

The disturbances to brain plasticity-dynamics can be defined by their time-scales and interactions with the environment. "Cognizance Plasticity" is in the millisecond range integrating brain organizations from instant to instant with the emergent property of Consciousness and the capabilities of cognitive functions such as problem solving and action planning. The brain is organized as a network with connectivity and hierarchy, thus altered Cognizance Plasticity involves disconnection or over-connection and hierarchical bottom-up or top-down connectivity alterations.

"Reactive Plasticity" is somewhat on a longer timescale. Cognizance Plasticity, that of minutes to hours, stabilizes the Cognizance plasticity in the face of perturbations caused from large alterations of environmental dynamics (i.e., stress). Large alterations of environmental dynamics, that typically characterize stressful occurrences perturb and destabilize the fast (millisecond-range) plasticity and thus requires a more lasting connectivity stabilization of Reactive Plasticity to "hold it together."

"Adaptive Plasticity" is slower. It spans time-scales of weeks. It reflects Hebbian Dynamics creating memories where neurons that fire together increase the connections between them (wire-together). Adaptive Plasticity sustains memories, which in turn build internal representations of the environmental occurrences. In effect, the fast Cognizance Plasticity, slower Reactive Plasticity and even slower Adaptive Plasticity generate an internal model of the environmental events in the brain. Such an internal model of the world organizes brain dynamics to predict and optimize the interactions with the environment assuring optimal effective survival for the individual. The brain acts to minimize the differences (Delta) between psychophysical occurrences in the environment and the internal brain-model of these same environmental occurrences. This is done by continuous "update" of the internal model based on sensory activity and by continuous adaptive interventions in the environment via motor activity in the surrounding environment. Thus, the slower Adaptive Plasticity is the one responsible for minimizing brain-environment bias (reducing free energy or delta in mathematical physical terms). This is done with Bayesian dynamics where the brain continually makes error predictions and corrections interacting with the environment.

Finally, "Developmental Plasticity" results from life-long processes of all the above plasticity dynamics. This lifelong developmental process is often defined as "Experience- Dependent Plasticity" and is composed of long-lasting, memories embedded in the brain network-configurations because of life-long Hebbian dynamics. The total life experiences acting on the developing brain from its first developmental stages create a lasting stable basic neural-network organization in the brain that encodes internal representations of the environment including occurrences that are more complex; those of social interactions including self and others-representations. Such neuronal network organization in the brain is basic (at rest), and is

conceptualized as the “Default-Mode-Network” because it is apparent when the brain is not engaged in stimulated rapid cognitive-related action. The emergent property from the activity of basic developmental Default-Mode-Network is the Personality style, reflected in the reactions and attitudes “shaped” by the life-long experiences of the individual.

According to the above conceptualizations, psychiatric disorders can now be reformulated. Disturbances to the fast millisecond-range Cognizance Plasticity will disturb conscious integration with symptoms of psychosis and schizophrenia. Disturbances to Reactive Plasticity, the reactive stabilization of neural networks in the face of environmental perturbations, result in the emergent phenomenology of anxious sensations and anxiety symptoms. The disturbances to slower Adaptive Plasticity that optimizes internal representations and reduces predictive error will result in mood disorders. De-optimized brain with free energy increases results in the emergent property of depression and vice versa. Optimization dynamics is mood elevating i.e., possible manic symptoms. Finally, altered internal representations of psychosocial occurrences due to “immature” biased Default-Mode Retesting brain network organization result in personality-related distortions, which lead to ineffective, biased social interactions and an emergent property of personality disorders. Table 1 summarizes the plasticity disturbances and their phenomenological correlates

Table 1: Plasticity disturbances and their phenomenological correlates

Plasticity disturbance	Brain system disturbance	Psychiatric emergent properties of phenomenology
Cognizance Plasticity	Disturbance to millisecond range integrating brain organizations. Disconnection or over-connection and hierarchical bottom-up or top-down connectivity are disturbed	Psychosis and schizophrenia (negative signs)
Reactive Plasticity	Disturbances to longer timescale those of minutes to hours, the stabilizing network plasticity in the face of perturbations caused from large alterations of environmental dynamics (i.e., stress).	Anxiety (general, reactive, phobia)
Adaptive Plasticity	Disturbance to slower time-scales, those that span hours to weeks and are responsible for reducing free energy. The differences between internal representations (memory constructs) and external environmental occurrences. De-optimization takes place when free energy increase and mismatch between internal representations and external events becomes larger	Mood disorders
Developmental Plasticity	Disturbances to the Default-Mode Retesting brain network organization resulting in distortions of internal representations of the psychosocial world which lead to ineffective biased social interactions	Personality disorders

Cognizance Plasticity

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. This dynamics can be fast dependent on neurotransmitter activity, or slower dependent on structural cell membrane formations. In any case, faster or slower, it is 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.

To understand in which context these activations occur one must consider the physiology and anatomy of the brain. 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, Wernicke'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 the highest mental functions. According to Mesulam, emerging properties from the highest level of sensation action interactions are those of motivation and volition, the total action on the total sensation.

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.

A useful method to understand how dynamic activity is presented in the brain network configuration is that of State-Space. 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 & 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) to 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 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. The strengthening of connection for that state of the system causes that state-related ensemble to activate, thus "attracting" the dynamic activity of the system to that state, activating it, or in other words activating the memory embedded in that state. 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.

The internal representations in the brain 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 (Tononi et al., 1994).

Baars postulated a theoretical workspace in which 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.

Tononi and Edelman (2000) combined the above insights with other findings and formulated the concept of the "dynamic core." The dynamic core explains which neural processes underlay conscious experience. Tononi and Edelman concluded that a group of neurons could 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, meaning 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 re-entrantly 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.

Both the description of global-workspace and dynamic core lend to the idea that emergent properties require massive whole-brain dynamics and organization. The emergent property from millisecond to millisecond range brain integrations is consciousness. Conscious experience is both serial in time and coherent in integrating experience. Serial coherent conscious experience reflects the vast integrative organization (coherence) and the instant-to-instant changing global workspace (or dynamic core) configurations, each sustaining its momentary content of conscious experience.

To summarize the fast millisecond range activity in the brain entails connectivity in the form of small-world network organization, this connectivity also enables hierarchal formations. The

higher-level hierarchal organizations are formed in hubs of brain higher-level organizations such as limbic, prefrontal and Basal Ganglia. In these transmodal integrative highly connected systems, concepts can be represented by "concept cells or neurons". These cells or neurons create a conceptual semantic network organization that is continually interacting with the environment via top-down bottom-up balance of processes, predicting and error-correcting the environmental occurrences (sensorium) as well as intervening and changing environmental occurrences via action (motor) in the environment. The higher-level dynamics with whole brain integrative capabilities creates an emergence, which is the emergent property of consciousness. The phenomenology of coherent stable adaptable and serially dynamic conscious experience is a result of "global workspace or dynamic-core higher-level brain organizations acting as the higher-level network dynamic organization of the brain.

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 is 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 bottom-up top-down process also disconnects causing illogical erroneous ideas of higher-level organization to 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 at., 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.

Schizophrenia is 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 hierarchal top-down and bottom-up disturbances.

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.

Reactive Plasticity

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.

Adaptive Plasticity

Fast Cognizance Plasticity and Reactive Plasticity continually shape the internal memories with the fast Hebbian dynamics caused by calcium flux and synchronized electrical ion-channels activation potentials. Repeated experiences, training, and skill acquisitions are all dependent 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.

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.

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.

Developmental Plasticity

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-related diagnosis

As already mentioned in the previous chapter titled "Plasticity-Brain Profiler Theory in a Nutshell**";** disturbances to brain plasticity-dynamics can be defined by their time-scale and interactions with the environments. "Cognizance Plasticity" is in the millisecond range integrating brain organizations from instant to instant with the emergent property of Consciousness and the capabilities of cognitive functions such as problem solving and action planning. Because the brain is organized as a network with connectivity and hierarchy, altered Cognizance Plasticity involves disconnection or over-connection and hierarchical bottom-up or top-down connectivity alterations.

"Reactive Plasticity" is somewhat on a longer timescale then Cognizance Plasticity, that of minutes to hours, thus stabilizing Cognizance plasticity in the face of perturbations caused from large alterations of environmental dynamics (i.e., stress). Large alterations of environmental dynamics, typically characterizing stressful occurrences perturb and destabilize the fast (millisecond-range) plasticity and thus requires a more lasting connectivity stabilization of Reactive Plasticity to "hold it together."

"Adaptive Plasticity" is slower, spanning weeks. It reflects Hebbian Dynamics creating memories where neurons that fire together increase the connections between them (wire-together). Adaptive Plasticity sustains memories that in turn build internal representations of environmental occurrences. Fast Cognizance Plasticity, slower Reactive Plasticity and even slower Adaptive Plasticity generate an internal model of the environmental events in the brain. Such an internal model of the world organizes brain dynamics to predict and optimize the interactions with the environment assuring optimal effective survival for the individual. The brain acts to minimize the differences (delta) between psychophysical occurrences in the environment and the internal brain-model of these same environmental occurrences. This is done by continuous "update" of the internal model based on sensory activity and by continuous adaptive interventions in the environment via motor activity in the surrounding environment. Thus, slower Adaptive Plasticity is the plasticity responsible for minimizing brain-environment

bias (reducing free energy or delta in mathematical physical terms). This is done with Bayesian dynamics, in which the brain continually makes error predictions and corrections interacting with the environment.

Finally, "Developmental Plasticity" results from life-long processes of all the above plasticity dynamics. This lifelong developmental process is often defined as "Experience- Dependent Plasticity" and is composed of long-lasting, memories embedded in the brain network-configurations because of life-long Hebbian dynamics. The total life experiences acting on the developing brain from its first developmental stages create a lasting stable basic neural-network organization in the brain, which encodes internal representations of the environment including its more complex occurrences; those of social interactions including self and others-representations. Such neuronal network organization in the brain is basic (at rest) and is conceptualized as the "Default-Mode-Network" because it is apparent when the brain is not engaged in stimulated rapid cognitive-related action. The emergent property from the activity of basic developmental Default-Mode-Network is the Personality style, reflected in the reactions and attitudes "shaped" by the life-long experiences of the individual.

According to the above conceptualizations, psychiatric disorders can now be reformulated. Disturbances to the fast millisecond-range Cognizance Plasticity will disturb conscious integration and result in psychosis and schizophrenia symptoms. Disturbances to Reactive Plasticity, the reactive stabilization of neural networks in the face of environmental perturbations result in the emergent phenomenology of anxious sensations and anxiety symptoms. The disturbances to slower Adaptive Plasticity that optimizes internal representations and reduces predictive error will result in mood disorders. A de-optimized brain with increased free energy results in the emergent property of depression and vice versa. Optimization dynamics is mood elevating i.e., possible manic symptoms. Finally, altered internal representations of psychosocial occurrences due to "immature" biased Default-Mode Retesting brain network organization results in personality-related distortions that lead to ineffective biased social interactions and an emergent property of personality disorders. Table 1 summarizes the plasticity disturbances and their phenomenological correlates.

Each patient needs to be assessed on all of the plasticity types and ranges. A diagnosis, which is the patient's diagnostic profile of brain optimization or breakdown, can then be made. Figure 1 demonstrates a Brain Profiler Diagnosis of a patient with moderate anxiety, depression, and mild extrovert-related personality disorder. Each vertical axis plots the type of plasticity relevant to the clinical phenomenology rated on that axis. From left to right, the first axis plots Cognizance Plasticity to rate schizophrenia and psychosis phenomenology. The second axis plots Reactive Plasticity to rate anxiety-related phenomenology. The third axis plots Adaptive Plasticity to rate mood-related phenomenology and the fourth axis plots Developmental Plasticity to rate personality-related phenomenology.

Figure 1

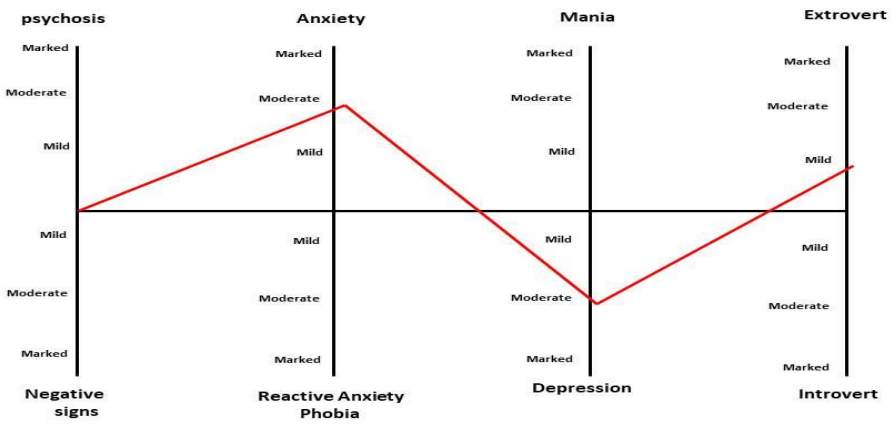

Figure1: Each vertical axis plots the type of plasticity relevant to the clinical phenomenology rated on that axis. From left to right, the first axis plots Cognizance Plasticity to rate schizophrenia and psychosis phenomenology, the second axis plots Reactive Plasticity to rate anxiety-related phenomenology, the third axis plots Adaptive Plasticity to rate mood-related phenomenology and the fourth axis plots Developmental Plasticity to rate personality-related phenomenology.

This Brain Profile diagnosis is not only informative regarding a spectrum of phenomenological manifestations that integrate and comprise the majority of manifestations of mental disorders, it is also informative regarding possible causal relationships with each profile. For example, in Figure 1, the patient suffers from a mixture of moderate anxiety and depression including mild extrovert-related manifestations in the personality disorder axis. Here we can deduce the causal relationships between findings within the profile as follows: the developmental plasticity suffers from a mild instability; this in turn hampers adaptive processes of the adaptive-related plasticity and such instability translates into inefficient reactive plasticity. Each of the disturbances contributes to the emergence (i.e., emergent property) of its specific characteristic type of phenomenology, presenting the symptomatic profile, i.e., the mixture of moderate anxiety and depression including mild extrovert-related manifestations of the personality disorder.

If cognizance plasticity is perturbed, then reactive plasticity will also become unstable. Thus, florid psychosis is often accompanied by high anxiety levels. If the reactive plasticity influences adaptive plasticity then depression can accompany the clinical picture as well. In turn, altered adaptive plasticity can influence the stability of reactive plasticity emerging as a mixture of depression and anxiety without personality-related disorders. Thus, interdependency between plasticity processes over short and long time-scales can explain interdependency and spectrum mixtures of symptomatology of mental disorders.

Brain-imaging validation

According to the theoretical construct of brain plasticity of mental disorders it is assumed that disturbances to fast millisecond range Cognizance plasticity is responsible for schizophrenia and psychosis. Disturbances to slower minute range Reactive plasticity is responsible for emergence of anxious sensations and anxiety disorders. Disturbances to slow week-range Adaptive plasticity are responsible for mood disorders and finally disturbances to life-long range Developmental plasticity are responsible for personality disorders.

How can we validate the theoretical propositions presented thus far? The only way to look into the brain is by using brain imaging and signal processing. The signal processing is applied to the brain imaging signals and must be sensitive for detecting neuronal network plasticity alterations. The best assessment of network dynamics would be one that ultimately allows brain imaging to become translated into a graph. In the graph, units are "Nodes" and connections are "vertices". The number of vertices connections to each unit defines the "Degrees" of such a unit, with "Hubs" being the nodes with the most degrees. Graphs of effective optimal information-transfer networks have been shown to have "Small-world" organization one that optimizes the balance of near-by cluster connectivity and long-pathway distant connections (Guye, 2010). These parameters can be calculated for the graphs extracted from brain imaging. In these graphs, nodes are neurons or groups of neurons and vertices are axon pathways and synaptic connections.

In extracting graphs of brain activity it is critical to use multiple (a battery of) signal-processing evaluations. For example, one may start with simple correlation matrices, but more non-linear correlation estimations should also be considered. Bayesian predictions of neuronal activity among units should involve assessment of connectivity, and Dynamic Causal Modeling should be applied specifically to the assessment of Adaptive Plasticity processes. Needless to say, all assessments should involve all of the time-domains, specifically, when studying the relevant phenomenology for each plasticity time-range.

Accordingly, plasticity dynamics of the healthy brain is considered to sustain small-world organizational characteristics. In addition, mental disorders are expected to show typical disorders-specific disturbances to the small-world organization, very similar to how cardiac arrhythmias underlie cardiac insufficiency. Similarly, "brain arrhythmias" generate brain-insufficiency of mental disorders; however, brain arrhythmias are considerably more complex than those of cardiac arrhythmias.

If detecting the causes (brain arrhythmias) of mental disorders is so simple then the question arises, why have we not already discovered them? The answer to that question can probably be found in the problem of complexity characterizing the brain. The brain is "noisy," relevant neuronal network activity masked by the shear enormity of "neuronal noise", and in addition the detection capabilities of signal-processing are limited (weak). Both noisy brain and weak signal processing impede the discovery of the presumed causes of mental disorders described thus far.

To overcome this obstacle of "noisy" brains and weak signal-processing, large-data is compulsory! Thus, our challenge to discover the causes of mental disorders is technological. The ability to collect store and process large-data is improving rapidly. The technology of brain imaging, specifically mobile and consumer-operated EEG devices enable the collection of large EEG data-sets. Thus, it is conceivable that soon we may be able to begin to discover the brain-related causes of psychiatric disorders and the plasticity-dynamics hypothesis may be the appropriate framework to guide such discovery.

In summary, it is important to apply signal processing to lager datasets of brain imaging, to apply it across all time-domains of brain plasticity from millisecond range to lifelong timescales. Signal processing should detect network small-world organization using graphs extracted from full batteries of signal processing methodologies. Presumably, the combination of huge data-sets with the theoretical construct of brain profiling-plasticity will prompt the discovery of the causes of mental disorders.

Therapeutic Directions

When discussing therapeutic intervention for psychiatric disorders, the most important insight from the plasticity brain-profiling theory is most likely, that of the time-scales of plasticity. For example, strong evidence refers to interventions into the slower-range of adaptive plasticity with Selective Serotonin Reuptake Inhibitors (SSRI). These are known to be neuro-genetic and synaptogenetic interventions (Gingrich et al., 2017) thus increasing adaptive plasticity. According to the described theory, SSRIs have an anti-depressant mood effect because the increase of adaptive plasticity offers better adaption of internal representations to altered environmental changes reducing free energy and triggering the emergent-property of anti-depressant mood elevation.

Thus, future therapeutic interventions should target plasticity of networks dynamics relevant to their time-scales and the biological factors relevant to the specific time scale activity. Discussing interventions to the millisecond range of cognizance plasticity, the biological targets would be factors controlling the membrane-potential signaling activity, probably calcium channels and other channel-receptors influencing such rapid potential activations. As for the location of interventions to such neuronal structures, they should be targeted to network hubs of the brain; the prefrontal cortex, the medial temporal hippocampal networks and the basal ganglia hubs deep in the brain. The technology for such interventions is currently being developed in the fields of nano-technology. Noninvasive technologies that can effect neuronal activity from an external source but one that is noninvasive is becoming relevant, as is a transcranial energy-vector that has precise effects on activating and suppressing hub neuronal activity. In the future, nano-devices logged in neuronal membranes of the relevant neurons will react to an external transcranial signal thus control the neurons from outside the scalp. The controlling device will also be miniaturized and will probably involve a small sticker placed on the forehead. The signaling device will control neuronal activity using a feedback loop mechanism because the entire intervention would probably be very sensitive to “balancing” dynamics of a highly optimized brain.

Magnetic and electric transcranial vectors that try to stimulate cortical neuronal activity are current technologies that come close to the above description. These technologies are the

precursors of future brain-pacing interventions and thus can be used to approximate the interventions that will be required in the future to cure mental disorders. For example intervention in fast cognizance plasticity will probably need control over prefrontal hub activity. The prefrontal cortex (PFC) is involved in many mental disorders (Arnstein 2010) and especially the more severe disorders such as positive and negative signs schizophrenia.

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 so far 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 of the field of noninvasive electrical stimulation of the human brain by directly interfering with cortical rhythms (Andrea & Walter, 2012). tACS is hypothesized to influences endogenous brain oscillations, If applied long enough 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 & 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 desynchronize can also attenuate neuronal oscillations and event-related oscillatory activity can be inhibited using a rhythm slightly below the stimulation frequency.

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

Brain dynamic organization of neuronal network activity is presumed to correlate with electrical oscillations measured over the scalp, propagating from brain neuronal activity. Gamma Oscillations (30-100 Hz) have been repeatedly correlated with distributed neuronal network activation over distant brain regions and also involved in performing higher-mental functions of attention and executive functions (Fortenbaugh et al., 2017). In addition, BOLD signal measured by fMRI correlates 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 were 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 have a 'hub-related control' over wide-spread neuronal networks in the brain. This is in 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 (Woo et al., 1998; Pierri et al., 1999; Hashimoto et al.,; 2003; Volk et al., 2001, 2002).

This is in correlation with many studies summarized by Sohal (2012) that found that patients with schizophrenia exhibit decreases in the 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 a simulated increase in 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 appearance of negative signs schizophrenia. This is relevant to re-conceptualizing schizophrenia in terms of brain network disturbances to the functional connectivity in brain systems.

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

Future therapeutic interventions should target plasticity of networks dynamics either by intervening in hubs of the network (as described) in or the whole network, which in turn affects

the whole network dynamics. A combination of the two could become especially powerful, for example, a brain-pacemaker hub controlling whole brain dynamics coupled with administration of SSRI-like plasticity inducers can rapidly intervene in whole-brain dynamics optimizing its activity and eliminating its relevant symptomatic and phenomenological manifestations.

Targeting developmental plasticity requires interventions that target experience. This is because experience-dependent-plasticity drives developmental plasticity. Currently psychotherapy is an experience-dependent intervention because the therapy sessions are actually interpersonal experiences that the patient undertakes. Individuals seek psychotherapeutic treatment out of distress that originates from interpersonal relationships in psychosocial situations. In the process of psychotherapy, changes occur in the patient that enable him or her to adapt to, act upon, and perceive these situations without accompanying discomfort.

The interpersonal relationship between therapist and patient is the experience-dependent intervention tool for creating the needed change. Initially the relations with the therapist will repeat the same patterns of interpersonal relations that caused the distress. The skilled therapist identifies these patterns and reacts in a way that gradually changes the attitudes of the patient toward similar future situations. Successively, this change continues both in and outside of the therapeutic setting. Better coping in psychosocial situations reduces the former suffering and enables the relief from symptoms. This relief is the outcome of the treatment.

Psychotherapeutic procedures have been described as overcoming resistance, offering appropriate interpretations, and increasing insight into relevant aspects of interpersonal relations. Using the plasticity brain profiler approach, the psychotherapeutic process can be described as a physical change that takes place in the brain of the patient. Initially, the relationships between the internal map of reference of the individual (internal representations) and some aspects of the psychosocial situations he or she encounters are incongruous (a mismatch). This incompatibility reaches the extent in which 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 as symptoms of anxiety and depression. The goal of the therapy is to reshape the internal representations to include the

appropriate representations to cope with the psychosocial situations at hand. At the initial phases of psychotherapy, the therapist is perceived by the patient as being more like one representation of similar people encountered in the past (transference). This is because the patient activates the attractor systems, described above, that represent these people. Since the therapist is not the same as the activated representation, a distorted perception of the therapist emerges. Because of this distortion, an inappropriate behavioral reaction to the therapist (transference) occurs.

Most probably, this distortion is there for other interpersonal situations outside the therapeutic sessions as well. This indicates that there is substantial mismatch between internal representation and psychosocial reality. The therapist has to enlarge the repertoire of representations of the individual to match various different psychosocial situations. An enlarged repertoire of internal representations will enable a better match between internal representation and psychosocial reality. Increasing the repertoire of internal representations involves creating additional and more complex attractor systems to match the events of the psychosocial settings in reality (i.e., adaptive plasticity). When the therapist reacts to the patient in new ways that were never perceived by the patient before, Hebbian mechanisms of plasticity will gradually create the new attractor systems needed for the additional internal representations. In this manner, the therapist shapes the space-state topology of the brain to form new internal representations. This involves actual changes in the functional connectivity of the neural systems involved,

Recently experience-control technologies such as virtual-reality (VR) are rapidly developing. It is just natural that such technology will be used to intervene in developmental plasticity. The powerful experiences generated from VR technology are often indistinguishable from real experiences. This is caller “presence” as the user forgets he is not in the real environment and substitutes the VR experience with the real one. Such powerful experience control over the patient opens the door for VR-related psychotherapy where social enjoinments can be played out to reshape developmental plasticity in ways that can help patients optimize their developmental plasticity and cure disorders related to maladaptive faulty personality traits.

Coupled insertions with other plasticity dynamics is also relevant in the case of development plasticity. Imagine that the psychotherapy of VR-related experience-control technologies will be

coupled with SSRI-like synaptogenetic interventions. Moreover, if such interventions could be applied to a brain conditioned to plasticity increases that match the developing plastic brain if a 3-year old child, which is very malleable, and thus effect change and education. As such, the effectiveness of technology-driven VR-psychotherapeutic interventions will increase enormously making this therapy many times more effective.

To summarize this section, it is important that after the patient receives a disturbed plasticity brain-profile diagnosis, s/he should receive the therapeutic intervention targeted to his/her deficient plasticity regime. Combinations should be tailored according to combinations of plasticity dynamics that enhance each other for global brain optimization dynamics.

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Bio

Abraham Peled is a Psychiatrist. –Clinical Assistant Professor at the Rappaport Faculty of Medicine, Technion, Israel Institute of Technology. Chair of department at Shaa'r-Menashe MHC Israel. Founder of "NeuroAnalysis," Author of four books and various publications applying physics of complex-systems to psychiatric diagnosis.
Correspondence contact: neuroanalysis@gmail.com