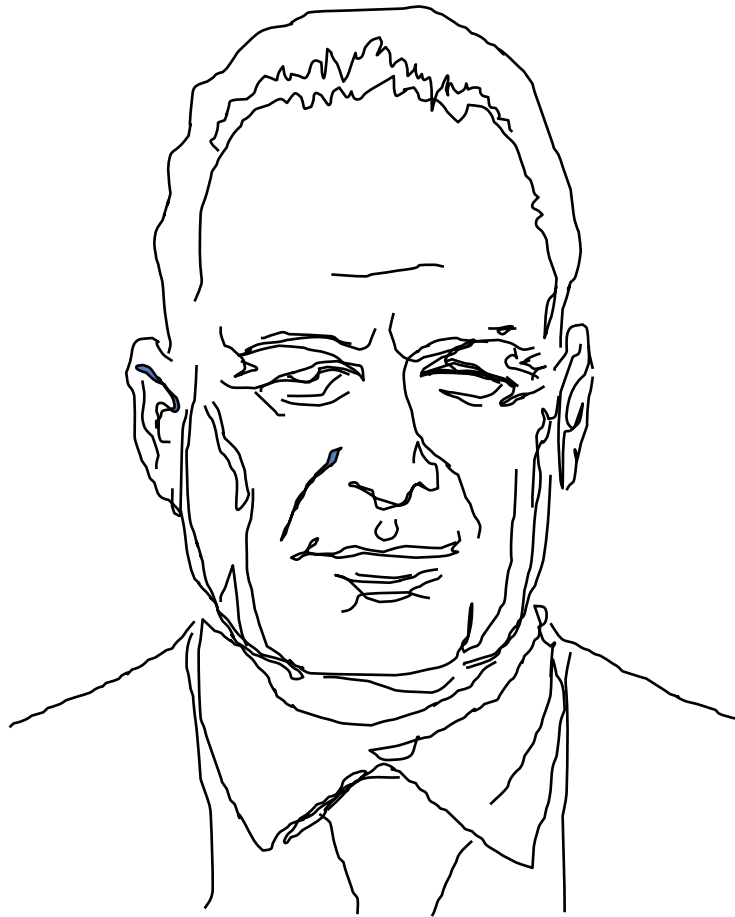


The Last Psychiatrist?

Predicting the End of Psychiatry

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***“Listen to the wind of change “ “the future is in the air, you can feel it
everywhere” Scorpions***

INTRDUCTION

Once mental disorders are conceptualized as brain-disorders, and the neurological brain-related causes of psychiatric illness are revealed, there will no longer be a need for “Psychiatry” as a distinct discipline. In medicine every specialty is organ-related; the cardiologist is the expert of the heart, nephrologist of the kidneys and so on. Similar to neurologists, psychiatrists are supposed to be experts of the brain, Psychiatry is part of neuroscientific neurology not a distinct discipline (Bullmore et al 2009). Initially in the beginning of the 19th century neurology and psychiatry were one, the division of psychiatry from neurology came when causes of mental disorders were attributed to “psychological” causes. However the term “psyche” is unscientific as it does not appertain to anything scientific physical or biological. As early as 1884 Meynert stated that the term “Psy” of Psychiatry “...*transcends the bounds of accurate scientific investigation*” (1884) and thus proposed to stop using the unscientific term “Psychiatry.”

Because psychiatry is “brainless” (not brain-related), the diagnostic system in psychiatry is descriptive and thus can lead to absurdities. For example complaining to a psychiatrist about sadness and depression, will lead to a diagnosis of “Depression”. An intelligent patient would think to himself, “well I just told you that, what added value you can give me?” Compared to other medical fields, if a patient complains to his physician, about a “stomach ache” he would expect a diagnostic procedure that results in an etiology (cause) of the disorder. Let’s say “Gastritis.” Such a diagnosis will relate to a place-in-the-body and to what has happened to it (the ending “itis” is infection). One would be very much annoyed if asking for medical opinion about stomach ache, the physician would say “well you have a stomach ache.”

If the causes of the disorders are unknown, they become incurable because the physician doesn’t know what needs fixing. With a diagnostic system that doesn’t inform about the place and cause of disease where and how can the physician intervene to cure it? This explains the inefficiency of treatments in psychiatry. An end to psychiatry will revolutionize treatment as it will become brain-related. The brain-related disturbances of psychiatric disorders are recently revealing themselves and with that the end of psychiatry can be forecasted. Psychiatry is a medical

scientific artifact of history, a transient incident due to ignorance of the brain-related causes of mental disorders.

In this short monograph I will try to describe concisely the science that will end psychiatry. I will introduce the term “NeuroAnalysis” for the more complex higher-level disturbances. The difference between “Neurology” and “NeuroAnalysis” is that of complexity not of etiology. I will then try to exemplify how our clinical profession of NeuroAnalysis will look like by describing two case reports their diagnoses and treatments. Finally I will end with my hopes of becoming the last psychiatrist and first NeuroAnalyst.

Chapter I

THE SCIENCE

The Basics and the Targets.

Before conceptualizing mental disorders as brain disorders, there are some basic premises we must adopt. First the brain is a physical system, thus subject to “Physics” as its fundamental science. As Meynert noted in his 1884 book, there is no place for terminologies such as “Psyche” and other general vague references which are non-scientific. There is a fundamental place for physics and mathematics in understanding mental disorders. Those phenomena considered mental such as emotions, feelings, consciousness and personality are “Emergent Properties” of an extremely complex system, the brain. An Emergent Property is a property of the system as a whole which is not a property of its elements, for example one neuron has no “emotions,” “feelings,” “consciousness” and “personality,” but the brain as a whole does. In addition to the fact that the brain is a physical entity and mental phenomena are emergent properties, , it is consequently logical to assume that mental disorders are global disorders, “Globalopathies” (Peled 2013) if you will. They are disturbances to the global brain organization transpiring from moment to moment. Finally it is reasonable to assume that the various different phenomenological descriptions appertaining to the different mental disorders are in themselves Emergent Properties from different patterns of “Breakdowns” of the global optimal brain organization. In other words symptom-free well-functioning individuals have optimal brain organizations enabling healthy mental Emergent Properties. Mental disorders emerge as properties caused by different patterns of brain disturbances i.e., breakdowns. One can use a cardiology metaphor where symptoms of cardiac insufficiency are related to the phenomenology of mental disorders, disturbance to brain organizations are the “arrhythmias” causing the symptoms. By correcting the arrhythmias cardiac activity is corrected and symptoms are eliminated. Such a metaphor readily points to the purpose of discovering the underlying brain disturbances in psychiatry. By discovering the exact brain disturbances a “brain pacemaker” can be devised to correct the disturbances and as in cardiology eliminate phenomenology, i.e., cure mental disorders. The future of this field of “NeuroAnalysis” is in the ability to discover and eliminate brain disturbances and develop relevant brain “pacemakers”, the corrective devices and procedures that are comparable to cardiac pacemakers, with which we shall cure mental disorders.

Brain Organization and Consciousness

Having this general description of the field and its general future aims, we can now go “deeper” and put down more specific predictions and theory to begin constructing a brain-related psychiatry. What kind of network is the brain network? It has been found that brain organization follows the formation of a “Small World Network”. It is so called because it is an effective network configuration for information transport. The small-world network organization is characterized by clusters and hubs. Just like in a social networks or in transportation networks there are multiple connections among nearby friends or locations. These clusters are then connected with other clusters via Hubs, i.e., those centers of communication (for example the major airports which have most of the junctions of flight destinations). Similarly, the brain is organized in hierarchal hub formation connecting multiple cluster formations and it has been found to have Small-World-Network organization. That organization offers the integrative power of brain organization. The brain needs to process multiple specialized segregated processes, for example visual signals, auditory signals etc., and at the same time integrate all processes into a one coherent integral conscious experience. In other words, at the level of primary sensory motor levels processes must be segregated to avoid interferences and at the higher integrative levels they must meaningfully integrate. Multiple partial processes (Barrs 1988) can flexibly and dynamically recombine to form ever higher integrations and at the top of brain hierarchy everything is connected to everything forming a global-workspace organization (Barrs 1988) from which our coherent stable organized conscious experience emerges (as an emergent property). Every second the brain generates a single conscious experience which then changes over time in the millisecond range of fast plasticity. If we vision the brain using “State-Space” formulation then each pattern generated by the brain is a point in a “Space” of all possible brain “States.” Thus, conscious awareness and thoughts could be defined by a trajectory (the collection of consequent states archived by the brain) in brain “Space,” i.e., the actual experience and awareness are generated by the brain from second to second, emerging from all possible “States.” The hierarchy also offers the possibility for the brain to generate higher level states

which embed information and generate internal models of the sensory experience. These models then act as predictors for the incoming experience and a dynamic interplay of matching internal representations to the ever-changing environmental occurrences. The internal models of reality guide effective and adaptive behavior thus the internal model must be effectively matched to the environmental situations. If a mismatch occurs then behavior becomes disturbed, thus a predictive error (Friston et al 2014) in the process of updating the internal representations must be kept to minimum.

Brain Disorganization Psychosis and Schizophrenia

One can imagine what will happen if the milliseconds range of small-world network organization is disturbed. If clusters disintegrate “Disconnection Dynamics” will take-over the brain, conscious experience will become fragmented and the network will become unstable. Thoughts will be disconnected, speech becomes disorganized with the collapse of associations and logical references. Clinically, loosening of associations will prevail. Fragmented experience allows for sensations that could not occur in organized brains. For example dissociation between auditory speech processing and the rest of brain network organization emerges as auditory hallucinations, where speech processing is activated not related to any visual or other experience. Disturbance to small-world-network disrupts Hub organization thus disturbing hierarchy and consequently predictive errors increase and with them erroneous references about environmental occurrences. With the collapse of associations and logic and with erroneous reference to actual environmental events it is understandable how “Delusions” (false unshakable beliefs) emerge. Clinicians know that disintegrated consciousness, instability, disorganization of speech, illogical assumptions and false delusional beliefs about transpiring events, are all characteristic of “psychosis”. If these signs appear at young age spontaneously, not in relation to intoxication or brain injury then such psychosis is titled “Functional Psychosis” and is typically the first main manifestation of a set of diseases called the “Schizophrenia spectrum.” Thus a brain-related etiopathology of functional psychosis can now be reformulated as disturbance to small world organization with disconnection destabilization of brain-network dynamics, and the delusional manifestations can

now become attributed to (caused by) disturbed hierarchal hub-formations and an increase of prediction errors in the physiological transfer of information going “Up” and “Down” the hierarchy (Peled 2013; Peled Geva 2014).

Plasticity Shapes Brain Organization

Psychotic phenomenology is related to “Fast Plasticity”. Mental functions such as thought and experience, occurring in the millisecond range, develop in time scales of days and hours and are subject to fast changes including when responding to medications. Thus the domain of conscious perception and action in psychiatry can be attributed to processes of “Fast Plasticity” physiologically related to firing patterns of membrane electrical activity among relevant neuronal ensembles. Fast brain dynamic plasticity is related to a more stable brain dynamics, i.e., slower changing brain organizations. Fast activity is embedded in a more basic brain organization which is much more stable, and where the plasticity is slower. In effect there are mutual relationships between the fast plasticity processes and the slower ones. It is like water running in a river-bed, the running-water represents the fast process and the river-bed represents the slow plasticity. This is because while the riverbed determines the direction of water-flow the water-flow at the same-time reshapes the riverbed, thus the fast plasticity (running water) is at the same time directed by the river-bed and also reshapes the riverbed. In this metaphor the slower plasticity (i.e., the river-bed) determines the activity of fast plasticity but at the same time the fast-plasticity (specifically if repeated) changes slow-plasticity-processing. This type of dynamics is known at the synaptic level as Hebbian algorithms. i.e., if neurons connect with each other frequently then gradually the connections between them become stronger. This happens with the well-known processes of synaptic transfer which initially depends on chemical fast changes and gradually via neuronal-nucleus and DNA activity creates more permanent membrane-based connections. Thus, to conclude: just as the metaphor of the river stream and its river-bed mutually influence each other, the water shapes the river-bed and the river-bed steers the water stream, such are the relationships between Fast-Plasticity and Slow-Plasticity where the fast electrical activity is directed by the network configurations, but such fast electrical

activity at the same time also reshapes the network connectivity configuration, i.e., the Connectom (Sporns and Betzel 2015).

This interdependent activity between fast and slow plasticity is very important because internal mental events generated with fast plasticity traveling the sensory-motor hierarchy can gradually become internal more permanent memories, and fundamentally the basis of constructing internal presentations of environmental reality, These are internal models of the world that are constantly updated and thus are flexible, renewable and adaptable. The adaptability of such internal constructs can be theoretically valued using matching estimates. In other words to what degree does the internal representation match the real-world environmental occurrences? Bayesian predictive brains that minimize prediction-errors are presumably in the best position to generate adaptive matching internal models of the world. Another way to look at this is by using the term “Optimization” meaning that the adaptive brain optimizes internal-models of the environmental occurrences, i.e., models of the world. In such a case Optimization dynamics describes a process where the differences between internal models and real-word occurrences are minimized and “De-Optimization dynamics” is such that the differences between internal models and real-word occurrences increase becoming less and less alike.

Plasticity Optimization and Mood

The world is ever-changing, thus the occurrences in the real world are constantly changing. Brain plasticity adapts to these changes by predictive and Bayesian mechanisms. Due to constant change there is never a situation of a full complete match. There is always a certain degree of mismatch between internal world-models and external real world occurrences. It is assumed that as the whole brain moves from less optimal to more optimal real world configurations and mismatch is reduced (i.e., Optimization), an emergent property of mood becomes elevated. Conversely it is assumed that as the whole brain moves from more optimal to less optimal real world configurations and mismatch is increased (i.e., De-Optimization), an emergent property of mood becomes depressed. What are the foundations for such a hypothesis? These are the

relationships between plasticity and mood. The most replicable findings related to depression are that they are associated with neuronal plasticity (Pilar-Cuéllar 2013; Wainwright and Galea 2013; Dwivedi 2013). Antidepressant medications are synaptogenetic, and spine-genetic, and increase brain plasticity. With the theory of optimization, linking plasticity and adaptability make sense. A more plastic brain is more adaptive and flexible thus it is in a better position to generate optimal internal models of the world thus triggering optimization dynamics in the brain. The brain then reduces mismatch between internal world models and external environmental world occurrences, thus triggering the emergent property of elevated mood, antidepressant effect. In short; more plasticity means more adaptability which leads to more optimization dynamics and results in the emergent property of mood elevation. The opposite can explain depression, De-optimization dynamics emerges as depressed mood. If such a hypothesis is correct then neuronal atrophy (the opposite of synaptogenesis) reduces brain plasticity and adaptability. Since world occurrences always change and fluctuate then mismatch will increase between internal repositions and real-world events. The non-plastic atrophic brain cannot catch-up with the regular environmental changes, and depressed mood ensues as the emergent property of that brain. Thus it is understandable why 40% of dementia patients also suffer from recurrent depressions. Their brain is just not plastic enough to reach optimization dynamics in the face of regular environmental changes.

This ideation of interplay between brain plasticity and environmental changes leads us directly to the concept of “Stress,” and its relationships to depression. We know from clinical experience that stresses, failures, loss and unfulfilled expectations typically lead to depressed mood. This happens also when plasticity is intact and well-functioning. We also know that great stressors are those involving abrupt and large changes in the environment. Death of a close relative, loss of a job, and other life-altering circumstances, all have in common a substantial change of environmental occurrences. These major changes differ from the internal models and configurations that are still representing the pre-stress internal formations. Obviously the mismatch between the pre-stress and stress occurrences is increased. Most times this mismatch is very large and very rapid, thus the emergent property of such an abrupt mismatch and de-optimization would be an emergent property of an extreme depressed mood. It can be concluded that life stresses are related to changes in the environment that cause alteration of mood as an

emergent property of relevant de-optimization dynamics caused by the environmental alterations characterizing the stress. Normally mood alterations of every-day life experiences are mild due to small optimizations and de-optimization dynamic changes related to every-day occurrences. Some are have a closer match to internal representations some less however large environmental changes due to significant stresses do cause clinical depression explained by the model of optimization dynamics and brain plasticity. The brain may assume oscillating optimization dynamics thus manifesting as the emergent property of bipolar disorders. The networks subject to such de-optimization shifts becomes unstable. In the sense that “Constraints” between neuronal ensembles shift rapidly, the Emergent Property of such alterations is hypothesized to become expressed as anxious mood. It is clinically evident that depression and anxiety typically occur together to a substantial extent. If depression is the emergent property of de-optimization dynamics then anxiety is the emergent property of generalized neuronal network instability where “Constraints” within the network are “Frustrated.” Frustration of constraints happens because of discrepancies between neuronal activity and weighted synaptic transfer functions (Peled 2011).

Internal-Configurations and Personality

Now we have seen how conscious experience is generated by fast plasticity and how these conscious experiences are embedded into internal memories which generate an internal model of reality. We have conceptualized how such internal configurations dynamically optimize and de-optimize in relation to real world environmental occurrences, and we have understood their relationships to mood and anxiety. Now, we are ready to conceptualize personality and personality disorders as disorders of the maturity and the configuration of internal representations. Personality is defined as the combined characteristics of feeling, thinking and reacting (Gunderson 2013). These are repeated stable patters of experience and behavior of the individual. Personality disorders are described as rigid non-adaptive behaviors that generate dysfunction and distress in the individual (Gunderson 2013). These are very general definitions. Psychologists, starting with Freud, have for many years understood that to comprehend personality, it is important to take a developmental approach to understand how our experience of

self and others develops gradually to its current configuration. It is intuitive that during development we experience life-events and these shape our personality. We learn from experience, and the memories remain to guide our behaviors and familiarities thus shaping our personality styles as adults.

As early as 1884, Theodor Meynert realized the relationships of personality to brain neuronal networks . He stated that experiences activate neuronal ensembles and these connect to other neuronal ensembles that are activated by associated experiences. Each one of us generates a brain-network organization shaped by experience-dependent brain activations. In other words experience-dependent-plasticity shapes personality attitudes. Meynert envisioned such a basic network brain-organization that incorporated who we are based on our experience. He called this basic brain network organization “Ego.” His description of the Ego as a basic brain network (at rest) is very similar to the description of the Default-Mode-Network discovered in the last decade (*). It is at-rest basic network organization capable of embedding information (memories) in its connection patterns. These are presumably life-time memories that shape the internal configurations or “maps” (Rogers 1965) that we use to experience ourselves and others and psychosocially react accordingly. From this description we can assume that the resting-state Ego organization is the substrate of our personality, configuring our experiences and reaction to the psychosocial occurrences and the world.

Internal-Configurations and Personality Disorders

Two important aspects of such personality related internal configurations are relevant when personality disorders are discussed. First the development of the internal configuration and second the congruency, meaning to what extent the internal configurations are congruent (matching) with the real world, i.e., the occurrences in the real environment. As for development of internal presentations we have already described how these are formed regulated and maintained. In the long-run they form pretty stable long-lasting internal configurations (shaping the river-bed, see above). Initially infants are born with very little experience. Their internal

configurations are probably rudimentary “simple starting-points.” The internal representations of early life probably have limited representation capabilities forming only simple constructs able to capture only partial distinct aspects of real-world events. It has already been described by psychologists that only simple opposing or distant aspects are initially incorporated into internal representations. The Object relationship psychologists call this “split” the early internal configurations tend to represent “all or none” “good or bad” patterns. Such simple rudimentary configurations cause the immature brain to perceive the world using an “all-or-nothing” algorithm thus psychological attitudes of “Idealization” and “Devaluation” of others and self are apparent. Attitude to others and self, all oscillate between either all positive or all negative comprehensions without the possibility of seeing the complexity of the more realistic world where many intermediate patterns exist. Self and others have multiple characteristics in-between “all good” or “all bad”, Actually reality is complex with many sides to every object, some good some bad in the same person. This complexity of the real-world which has many sides to the same event (or object) requires a more mature internal model of the world. The more mature the internal model of reality, the more realistic is the comprehension of the complex reality. Such matching complexity is also a better match with better optimization and adaptation between internal and external representations. Following this reasoning (and including our discussion above about optimization and mood), it is conceivable that immature internal configuration (being rudimentary, and too undeveloped to represent an accurate model of the complexity of the real world), would obviously mismatch real events, and would lack optimization dynamics required for appropriate representations. Thus, there would be a continuous de-optimization dynamics and thus continuous long-standing depressed mood (that is currently typically named “Dysthymia”). In fact, clinically, we know that the typical complaints of patients suffering from personality disorders (immature personality) relate to long-lasting depression at one level or another. To summarize, individuals with immature personality disorders are non-adaptive and distressed because they suffer from undeveloped, rudimentary internal configurations that are incapable of representing the complexities of reality and are thus mismatching and non-adopting to real-world events. Such continuous brain de-optimization dynamics generate the emergent property of distress and depression typical to such patients. De-optimization dynamics expose brain organization to instability and thus explains both anxious mood typical to these patients, and in case of more severe destabilizations, where connectivity is at risk, also psychotic

manifestations, Brief psychotic episodes are well known in severe personality disorders such as Borderline personality disorders.

In addition to the maturity and development of internal configuration, it is important also to understand the configuration itself, because different configurations lead to different styles of personality disorders. The configuration is like an “internal map” which guides one’s experience (Carl Rogers called them “Organismic Maps” (Rogers 1956)). If the map is distorted then the experience of events is consequently also distorted. Obviously such distortion increases mismatch as there is great discrepancy between the internal configuration and external real events. Such Deoptimization is accompanied by depressed mood similar to undeveloped configuration and personality disorders previously described. Distorted and biased internal configurations are formed in the same way that optimal and adaptive configurations are formed. However the distortion is caused by the experience. If experiences are radically distorted and biased from regular optimal ones, then also the internal configurations will be distorted to the same extent. In short, optimal mainstream upbringing experiences generate optimal adaptive internal constructs while biased life-experiences of unstable and distorted upbringing will generate biased distorted internal-configurations. Here it is important to assess the history of patients and reveal their life-story in terms of early to adult life-experiences. Psychologists have already described that if neglected and humiliated; such individuals grow up having low-self-esteem and sensitivity to criticism. On the contrary if brought up praised continually and protected from any frustration or criticism, then unfit exaggerated sense of self-worth emerges and incapability of dealing with criticism is evident. These patterns of distortions have been described by Kohut and others (Michael 1986) and typically received the term of “Narcissistic personality disorders.” This is one example of altered internal configuration related to altered experience-dependent plasticity. Both immaturities and biases of internal representations coexist together to generate the different personality disorders. Taken together, a brain-related description of personality disorders would be that of measuring both “Maturity” “Complexity” of basic at-rest brain networks (Egos) and their types of “Configurations”.

Generating a New Psychiatric Diagnosis

If we try to summarize the above intuitions and insights we are dealing with a brain that is an extremely complex network organization (Connectom) with small-world-network organization creating the hub-related brain hierarchy. It evolves and develops as a basic (at rest) configuration which is basically an experience-dependent-plasticity product. Fast millisecond-range plasticity creates the conscious experience which is accumulated as memories via a slower plasticity process which itself shapes and configures the basic brain connectivity organization embedding personal experience which then guides behavior as personality style. Disturbances to consciousness such as psychosis and residual schizophrenia phenomenology, is caused by disturbances to fast millisecond-range plasticity. Either disturbances to a different extent to the Connectom itself, or to hierarchy and small worldness, (probably to both) explains the high spectrum-variability of clinical manifestations of schizophrenia spectrum disorders. Mood and anxiety are caused by disturbances to optimization dynamics related to slower adaptive plasticity processes. Finally altered distorted internal-representations explain personality disorders and their relationships both with altered optimization dynamics and network stability explaining the clinical interplay among clinical manifestations such as the fact that personality disorders are typically manifest with depressed and anxious symptomatology (Peled 2012).

Following these initial insights (above) about the brain-related causes of mental disorders we can begin to sketch a brain-related diagnostic terminology for psychiatry. No more descriptive terminology such as “psychosis” and “depression” but etiopathological terminology such as “Disconnection” “Small-World Disturbances” and “De-Optimization dynamics,” respectively. Table 1 exemplifies one possibility for future brain-related psychiatric diagnosis which I call “Clinical Brain Profiling (CBP Peled 2009; 2011; Peled Geva 2014) because this term emphasizes the clinical aspects, the brain and profiles, i.e., patterns of disturbances to brain organization.

Table 1:

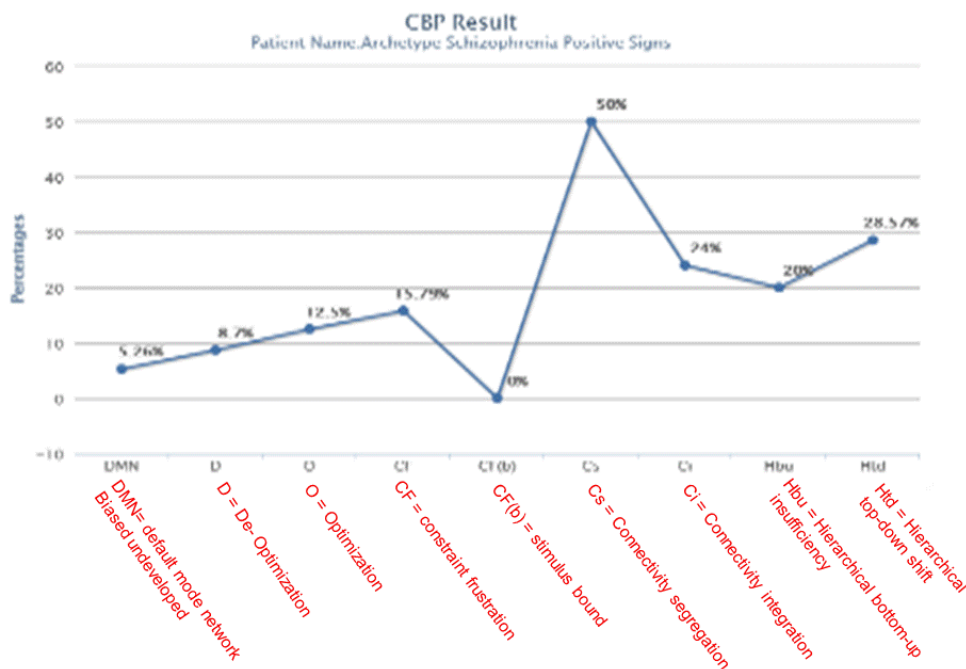
Brain disturbance	Code	Phenomenology
Undeveloped disturbed DMN organization	DMN	Personality disorders
Deoptimization dynamics	D	Symptoms and signs of depression
Hyper-optimization dynamics	O	Symptoms and signs of mania
Constrain frustration	CF	Symptoms and signs of anxiety
Stimulus bound Constrain frustration	CFb	Symptoms and signs of phobias
Disconnectivity dynamics unstable small wordiness	Cs	Psychosis and positive signs schizophrenia
Overconnectivity dynamics	Ci	Repetitive poverty ideation perseverations
Hierarchical bottom-up insufficiency	Hbu	Avolition and negative signs schizophrenia
Hierarchical top-down shift	Htd	Systemized organized delusions

To make the brain-related conceptualization of mental disorders intuitive for clinicians the CBP is implemented in a computer program available on the web at: <http://neuroanalysis.org.il/cbp/index.php>. It is a translation matrix which pulls together different “Signs” “Symptoms” and “History” of psychiatric phenomenology and cluster them based of the hypothetical causes described so far. This results in a “profile vector” indicating to what extent each of the different brain disturbance manifest in the patient according to his phenomenology. This CBP system has the attributes of modern medicine, it is “Etiological,” (initially validated (Peled Geva 2014) but still waits full validation) and it is “Personalized,” i.e., relating to the specific individual patient. CBP is made accessible to clinicians to use with patients in order to give them the sense of possible re-conceptualization regarding their patients, i.e., diagnosing them in terms of brain-disturbances not merely in terms of descriptive phenomenology. This is with the hope of making a “game-changing” step toward brain-related neurological neuroanalytical psychiatry.

Figure 1 exemplifies one way brain-related diagnosis maybe represented. It is actually a profile vector where the entries are all the possible brain-disturbances explained above and in the table (X axis). Each disturbance in this profile is predicted based on the clinical phenomenology of the

patient, thus the Y axis represents percentages of related signs and symptoms for each disturbance. In this case many signs and symptoms of psychosis caused this patient to be high on “Cs” i.e., “Connectivity Segregation” indicating that the patient suffers from disconnection dynamics, a collapse of small-world-network organization spread in the cortex. As evident, this kind of diagnosis is both personalized (specific to the patient) and etiopathological i.e., indicating a place-in-the body (brain cortex) and what has happened to it (i.e., disconnection).

Figure 1

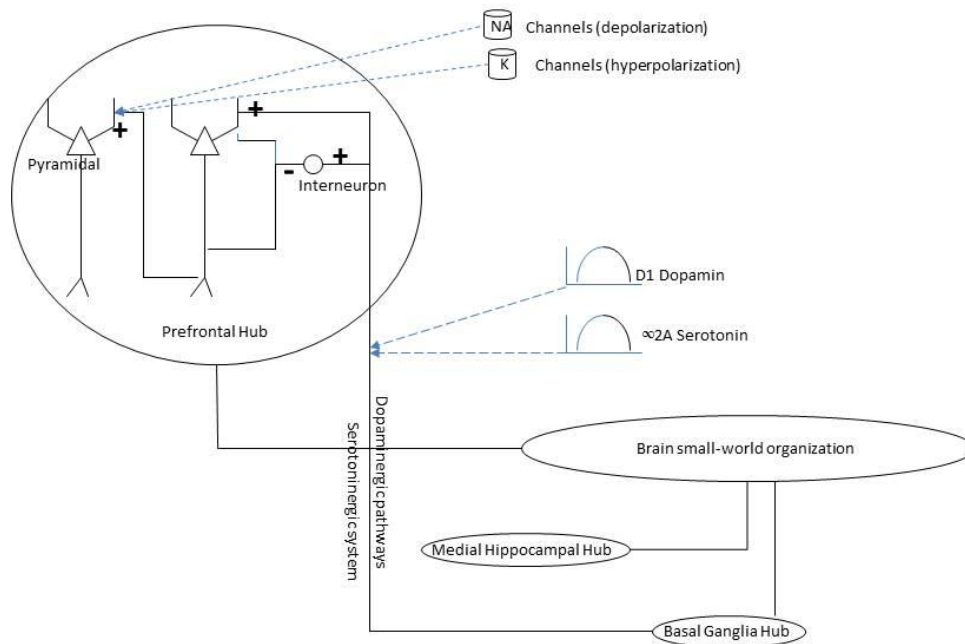


“Brain-Pacing” to Cure Schizophrenia Spectrum Disorders

In the end we aspire to cure our patients, to achieve knowledge of the etiopathology. As already mentioned, descriptive diagnostic formulations cannot be validated because they do not conceptualize causes of disease or sources of disorders that can be treated. Compared to a medical diagnosis such as “Appendicitis” which indicates a place in the body and its pathology (infection) the term “Depression” is not a place in the body nor a pathological mechanism of any sort. Not knowing what went wrong, impedes the ability to fix it. Thus having a brain-related etiological formulation for psychiatric disorders is a critical necessary step to cure.

How will the cure for mental disorders look? According to the science described so far, it will clearly have to do with regulating and normalizing fast plasticity, improving brain optimization dynamics via plasticity regulation and moderation, and correcting developing resting-states and basic network configurations, thus alleviating psychosis schizophrenia, mood and personality disorders respectively. Because fast plasticity has to do with millisecond-range electrical activity, to control and regulate fast plasticity, devices capable of activating/inhibiting electrophysiological neuronal activity are warranted. Currently In development, are a range of such technologies starting from the more traditional DBS (deep brain stimulation) of direct electrode implant, to the more technologically advanced methods of Optogenetics (Yizhar et al 2011; Peled 2011; Tompson et al 2015), light control via opsins and other membrane potential inducing receptors. There are good preliminary results with additional technologies such a Focused Ultrasound which has the advantage of being non-invasive, and has recently been found to be capable of membrane excitatory activity (Mueller et al 2014). However it is becoming clear that any brain-machine interface will have to be interactive with the neuronal tissue, thus it will have to be miniaturized to sub-neuronal dimensions, and safe. Thus, any interaction with that device will be remote and non-invasive (or at most minimally invasive). Thus the technological solution would probably involve nano-technology, the only technology relevant for sub-neuronal dimensions. In my mind future brain-pacing therapy will need to be composed of sensing-stimulating nano-particle devices and a microelectromechanical-equipped sticker on the forehead, one that “detects-corrects” small-world organization. Thus people suffering from serious psychiatric disorders could come in to the clinic for a simple intravenous injection of

quantum-dot sensing particles and finely tuned heat-sensitive nanoparticles that reach the prefrontal cortex to interact with two bilaterally positioned forehead stickers. This is because the Prefrontal lobes of the brain have been extensively related to schizophrenia spectrum disorders (Zhou et al 2015). More specifically small-world-network organization of the prefrontal cortex seems to be impaired in these disorders (Tijms et al 2015; Ottet et al 2013). Anatomically and functionally it seems that the prefrontal cortex (layer 2, 3, and 5 pyramidal neurons) is a critical Hub for global brain network organization as it manifests with extensive connections to most brain regions, especially to medial hippocampal and subcortical brain regions, or Hubs in their own right (Figure 2). The dopaminergic and serotonergic influences on prefrontal hubs seem to be regulatory (especially the dopaminergic system) having both excitatory and inhibitory (via inter-neuronal excitation) effects on the pyramidal prefrontal neuronal network. In addition both systems tend to have an inverse U shape influential activity on prefrontal cortical activity (Figure 2).



The cellular, molecular level of prefrontal “machinery” is detailed in the work of Amy Arnsten (Arnsten and Casey 2011; Arnsten and Jin 2014) and the relevant “switches” for intervention (in addition to dopaminergic and serotonergic regulation), seems to be the “Na” depolarizing ion-channel receptors and “K” hyper-depolarizing ion-channel receptors. Taken together the polarizing ion channels and the regulatory neurotransmitter dopamine/ serotonin, dual excitatory/ inhibitory activity, probably have control over small-worldness within prefrontal cortical activity, one that effects also global brain small-world organization. A clue to such brain-control capability was demonstrated by Yizhar and colleague (2011) in a Nature article that described intervention with an Optogenetics technique within excitatory inhibitory neural prefrontal microcircuitry. Their intervention had social effects correlated with brain electrically-measured brain-connectivity alteration in rats. In summary it seems that in order to cure serious mental disorders such as psychosis and schizophrenia the prefrontal cortex should be targeted and its small-world organization should be optimized. This should be achieved via interventions directed to polarizing ion channels (Na and K) as well as to excitatory / inhibitory dopaminergic serotonergic activities. As mentioned above, to correct dynamic ongoing disturbances to the small-word-network of the prefrontal cortex a sensing-stimulating apparatus should be mounted in-place. Voltage-imaging signaling quantum dots nano-particles positioned in the prefrontal neuronal-network tissue will serve as sensor detectors of small-world dynamics, thus spotting any altered changes in small-worldness of prefrontal neuronal systems. In response to spotting any altered changes in small-worldness of prefrontal neuronal cortex, a “corrective” trigger will be activated. The trigger will result from thin lightweight prefrontal bilateral stickers on the forehead equipped with the relevant microelectromechanical systems for triggering and then delivering a “corrective” response. The corrective therapeutic response is in the form of radio-magnetic fields that non-invasively and remotely cause neural-excitation through the activation of the heat-sensitive capsaicin receptors (Chen et al 2015). The process is continuously iterative thus any correction achieved by the small-word organization is still monitored for additional correction if needed, thus a feedback homeostatic regulatory process is installed.

Certainly, any attempt to alter brain organization will require a plastic brain ready for changes. Increased plasticity will make the brain prone to alterations, thus inducing plasticity for relevant periods of intervention seem warranted. It is thus conceivable that the plasticity inducing

medications can be administered for planned “brain pacemaker” periods. The medications “prepare” the brain for change. The pacemaker optimizes and corrects malfunctioning brain organizations. Once correction and cure is achieved, there is no need for further changes and plasticity inducing medications can be discontinued. As already mentioned, thus far we can envision that like in cardiac insufficiency induced by cardiac arrhythmia; cardiac pacemaker corrects arrhythmias eliminating disease of cardiac insufficiency, brain insufficiencies (schizophrenias) will be cured by eliminating fast-plasticity arrhythmias “brain arrhythmias” restoring brain optimal organization thus eliminating schizophrenias. This can be done in a plasticity controlling feedback-loop brain pacemaker.

Plasticity induction Curing Mood Disorders

What about the cure for mood, anxiety and personality disorders? We have described (above) that plasticity is prevalently relevant for mood. We have also described, how experience-dependent plasticity is relevant to personality disorders. Thus induction of plasticity, is obviously the mainstay of treating mood and anxiety disorders. Future medications will induce plasticity by directly intervening in the nucleus and DNA unlike current plasticity inducing medications (SSRIs) that act on synaptic levels requiring long periods (6 weeks) to activate cascades of intra-neuronal signaling molecules which finally reach the brain to generate increased plasticity. Direct DNA targeting can both reduce plasticity induction times and also probably enable control over the extent and degree of the plasticity process. Brain electrical stimulation can further add more fine-tuning control over plasticity processes for example transcranial Random Noise Stimulation (tRNS Antal et al 2014) can be directed to relevant scalp locations increasing plasticity in a targeted manner directed to frontal parietal and other cortical regions. Fast plasticity influences slow plasticity (see riverbed metaphor above) thus radio-frequency magnetic-field heating of nanoparticles to remotely activate temperature-sensitive cation channels in cells can be used in massive global-spreading of random-noise activation patterns, inducing unspecific global plasticity dynamics. In effect future treatments of mood will require a much better control on the types, durations and locations of brain plasticity. For typical

depression (what was in the past called major endogenic depression) a global all-brain encompassing plasticity induction would probably represent the best treatment. This is based on the above stated assumption that whole-brain global optimization dynamics result in the emergent property of mood elevation. Thus the whole brain becoming more plastic will adapt better to environmental changes triggering global optimization dynamics.

Shaping Internal-Configurations to Cure Personality Disorders

As for treating personality disorders, plasticity also plays a fundamental role but is only part of the story. As a more in-depth fine-tuning internal-model-related plasticity changes are warranted. Here we can compare the therapeutic intervention needed for the process of upbringing and education of children. We know that the developmental process in children is possible due to their incredible learning and adaptive capabilities; we also know that these relate to the extraordinary plasticity characterizing young children's brains. It is also known that psychological interventions at early age are more effective than when people become older and windows of learning capabilities close. This is due to phases of plasticity which as development proceeds are known to become consolidated and reduced. If we can control such process, reversing the brain plasticity to that of early childhood we can offer the brain a powerful additional chance to change, by reversing brain plasticity to childhood periods we actually offer the brain a second chance to better develop immature internal configurations that did not have time to fully mature and we can also offer the brain another chance at correcting biased non-adaptive non matching internal configurations. To correct internal configurations and cure personality disorders it will not be enough to reverse the brain to childhood plasticity dynamics, we will also need to intervene on this plastic brain to "steer" it toward the corrective configurational patterns. Thus according to this rationale there should be three stages to the intervention for curing personality disorders. The first step is induction of brain plasticity reversing it to early childhood plasticity dynamics, thus actually going back in "brain-time" to achieve a re-experiencing re-shapeable brain. The second phase is actually reshaping the brain to achieve adaptive optimal internal configurations, and the third and last phase is inducing the

correct amount of brain plasticity dynamic to maintain the adaptive dynamics for that new optimal internal configuration that has eliminated the phenomenology of personality disorders.

How do we shape the internal configurations once childhood brain-plasticity is achieved? In principle this is done as proper psychodynamic psychotherapy is done today, using experience-dependent plasticity. Proper successful psychotherapy is actually an experience-dependent process. The treatment sessions are periods of the ongoing patient life experience having the same capacity to mold and shape the internal representations. Typically the internal representations govern (the riverbed described above) the experience and patients tend to repeat non adaptive behaviors. In therapy compared to routine life, the difference is that a skilled psychotherapist is aware of these repetitions and acts to generate a different experience, a “corrective experience” one that is aimed at more adaptive thinking. If this corrective experience is repeated many times (as is typical to psychotherapy technique) gradually changes to the internal representations is achieved by the Hebbian-dependent reshaping of internal representations. In short the change is achieved by corrective experience-dependent plasticity process. Now imagine that the same, or a similar therapeutic process such as dynamic psychotherapy is applied to a patients whose brain plasticity has been reversed to early childhood plasticity dynamics, what corrective effects can be achieved? It can be predicted that the therapeutic process will have the efficacy of the same magnitude as regular educating and upbringing of children. This will make psychotherapeutic interventions enhanced, becoming many times more effective. Interventions of corrective experience-dependent therapies will be at multiple magnitudes more effective. The combined interventions of plasticity induction and corrective experience inductions will have powerful brain-changing potential and with that game-changing prospective for treating personality disorders.

The experience-dependent plasticity altering agents in typical psychotherapy are the therapists, and the change of experience is limited to “hourly bits” sessions, with the therapist as a single experience-inducing figure. Future experience-dependent therapy for personality disorders must not stay limited as such. Multimedia technology of virtual-reality and augmented-reality offer powerful unprecedented control over experience (Sorkin et al 2006). Controlled environments can be delivered easily for long periods. These virtually controlled environments can generate

accurately preplanned therapeutic interactive experiences such that can mold and reshape internal representations quickly and accurately having a much stronger effect on changing brains and their “maps” of internal representations. In short, modern multimedia of virtual environments can act very powerfully on the internal object representations altering and effectively correcting relevant aspects of the internal configurations embedded in the default mode network of our brains. Imagine the combination of reversing patient’s brain-plasticity to childhood changeable brains and concomitantly subjecting the patients to intensive corrective psychosocial (and other) experiences using immersive controlled virtual-environments. This will probably be powerful enough for effective therapeutic changes that will cure even the more difficult personality disorders. Technology of Virtual Reality creates “Presence” a term used to indicate to what extent the patient feels as if he is experiencing a real environment. The Presence with modern and future multimedia technology will reach levels making it hard to distinguish real from virtual. Humanoids (also called Avatars) are virtual-reality human characters which interact with the patients in the virtual world as if it was a real world. This offers a great opportunity to create controlled interpersonal situations which elicit interpersonal relationship typical to the patient (Borst and Gelder 2015). For example, let’s assume that the patient suffers from sensitivity to criticism, or becomes offended and depressed if criticized or avoided. Thus it is possible to control the virtual reality psychosocial event such that an Avatar would present a critical attitude toward the patient or ignore him to elicit the psychological distress typical to the personality disorder of the patient. It is conceivable that with such technology diagnosis of the patient’s sensitivities within complex psychosocial situations can be assessed and monitored. The interactions with the virtual reality is obtained via behavioral interactions with that environment via the computer thus every movement or action of the patient is inevitably registered and monitored. Such patient-computer interface can generate the patterns of response style and behavior of the patient in the virtual world characterizing his personality styles within virtual psychosocial events. For example, if personality traits are that of shyness and avoidance within an interpersonal relationship then such a subject is predicted to avoid (get out of the virtual-room) where there is a party of many avatars dancing and being intrusive toward the patient. Thus the patient will tend to leave the virtual room of the party and move elsewhere in the virtual environment perhaps to a specially-designed quiet room without any avatars. Such a reaction of avoiding the avatar party is monitored and in relationship to the known context of the situation can

be very informative about the reaction style of the patient. “Presence” in virtual psychosocial environments was found to be very powerful (Chicchi Giglioli et al 2015). Avatar therapists have been shown to be effective in psychotherapy. With virtual interactions (Bohannon 2015) there is reason to expect that virtual environments of psychosocial events can become both diagnostic as well as powerful experience-dependent correction-inducers. A typical protocol treatment of personality disorders would probably begin with experiencing multiple psychosocial virtual occurrences that map-out the personality styles sensitivities and reactions. After a diagnostic mapping of the personality styles are concluded the treatment protocol would require a few days of plasticity induction with specially designed medications and also with some kind of stimulating plasticity devices such as scalp spread transcranial random noise stimulation tRNS. Those plasticity inducing interventions will regress the brain plasticity to an early childhood plastic brain ready for reshaping and changing. Thereafter virtual-reality sessions intended to create “corrective-experiences,” thus inducing like-wise corrective experience-dependent plasticity will reconfigure the internal representations to become more adaptive and optimal. Time tapering down the general plasticity induction together with concomitant tapering down of corrective-plasticity induction will stabilize the patient’s brain dynamics to continue operating optimally in the future. With this the internal configurations will reach better optimization levels over time thus curing personality disorders.

Concluding Summery

To conclude this chapter, in summary I have roughly sketched my intuitive hypothetical approach to reformulate mental disorders as brain disorders and I have given some putative suggestions for possible future therapies for the various mental disorders.

In the next chapter I will try a narrative case-report mode to exemplify how the future of our field may look.

Chapter II

CASE REPORTS 2050

The Setting

The year is 2050, the “NeuroAnalysis” unit is the medical neurological unit for diagnosis and treatment of the highest brain disorders and functions, that were once called “mental disorders” and were treated under the historical (by now extinct) field of “Psychiatry.” Two clinical cases are described (Steven and Patricia). These clinical cases are spanning phenomenology of psychosis, mood and personality disorders thus exemplifying most of psychiatry’s phenomenology.

Steven

After being cured from severe disconnection brain disturbances (once called schizophrenia psychosis) Steven’s case is presented by Doctor Jones to medical students. Steven was brought to the emergency room by his parents after he smashed the TV screen at home. When Steven arrived, said Doctor Jones, he was disorganized, restless you could barely understand what he was talking about because he had loosening of associations and disordered speech. You could only understand the general complaint of hearing voices coming from the TV telling him that he is about to get killed by spy agents that are following him. This disorganized and fragmented experience with delusions and hallucinations raised the assumption (see scientific section above) that he suffered from disturbances to the connectivity formation of his brain Connectom. It was assumed that Stevens’s small-world organization collapsed with reduction of cluster connectivity causing his global brain organization to become unstable subject to fragmentation with the risk of losing Hub organization requiring immediate intervention.

We used Clinical-Brain-Profiling (see CBP scientific section above) to predict his brain-disturbance diagnosis, and immediately sent him to the scanner with an exact prediction about disconnectivity and disturbances to the hierarchy and error predictions of Bayesian dynamics (see scientific section above). Using voltage-imaging sensing nano-technology we can image large-scale neural networks with millisecond-scale temporal resolution and have found disturbed

small-world prefrontal neuronal network organizations in Steven's brain. We monitored him for a few hours using a Head-Mounted-Device designed to sample synchronously both his phenomenology and brain imaging for voltage-sensitive electrical activity.

Conformation of prefrontal cortical disturbances to the small-world network, extended to whole-brain destabilization indicated the immediate use of "Nano-Brain Pacing." Two thin lightweight prefrontal bilateral stickers were placed on Stevens's forehead equipped with the relevant microelectromechanical systems for sensing; triggering and delivering a "corrective small-world" response (see science section above). He then received a regular intravenous injection containing fluid with quantum dots nano-particles and particles for the heat-sensitive capsaicin receptors. The sensing used quantum dots nano-particles for voltage imaging and for the stimulation particles for heat-sensitive capsaicin receptors were used. Once in place this nano-brain pacing device process is continuously iterative thus any correction achieved to the small-world organization is still monitored for additional correction if needed, thus a feedback homeostatic regulatory process is installed, explained Doctor Jones. Six weeks with the device were enough to reorganize and re-optimize small-worldness in Stevens's brain. With that his symptoms and signs would be eliminated achieving full cure. To avoid possible repeated destabilization of Stevens's brain he will need to undergo a one year follow-up using CBP validated assessments, concluded doctor Jones.

Patricia

On returning to the department after he completed teaching his students, doctor Jones went to see his patient Patricia. Patricia was admitted after a failed suicide attempt, "I am depressed Doctor I feel hopeless nothing matters, what do I have to live for, they sent me here because I took all the pills my stepmother uses for her different illnesses." Quick interview and a glance at her intake file revealed unstable upbringing beginning with adoption after her mother's death in a car accident. This happened when she was a baby just a few month old, thereafter she spent one year in an orphanage, and only then was she adopted by her current stepmother, Her mother, a career hardworking executive, did not really have time to attend to Patricia. As far as physical living

conditions Patricia was well-taken care-off, but as for affection and love, these were totally lacking. Patricia could not report even one instance where she was picked up and hugged in her stepmother hands, she was subject to continual criticism as her stepmother's expectations from here were exceedingly high. Thus she grew up with lack of support, compliments and encouragement, She was "never good-enough" and grew-up feeling worthless insecure and and with very little self-confidence.

Having experience in treating personality disorders for many years, Doctor Jones started immediate synaptogenetic medication, as the protocol for this case is well-known to him,. First a plasticity boost to the brain will prepare Patricia's brain for reconfigurations of internal representations. For that to happen, her brain-plasticity must increase to achieve capabilities similar to those of a 3-year-old child. While this is taking place she will be admitted for an intensive 7-day long virtual-reality-experience, typically presenting a series of gradually more complex psychosocial situations. Her reactions within these situations will be recorded and monitored via her interactivity with a multimedia virtual-reality computer device. The patterns of her activity are scanned online to detect specific "sensitivities". It is expected that she will back-out of certain virtual psychosocial situations, specifically those where higher self-esteem is required for operation. According to her internal configurations of the resting-state "Ego" brain network (see science section above) it is predicted that she would choose easy-way-out situations and avoid social interactions which can present criticism. As Patricia is experiencing the virtual-psychosocial interactions her brain is monitored for alterations in the resting-state brain network organization where patterns of connectedness related to the diagnosed sensitivities are detected. After approximately one week of virtual-environmental-assisted diagnosis of altered resting-state configurations (personality disorders as it was historically called), the corrective experience kicks in repeatedly and gradually. It will take another month of repeated intensive corrective experiences coupled with high brain plasticity maintenance to completely reshape and correct biased internal resting-state-network-configurations. Typically this 5 to 6 week therapy shows good results and after cessation of virtual experiences and tapering-down of plasticity induction, most patients do not need additional therapeutic session, it is custom to wait 6 months to provides the time-space for the results of therapy, these typically become apparent as the brain completes last adaptations using the remaining plasticity dynamics being tapered-down. Doctor

Jones envisions that Patricia will do as well as others did, and will be completely cured from her personality disorder in a single therapeutic session. Of course, this therapy algorithm can be repeated if results are incomplete.

Chapter III

PERSONAL

My Personal Intro

As early as 1990 I began using neural-network theory and models to conceptualize mental disorders as disorders of brain organization. Although historically eminent figures such as Meynert, Ramone Cajal, Wernicke and others have addressed this level of brain organization in the beginning of the 19th century, when I started residency it was common to emphasize the molecular, gene, level of brain-research and attempt direct causal linkage of molecular events with phenomenology of mental disorders. To me “skipping” the neuronal-network level of the brain, when going from molecular to phenomenological conceptualization was disturbing, especially when it seems logical that the best understanding of the psychiatric brain seems to be exactly at the network level as it is in-between molecular and whole-brain levels. The neuronal network level in an ideal “position” bridging the molecular level, (going down the brain physical hierarchy), and the whole brain organization level, (going up the brain hierarchy).

The science of neural-network was developing fast in those days and it seemed promising to use these models especially as they seemed intuitively related to phenomenology of mental disorders. Disconnected unstable network behavior was very much, (even though metaphorically), similar to a psychotic disorganized patient. Interestingly since my initial convictions about conceptualizing mental-disorders as brain-network disturbances, the field evolved in favor of my beliefs,.Investigators began giving fancy names to neural-network formulations, “Connectom” first appeared in the literature (Worbe 2015) and immediately thereafter terms such as “Connectopathies” and “Pathoconnectomics” appeared to describe the neuronal network based pathology. If there is such a thing as “temporal-validation” then my predictions about the brain-related diagnosis in psychiatry are approaching validation. If my predictions from 20-years ago have been faulty, then the field (literature) would not have gone in the directions of my predictions with the predominance of “Connectopathies” and “Pathoconnectomics” as explanations for psychiatric disorders.

Fortunately I can look back and see the field going in the direction of my preliminary predictions from the early 90’s, and happily the developments in the field make it more likely to achieve full

brain-related psychiatry soon. This gives me the confidence to continue my arguments that I first proposed twenty years ago.

Early days

For me it all started with fascination about the higher-mental functions of humans and how they are generated by the brain, a fascinating organ, and the highest level of achievement of evolution. I wanted to have a career that directly relates to these topics and ended up going to medicine in order to become a psychiatrist. I was eager to begin residency and start my psychiatric training. In September 1990 that I began my residency and by then I had already some general intuitions about how I think basic premises should be laid down in proper psychiatry. I thought to myself, the brain is a physical system, thus psychiatrists should know physics. The psychological “psyche” conceptualizations are non-scientific and useless because they are explainable, empirically as physical brain-related phenomena. This led me to become interested in the workings of the brain as a physical system. At that time psychiatry research was all about biochemistry and genetics. Psychiatrists tried to follow the successes of other parts of medicine by trying to find a gene, a neurotransmitter activity which they thought would directly relate to a disease-entity or syndrome in a linear manner, e.g., more antibiotics less infection, inverse linear relationship. Linearity they thought, will probably lead to causal connections to understand the etiology of the disorders. For me these studies seemed heading nowhere. I grasped the enormous effort invested in searching for disease-linear-causality, molecular gene biomarkers and realized that it did not advance the field, and did not affect our understanding at all. It was more and more clear to me that the brain must be studied as a “System,” physical operational mechanistic system, and I became fascinated with the mathematics of neuronal-network-systems. In those years the models of neural-networks were just evolving with simple architectures and simplified operations of simulating limited principles of neuronal interactions. Still it was fascinating. If we can build a model of a rudimentary simplified brain-like system and simulate with it some aspects of a cognitive-process like thought-associations, then we can carefully “damage” different aspects of its function and run it to see what disturbances will occur to the simulated cognitive psychological reproduction. Here we could for the first time relate specific neuronal-

network disturbances to associated cognitive computational disturbances with the hope that these simulations will provide us with predictions about the real-brain disturbances.

It was exciting; here is the “holy-grail” for finding the causes of mental disorders and curing them. From the time I realized that in 1990, my first year of residency, I was no longer a regular psychiatrist. I progressed in my residency requirements and learned all the necessary biochemical and genetic theories, but was convinced that I should know even-more about neuronal-networks and computational neuroscience. Very uncommon to psychiatrists, I went to the computer and electrical engineering faculty of the Israel Institute of Technology the Technion, and educated myself in the field of neuronal-network models. I have even dedicated my basic-science period and all my spare time to acquire the skills of programing a simple neuronal-network model using MatLab (version 2 on DOS in those days). Together with Amir Geva (Geva and Peled 2000; Peled and Geva 2000) who was kind enough to teach m. We programed a neuronal network model that could simulate some aspects of thought processes and working memory, and by “damaging” i.e., altering certain parameters of the network, comparable to possible real neuronal damage, we demonstrated that (at least metaphorically) certain mental disturbances such as thought disorders can be simulated by perturbing the network connectivity and neuronal transfer functions (Geva and Peled 2000). The idea that connectivity disturbances at the network level can generate disturbances at cognitive psychological levels was fascinating, and made a strong argument in favor of studying the neuronal network level of the brain in psychiatry. Enthusiastic about this prospect we later simulated a neuronal-network that identifies Rorschach inkblot number 3 according to popular (normal) responses. Also here with perturbations and alterations to connectivity and neuronal threshold-functions we could generate schizophrenic-like responses for the inkblot perception, once again showing possible relationships between network disturbances and mental disorders (Peled and Geva 2000). Even-more, the general fact that a physical change in a simple but still complex physical system, can metaphorically cause a change in a “psychological manifestation,” that of inkblot perception, was enthralling. It showed the possible link between physical phenomena and psychological phenomena, here we are at the verge of solving the psycho-physical problem. A problem no psychiatrist can ignore, because to cure patients we will have to intervene physically in the brain to cure psychological phenomenology, emergent-property disorders.

As exciting as this was, as I reached the end of my residency, the enormous challenge of such a task was becoming evident. What was I thinking to myself, that here I was on the verge of identifying the causes of mental disorders. As I was investing more and more in the investigation of models, their development and their relationships to the brain, many discouraging facts became evident and the overwhelming task of understanding mental disorders became apparent.

One thing that was immediately evident was that models are good as models and may serve to generate testable predictions; however these have to be tested in the real-brains. Lucky to have the opportunity, after my residency I was invited for a post-doc at UCDCM, (University of California Davis Medical Center, from 1995 to 1998). There I thought was my opportunity to try and move from models to real brains. Why not test the model directly on patients? I thought to myself. At UCDCM I transformed a clinical EEG lab into a research lab and started sampling EEG from patients and normal controls during a Working Memory task. Together with Amir Geva we constructed correlation-matrices assumed to be approximations of the network connectivity organization of the sampled EEG from brains of the subjects. We used a cognitive test similar to that of our simulation model. We demonstrated that correlations of electrical signal among EEG sensors (or brain regions) was altered in schizophrenia something that the models predicted.

Working on Theory

By the time I returned from the post-doc and took position as chair of department at a Technion affiliated hospital in 1999 the field of neuronal networks was developing fast. An explosion of research and knowledge accompanied the field with its relevance to artificial intelligence, cyberspace internet-algorithms and machine-learning. This massive development in the field was quick to impact neuroscience as the study of the brain used these models in research and development. Even though fundamental for neuroscience, the ideas of neural-network brain-organizations for psychiatry were not yet common. Neural-network theory had not yet reached psychiatry. During the first decade of the 21st century I was busy studying the literature as it came out, and related it to my knowledge and experience in clinical psychiatry. It was a long

period of theoretical investigation using theoretical mental-experiments that generated a preliminary theory for brain-related psychiatry, reformulating mental-disorders as brain-network disorders. Systematically I have researched the existing knowledge of complex-systems physics to use it to explain complete variety of mental disorders. I was busy with the task of generating a new and brain-related psychiatric conceptualization to use as diagnosis. This work has yielded three books “Brain dynamics and mental disorders,” “Optimizers 2050” and “NeuroAnalysis” (Peled 2004; Peled and brand 2005 and Peled 2008 respectively). Later on my theory would be titled “Clinical Brain Profiling” i.e., CBP (Peled 2009; Peled 2013; Peled and Geva 2014) as it seems to me appropriate to use the term “clinical” “Brain” and “Profiling” to describe the diagnostic profiling of the disturbed-brain causing clinical-manifestations. This work revealed even more the difficulty of the task, as reliability and validity of CBP was now warranted. It is apparent that validation of CBP is going to be a tremendous challenge, one that will require the help of large scientific bodies such as signal-processing, large-data mining, and machine-learning. It may even be that this challenge will not be surpassed with current existing knowledge and technology, and will need to wait for further future scientific developments.

If during the 90’s there was not much of neuronal network science entering mainstream psychiatry, a decade later until 2010 while I was in my theoretical development phase, a steady increment of neural computation models and theories began to emerge in psychiatric literature. Twenty years after I contemplated neural network science for psychiatry it finally reached psychiatry with various authors inventing new terminologies for it. As already mentioned, the term “Connectom” was vastly used and adapted to pathology with terms such as “Connectopathies” and “Pathoconnectomics” all destined to describe mental disorders as disturbances to the neuronal-network (Connectom) organization of the brain. Even though psychiatry has begun positioning itself correctly toward attaining the last leap of concept and becoming truly brain-related, and even though institutes and organizations under the title of “computational psychiatry” are sprouting everywhere in different countries, still many psychiatrists are unaware and uneducated in the disciplines of complex brain systems and their relationship to the clinical manifestations of everyday work at the ward, or clinic. To make clinicians more aware of neuronal computation neural-network relevance to psychiatry I have created a web-based CBP computer program that translates the theoretical formulation of mental

disorders as brain disorders, (see above science section). All psychiatrists need to do is enter the “signs” “symptoms” and “history” of a specific patient and press a “Brain Profiling” button to receive a personalized brain related formulation of that specific patient's brain disturbance (at: <http://neuroanalysis.org.il/cbp/index.php>). Hopefully, the availability of such a web-based program can trigger interest in clinicians to understand their patients based on their brain disturbances. Hopefully psychiatrists and neuroscientists can use this program as a starting-point to develop successful research in finding the underlying causes of mental disorders and hopefully the task of validating CBP can be achieved from this starting point. With the help of Amir's fuzzy hierarchical clustering algorithms, I have showed that CBP can be reliable, (Peled Geva 2014) both as interrater-reliability as well as “curving nature at its joints” in the sense that data-driven algorithm alone shows that CBP reflects patients phenomenology patterns in the clinic.

The Challenge Ahead

We stand now in front of the most amazing and colossally challenging task that of validating a CBP-like hypothesis and discovering the causes of mental disorders. Our hopes and limitations lay in the technology, signal processing capabilities and the “noisy brain.” It seems that large-data analysis will be required to cope with “noisy brains” and weak signal processing. Sensors technology is promising for collecting large-data, large data collection of phenomenology coupled and synchronized with large data of brain activity may begin to reveal the relationships between the brain and its functions, thus the disturbed-brain and its phenomenological-malfunctions. These discoveries will probably need deep-machine learning investigation but will also need a theory-driven understanding of the predictions described in this monograph.

If we surmount this task of validation we are a small step away from reformulating mental disorders as brain disorders making it unnecessary for psychiatry to differ from neurology. This will be the end of psychiatry. Brain interventions will cure mental disorders and the cost of losing psychiatry will be counterbalanced by the gain of curing patients. I wish I may live to become the last psychiatrist and the first NeuroAnalyst by validating a CBP-like psychiatric diagnosis, thus providing the ground for effective therapeutic interventions with the brain-curing neuronal-control technology that is currently rapidly developing.

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