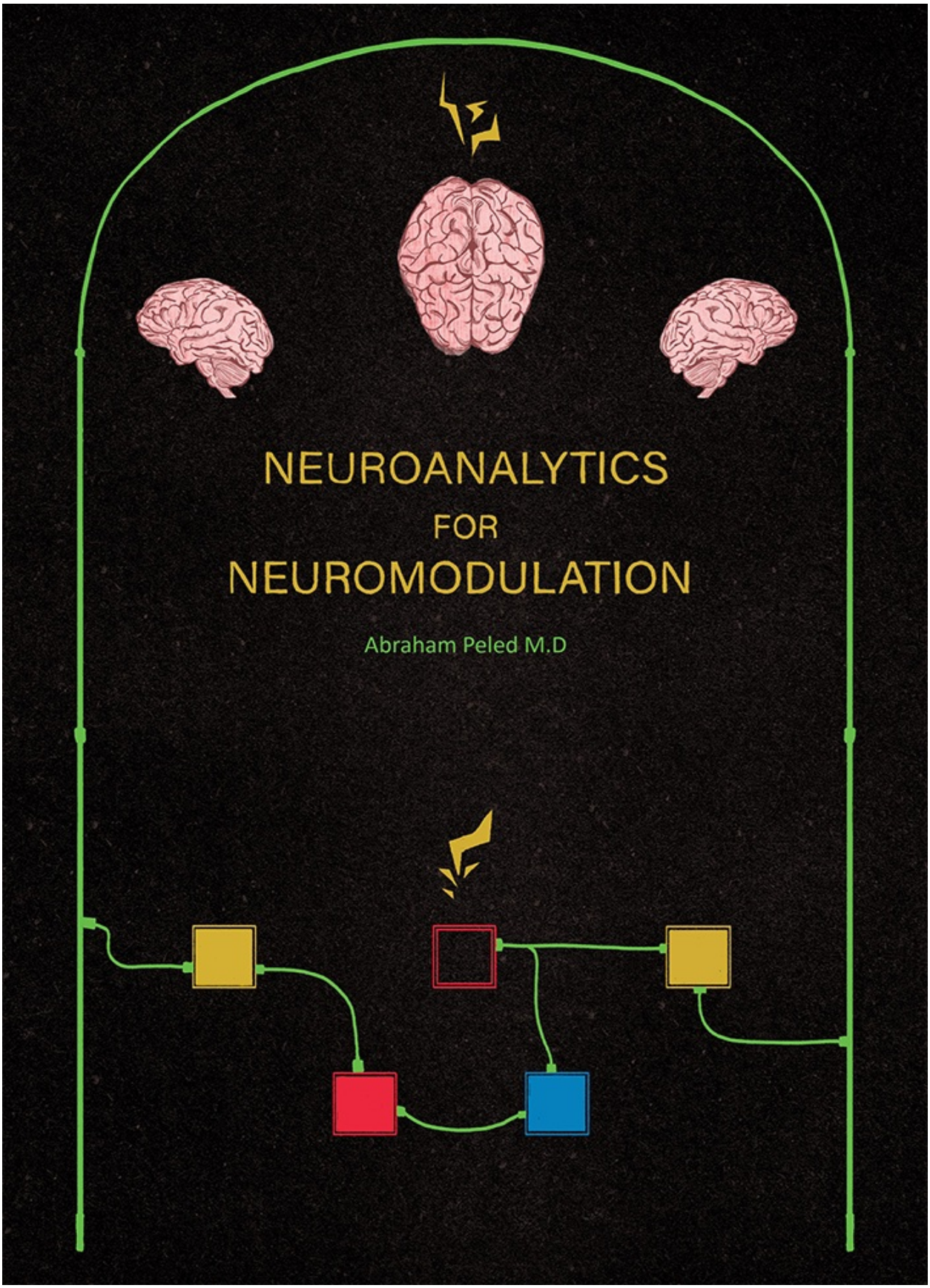
NEUROANALYTICS
FOR
NEUROMODULATION
Abraham Peled M.D

NEUROANALYTICS FOR NEUROMODULATION

Author

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Brief introduction:

Neuromodulation is the next big challenge for Psychiatry. Technology of Neuromodulation is advancing fast and is being tested on patients. However, the challenge of where and when to stimulate reminds us that we have not fully defined the underlying causes of mental disorders. Moreover, the etiology of mental disorders is essentially still lacking. This book was written bearing in mind that before advances in Neuromodulation can be achieved, a reasonable theory for guiding modulation needs to be formulated. Such a theory should be based on the available knowledge accumulated in the field of computational neuroscience.

About the author:

Abraham Peled graduated MD from La Sapienza University of Rome, Italy, proceeded to complete his residency in psychiatry in the Department of Psychiatry at Rambam Medical Center in Haifa, Israel. He completed a Post-Doc in Neuroscience at UCD Medical Center California USA. For over 20 years Peled has been Chairing a Department of Psychiatry at a university-affiliated Mental Health Center in Israel, and has an academic appointment at the Rappaport Faculty of Medicine, Technion, Israel Institute of Technology.

Founder of “NeuroAnalysis,” and cofounder of ‘Brain Profiler’, Peled has authored several books and numerous publications that apply the physics of complex-systems to psychiatric diagnosis.

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INTRODUCTION

Neuromodulation is the term used for regulation of the brain, usually for therapeutic purposes. Technology has recently offered various approaches for neuromodulation, ranging from non-invasive transcranial direct current stimulation and transcranial alternating current stimulation to invasive deep brain stimulation. Recent studies have shown that these neuromodulation technologies have promising therapeutic effects for psychiatric disorders such as depression (Sonmez et al., 2019), aggression (Bell and DeWall, 2018), and for negative signs of schizophrenia (da Costa Lane Valiengo et al., 2020). However, since this is a novel emerging field, treatment is somewhat ineffective and therapeutically inadequate.

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, appear to be safe. No serious adverse events have been reported to date in over 18,000 sessions administered to healthy subjects, neurological and psychiatric patients (Antal et al., 2017). Specifically, tACS seems likely to open a new era in the field of noninvasive electrical stimulation of the human brain by directly interfering with cortical rhythm (Antal and Paulas, 2013). tACS is hypothesized to influence 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 and Schutter, 2017). Phase synchrony of tACS is thought to entrain and enhance neural network oscillations, however, antiphase stimulation desynchronized theta phase coupling and impaired adaptive behavior in one study (Reinhart, 2017). Thus, tACS when desynchronized, can also attenuate neuronal oscillations and event-related oscillatory activity can be inhibited using a rhythm slightly below the stimulation frequency.

Most literature in the field indicates that effectiveness and usefulness of neuromodulation depends on knowing the causes of the disorders being treated. These publications note that we do not know enough about the electrical signature of the disease, or about the psychological markers of the disease, or neurological brain signature, and other terminologies which are used aptly to indicate that we do not know the etiology of the disease. In sum, it is clear that etiology of mental disorders is lacking. One can argue that the entire field is 'positioning the cart before the horses,' as one cannot design effective interventions for mental disorders without knowing the exact etiology, the exact algorithm of disturbance that requires

corrective action.

In this handbook I will concentrate on formulating relevant etiology to support neuromodulation. I will NOT provide a comprehensive overview of the technology, or the research findings of neuromodulation. Rather, I will present the minimum insights required to focus on the real need, that of revealing the etiology of mental disturbances for neuromodulation purposes. These insights are titled 'Neuroanalytics' hence the title Neuroanalytics for Neuromodulation

The chapters in this handbook will be organized as follows: Psychiatric phenomenology will be mentioned and the relevant neuroanalytic theoretical construct related to it will be discussed. The neuroanalytic insights will then inform about the general neuromodulatory action required for the specific phenomenological psychiatric manifestation.

In-depth comprehensive discussion of neuromodulation technology and neuroanalitic theory is not within the scope of this manual. However, a "theory in a nutshell" is provided.

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 synergistically; the "whole is greater 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 have 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 organization with hubs set as Central Executive Networks for fast millisecond range plasticity, Default-Mode Network for lifelong stable plasticity and Salient Network for in-between months, weeks, plasticity adaptations. 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 network 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. "Fast

Plasticity" is in the millisecond range integrating brain organizations, that of Central Executive Network, 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 fast plasticity involves disconnection or over-connection and hierarchical bottom-up or top-down connectivity alterations.

"Reactive Plasticity" is somewhat on a longer timescale. Fast Plasticity, that of minutes to hours, stabilizes the fast 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 and spans time-scales of weeks. It reflects Hebbian Dynamics (Hélie et al., 2011) 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 Fast 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 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. The Salient Network subcortical hubs are probably most operational for such intermediate-range (weeks. months) plasticity regulation activity

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 Fast 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. Disturbances to slower Adaptive Plasticity that optimizes internal representations and reduces predictive error will result in mood disorders. The de-optimized brain with 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 resting 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	Network involved	Brain system disturbance	Psychiatric phenomenology
Fast Plasticity	Central Executive Network	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	Salient Network	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	Salient Network	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	Default mode network	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

PSYCHOSIS SCHIZOPHRENIA AND NEUROMODULATION

Psychosis and schizophrenia phenomenology can be divided into 'Psychosis,' where there is a disintegration of mental functions; disintegration of consciousness. Delusions and hallucinations overtake the phenomenological manifestation. Delusions would be 'false unshakable beliefs,' while hallucinations would be 'perception without stimulus.' This phenomenology is related to disorganization fragmentation of consciousness, and instability of mental functions which bypass the patient's reality testing and experience, causing what we call 'psychosis.'

In 'Schizophrenia,' psychosis passes over time, and is often followed by manifestations of negative symptoms, where there is a reduction of mental functions and especially elimination of higher mental functions, such as 'volition,' 'motivation,' 'mood' and so on. The patient typically experiences periods of psychosis, alternating with increased deficiency, and lack of motivation and function. The disease is a progressive ongoing disorder, irreversible, and to date, typically has very low response to medications.

The relevant information currently known about the brain-related mechanisms of schizophrenia
is limited. The etiology of this disorder remains unclear, though many studies point towards the pre-frontal cortex (Howes and Kapur, 2009), and networks relevant for brain connectivity with frontal limbic, and other high-level connectivity structures in the brain (Dietsche et al., 2017). The dopaminergic system in the pre-

frontal cortex has been implied in the theories about the etiology of schizophrenia and psychosis (McCutcheon et al., 2019), and the dopaminergic pathways are probably relevant to this disorder. Studies about the negative symptoms of schizophrenia, typically also relate to the pre-frontal cortex, where hypofrontality has frequently been reported (Williamson 1987).

When considering neuromodulation, the pre-frontal regions and their functions should be considered. Studies have shown that in psychosis, there is a fragmentation of brain organization, where there is a disconnection dynamic, in the sense that different brain regions act statistically independent from each other (Friston and Frith, 1995). According to the more recent literature, this kind of fragmentation, is actually a disturbance of what is called the small-world network (Li et al 2012).

Small-world network organization, is an optimal organization of the brain, where there is a balance between near-by connections and far-away connections – also called clustering coefficient for the clusters of nearby connections, and long pathway for the long, far-away connections (Lin et al 2018).

This kind of balance between these types of connectivity is optimal, and is called small-world because it follows the rule of 6 points of separation, which show that these systems have a good communication capability. This is probably why the brain naturally follows this kind of organization.

Thus, the optimal brain function would be a good algorithm of small world organization, while disturbances to this organization, can cause disturbances to whole brain organization. On the one hand the brain system either becomes disconnected, unstable and fluctuating, just like the instability characterizing psychosis, or on the other hand, an opposing disturbance to the same small-world network organization can cause fixation, reduction, over-stability or over-connectivity of the network. These types of alterations are metaphorically and intuitively relevant to the clinical phenomenology.

As in psychosis, there is instability, fragmentation, and disconnection. The patient can experience hallucinations, which are, for example, voices unrelated to the visual cues, or concepts that jump unrelated from one concept to another, due to disconnection between neural assemblies that represent these thoughts. At the same time, an over-fixated and over-connected system, is metaphorically very similar to what is seen among patients with negative symptoms, where they have a reduced thought process, reduced states of activations, repeated activations with perseverations and so on.

Thus, we are dealing with the pre-frontal cortex, but in essence, we are also dealing with whole-brain organization and dynamics. This local versus distributed manifestation, can be explained by the fact, that the pre-frontal cortex probably acts as a hub, with centers that influence and disperse wide-spread communications of the cortex.

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

Brain dynamic organization of neuronal network activity is presumed to correlate with electrical oscillations measured over the scalp, propagating from the brain neuronal activity. Gamma Oscillations (30-100 Hz) have been repeatedly correlated with distributed neuronal network activation over distant brain regions and are also involved in performing higher-mental functions of attention and executive functions (Fortenbaugh et al., 2017). In addition, BOLD 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 have been 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 oscillation i.e., interneuron gamma, "ING,". Alternatively, gamma oscillations may result from interactions between excitatory and inhibitory neurons, in which excitatory neurons fire, triggering interneuron firing, which, after a delay, suppresses excitatory neuron firing i.e., "pyramidal-interneuron gamma", PING (Sohal, 2012).

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

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

But how can hub-related control and activity of prefrontal cortex PV interneurons explain brain-related disturbances in severe mental disorders such as schizophrenia? A computational neuronal network model (Geva and Peled, 2000) uses dynamic thresholds

that act in a way similar to gamma oscillations. In this model clustered memories simulate spread activation that is hypothesized for semantic networks in the brain. By altering the parameters of the dynamic thresholds, i.e., hypothesized alterations of gamma oscillations, a large range of disturbances can be generated in the model. These disturbances show metaphorical resemblance to certain general clinical descriptions of mental disturbances found in psychiatric patients suffering from severe mental disorders such as schizophrenia (Geva and Peled, 2000).

This correlates with many studies summarized by Sohal (2012) which have found that patients with schizophrenia exhibit decreases in the power or synchrony of gamma oscillations during responses to sensory stimulation or cognitive tasks (Cho et al.,2006; Ford et al 2007, 2008; Gallinat et al 2004; Spencer et al 2004; Symond et al 2005; Wynn et al., 2005;). 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; Mulert et al., 2010; Spencer 2009). 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 the assumptions of computational psychiatry (Peled 2013) that suggested that

increased threshold activity to the prefrontal lobe may disconnect the brain dynamic neuronal network organization and that reduction of threshold activity may 'over-connect' the same neuronal network organizations. Increase of gamma may thus relate to positive signs and reduction or suppression of gamma may relate to the appearance of negative signs in schizophrenia. This is relevant if we reconceptualize schizophrenia in terms of brain network disturbances to the functional connectivity in brain systems.

To summarize, we can discuss the pre-frontal regions as relevant both for schizophrenia phenomenology, and for the underlying possible disturbances of network distributed organization in the brain (Peled, 2013; Peled and Geva, 2014). With these findings, it follows that neuromodulation would focus on the pre-frontal cortex.

Another important factor for psychiatric phenomenology, is the time frames in which these disturbances manifest. Things like thoughts and perceptions, are in the milli-second range time-frame, and occur very quickly. Also, the assumed hypothetical disturbances of the network have a milli-second range activity. Thus, if you have a memory activation it is in a milli-second range. If you have a perception, the perception happens very quickly, in a milli-second range, so the connectivity and the stability of the network, the small-world network formation and disturbances, are all in a milli-second range time frame, and this is probably a hallmark of neuromodulating brain activity in this type of phenomenology of psychosis and schizophrenia.

We can now conclude that if we aim our hypothetical attempts to intervene in psychosis and schizophrenia with neuromodulation, we should first consider the pre-frontal cortical regions which act as hubs, which in themselves act as regulators of wide-spread connectivity in the brain. We know that in the pre-frontal cortex there are pyramidal cells. The inter-neurons which govern the input-output relationship of these pyramidal cells, are actually acting as units of transfer-processors, regulating the input-output received in these hubs (Peled, 2013; Peled and Geva, 2014). Thus, if there is a disconnection between the input and the output, (which could be affected by activity of inter neurons, which inhibit the input and output relationship), there would then putatively be disconnection dynamics – in the sense that the incoming signals are not connected to the outcoming signals, and vice versa. If there is a good transfer of input-output relationship, immediate input influences immediate output, then there might be an over-connectivity dynamic, and as such, the whole brain might be reduced in activity and flexibility (i.e., negative signs).

Thus, we now know, that the pre-frontal cortex is a good target for neuromodulation in schizophrenia spectrum disorders. We also have a general idea of what we need to manipulate in order to try and control a milli-second range stability of whole-brain connectivity dynamics. This is where the main findings of pre-frontal cortex, and network dynamics, and small-world network dynamics, all transpire in a millisecond-range, conscious instant-to-instant experience.

For neuromodulation, all of the above point towards a therapeutic manipulation which is in the time frame of a millisecond-range, and directed towards prefrontal hubs of high connectivity. As mentioned, the hubs are mainly in the pre-frontal cortex, but there could also be other high-level hubs of connectivity, such as the 'medial hippocampal,' the 'basal ganglia,' and perhaps even all together. However, one would consider starting with the pre-frontal cortex because of the reported research findings mentioned above.

To summarize the chapter of schizophrenia and psychosis related to neuromodulation, we have seen that attention should be directed to the pre-frontal cortex and to whole-brain organization. This is because fragmentation in psychosis is a whole brain disturbance, where the integrated whole brain activity represents an emergence of conscious activity, and consciousness. Consciousness becomes fragmented, when whole brain disorganization afflicts the brain. The idea of disconnection dynamics as an etiology for psychosis, has been documented, and we are actually dealing with the translation of the phenomenology of psychosis into a brain related terminology, meaning brain spread disconnectivity.

Thus, an etiological reformulation of psychosis into brain-related disturbance is possible. We have a location in the body which would be the cortical structure, and the disturbance or pathology is the disconnection dynamic. In this sense, we are actually translating the phenomenology into etiology just like in other fields of medicine where etiology involves a body part and its malfunction. For

example, in ‘Appendicitis’ the appendix is part of the gastrointestinal system, and it is infected. The most important facet in this handbook theory, is the ability to first reformulate the phenomenology into brain related disturbances and once we have a brain related disturbance, we can direct our hypothesis and our efforts towards a physical event in the brain. In this sense, controlling the distributed whole brain dynamics, and intervening in the hubs. Thus, in terms of brain pace-makers, or brain pace making, we have a location or malfunctioning body part where we can intervene in order to control the whole brain dynamics. Just as in cardiology, we can build a cardiac pace maker, which intervenes in the nodes of the system and control the dynamics of cardiac activity. This is the important link between first formulating an etiological reasonable hypothesis based on the literature which will guide us to eventually create an effective brain pacing device.

In the case of schizophrenia and psychosis, the patients will come to the clinic in a psychotic state, which will probably be related to disconnection dynamics and collapse of small world network organization. The future psychiatrists will make a diagnosis using brain imaging, followed by designing an intervention, a brain pace-maker for interventional neuromodulation. This brain pacemaker will control the connectivity state of the brain, and re-optimize it by ‘pushing’ it to a stable flexible connectivity balance and thus putatively reintegrate the conscious experience and eliminate the biases formed, such as the delusions and hallucinations.

Another important consideration for brain organization at the millisecond range, is the fact that the brain is also a hierarchical structure: there are lower level, processors going up to a higher-level processor in the brain, and this has been clearly described by Marcel Mesulam (1998), Fuster (2000) and others. There is a description of the brain as a system of unimodal networks or centers, multi-modal integration units, and trans-modal whole brain connectivity. Traveling from lower level to higher levels of the hierarchy, information is being represented in the brain. With this hierarchical system the brain actually acts as a 'Bayesian Brain' (Friston, 2012), predicting what will transpire in the environment, and processing environmental information based upon higher level context. The context can help identify what is happening in the environment, and the optimal balance between higher-level and lower-level integration is crucial for creating a good predictive representation of the world in the brain. Thus, if hierarchical processors overtake the dynamics and there is a hierarchical 'Top-Down shift,' then distortion biases can occur and information coming from the lower levels can be biased and distorted**.** In this sense, if there are errors in processing and representing the information, then we can be subject to false thoughts regarding the environment and false ideations would be presented as delusions. Thus, top-down shifts of the hierarchy can be interpreted as causing delusions in patients.

Alternatively, the bottom-up processors, at higher levels, create an emergence property of very high mental functions. For example, one

of the highest mental functions is that of 'volition.' The patient's volition could be disturbed or even eliminated if higher-level organizations are lacking. Also, other high-level dynamics, such as emotions, personality, thought, decision making, and so on, could be hampered if the hierarchy formation going up the hierarchy is disturbed.

Thus, 'hierarchical insufficiency' can be formulated in the event that higher levels of brain organization are not achieved, and this will cause elimination of high mental functions such as' volition' or 'motivation,' and this will be expressed in the phenomenology of 'negative symptoms' in schizophrenia (Peled, 2013; Peled and Geva, 2014).

The above insights point toward the importance of considering the hierarchical top-down and bottom-up balances, which also contribute both to delusions which comprise some of the positive symptoms of schizophrenia, and loss of volition, which contributes to the manifestation of negative symptoms of schizophrenia. Considering all of the above, we are now dealing with a system which is in the milli-second range which is both global and hierarchical, both spread and local in hubs, and when combined, point to the pre-frontal cortex, and its connectivity. These are the targets and the dynamics that should be considered when developing any kind of neuromodulatory intervention.

If we are dealing with direct current stimulation or alternating current stimulation to the pre frontal cortex we should carefully

discuss and take into account all of these etiological hypotheses and think, what we are actually doing when we apply these types of currents to the forehead going into the prefrontal cortex. If the plan is to design the future of deep brain stimulation, we should consider whether we are targeting the pre frontal cortex, and if so, should we target the pyramidal cells which are the processors of input output relationships, or should we target the inter neurons which in themselves could actually influence the incoming outcoming transfer of pyramidal activity? We can also consider targeting both of these interventions and the way they influence the hub activity for integrating the whole-brain small-world organization.

Assuming that increased gamma activity related to positive symptoms and relevant to 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 networks activity. Contrary to such an intervention in patients with negative signs of schizophrenia where over-connectivity is the predicted pathology, then 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 of schizophrenia and reduced desynchronized personal gamma tACS for positive symptoms of schizophrenia is a reasonable therapeutic approach using personalized feedback loop tACS.

Additionally, if we are discussing a ‘Focus Ultrasound intervention’ or even other future interventions where there are no electrodes inserted into the pre frontal cortex, all of these should be evaluated in light of what do they do for the specific phenomenology of whole brain organization and small-world-network dynamics in this complicated disorder called psychosis and schizophrenia.

MOOD ANXIETY AND NEUROMODULATION

Before discussing mood disturbances, such as depression and anxiety, a philosophical issue needs to be elucidated; i.e. the 'Biopsychic problem' which deals with how a psychological phenomenon, emerges from a physical system. Thus, the complex system theory, uses the term, 'emergence.' 'Emergence' is a property characterizing the system as a whole, rather than the elements of the system. In the brain, for example, one neuron, or a few neurons, or even hundreds of neurons, do not possess characteristics such as 'personality,' 'emotions,' 'thoughts', consciousness and so on. But the whole brain, as a system, has these characteristics, which manifest under the synergistic characteristic of "the whole is greater than the sum of its components". When referring to mood, for example, and sensations, that are whole brain emergent properties, we are actually dealing with the fact that we are going to look for a whole brain dynamic and whole brain organization, when seeking to understand depression, mania, anxiety and mood.

The first thing to consider is whole brain dynamics, beginning with facts; depression and anxiety are in time scales of weeks, months and minutes. For example, – regarding anxiety, we know that panic attacks occur in a minute range. They can happen very fast, over 5-10 minutes, or perhaps a bit longer. In 'Depression' and 'Mania,' fluctuations of mood typically take place over weeks and months. It is well known that after anti-depressant treatment, the patient should actually expect improvement in depression only after four to

six weeks.

The most important and relevant finding regarding the dynamics, underlining anti-depressant effect relates to plasticity. Plasticity is the, changes that occur in neurons, that offer better dynamic output-input relationships. In fact, plasticity involves an increase in the numbers of dendrites, increase in the numbers of spines, and actually growth of neurons, and even growth of the numbers of neurons in the brain (Kolb et al., 2017).

The most substantial findings related to treatment for depression is the fact that Selective-Serotonin- Reuptake Inhibitors (SSRIs) are effective antidepressants. They are known to be neuronal genetic, synaptogenetic and dendrite-genetics in 60% of cortical pyramidal neurons thus increasing brain plasticity (Uchida et al., 2017). In dementia where brain atrophy is the rule and brain plasticity is hampered, depression is common in up to 40 percent of the cases. Thus, the relevance of brain plasticity is evident for depression and also for anxiety as SSRIs are equally effective in treating anxiety symptoms. As the effects of plasticity in depression and anxiety are widespread it can be assumed that whole-brain plasticity dynamics is relevant in these disorders. It is proposed that brain plasticity is relevant to adaptability in computing environmental occurrences and is thus related to optimization dynamics of the brain in relation to the computational load.

The process of plasticity is time consuming, because it involves metabolic events, which have to do with intra-cellular growth

(Guillaumin and Burdakov, 2021), which takes weeks. It is known that SSRI anti-depressant medications are actually synaptogenetic agents. Once the serotonin re-uptake inhibition is blocked, and there is more serotonin in the synaptic space, there is a cascade of metabolic events, that enter the cytoplasm of the neuron, reach the nucleus and release a promoter. The promoter, in turn, creates the growth of more proteins. These proteins go out to the cytoplasm, and are responsible for the increase of synapse and dendrites (Valenzuela et al., 2011).

Hyper-plasticity has an antidepressant effect, and this has also been repeatedly found in different types of interventions such as electro-convulsive therapy (Bouckaert et al., 2014) which shows that electro-convulsive therapy exerts the same synaptogenetic effect.as that of SSRIs. Thus, the discussion is now about global brain activity and synaptogenesis. Following these two assumptions, the synaptogenesis effect should be global and spread out in the cortex. It is well documented that 60% of the neurons in the cortex respond to SSRI therapy, meaning that there is wide spread cortical synaptogenetic activity (Micheli et al., 2018).

These two findings guide our discussion of neuromodulation. We should then consider an intervention that involves a duration of weeks to months with an intervention that involves massive spread of neuronal cortical activity. The challenge is then whether plasticity and synaptogenesis become relevant for brain activity in mood alterations. Karl Friston (2012) provided a good understanding of

the process in his article on dynamic brain activity, which he calls the 'Bayesian brain,' or Bayesian brain dynamics. Friston claimed that the brain continuously predicts occurrences in the environment and adapts to them, in the sense that when it adapts to environmental occurrences, it is actually reducing a factor called 'Delta,' which is the difference between the occurrences in the environment, and the internal states of the brain. There is a continuous attempt for the brain to reduce the 'Delta function,'. This kind of reduction is also called 'Free Energy (Friston 2012).' The Delta reduction is a Free Energy reduction, which is a term taken from entropy measurements, where the entropy measurements of the internal states of the brain are continually reducing the free energy, i.e., the differences between internal states and environmental occurrences.

In order for the brain to effectively reduce the free energy, it should be more flexible, i.e. more synaptic. Increasing synaptic capacity, the increase of plasticity in the brain, offers the brain changeability and with it the capability to reduce free energy more effectively.

If the emergent property of depression is to be connected to plasticity, it should be assumed that the dynamic going from high-level free energy to low-level free energy, has an elevating-mood antidepressant effect. The dynamic itself, the reduction of free energy dynamics has an emergent property of improved mood. If the free energy increases, meaning there is an increase in the difference between the internal states of the brain and the

environmental occurrences, then increase of free energy dynamics occurs, moving from more adaptable to less adaptable states, thus causing the emergent property of a depressed mood.

We can also adapt terms taken from optimization theory and optimization dynamics, meaning that the brain optimizes the environmental occurrences by reducing free energy. So, optimization dynamics would have an anti-depressant effect, while de-optimization dynamics, increasing the free energy will cause an emergent property of a depressed mood.

The major findings: increased plasticity with its antidepressant effect (Peled 2013), whole brain dynamics, as a whole brain adaptability state (Peled 2013), and adapting to the environmental occurrences and the Delta Free Energy reducing dynamics connected to the emergent property of mood.

The above findings need to be considered when deciding to intervene with neuromodulation, which should be spread out for huge cortical regions. This would be akin to activating, neuronal networks spread across the cortex. This would be like having a direct current stimulation or alternating current stimulation in multiple locations concurrently in the cortex. On the other hand, we could consider stimulating local hubs, that have high connectivity, and will themselves activate wide spread cortical networks. Indeed, recent studies (Coenen et al., 2019, Riva-Posse et al., 2014), with deep brain stimulation and depression, revealed that the best anti-depressant effects were achieved by stimulating brain regions that

relate to bundles of white matter in the cingulate which, by themselves, have massive connectivity, or connections going from the prefrontal to posterior regions in the brain. This type of high connectivity is based on the assumption that massive spread-out activity is being stimulated, even though the electrode is localized and is inserted into white matter bundles. Both local and spread stimulation must be taken into account when considering neuromodulation for an anti-depressant effect.

While depression and mania could be fluctuating states of whole brain dynamics of optimization and deoptimization, anxiety is probably an instability of these networks (Peled 2013); i.e., during high computational activity, the interactions between the neurons in the networks are perturbated. Each neuron has an input-output relationship that follows a physiological mathematical formulation, in which there are inputs, and there is a summation function for the neural cell body. There is then an output, a type of threshold function that could be similar to a sigmoid function. The mathematical values of the input and output from each neuron, correlate with the values of the whole network transmission. Once the network is perturbed, these values, which actually represent multiple constraints between the neurons, are disrupted in the sense that they no longer match the mathematical formulation, similar to a stone thrown into a pond which causes the water to begin to ripple. There is instability when that spreads into the network. An emergent property of such a perturbation, would likely emerge as a sensation of anxiety. It is commonly observed that when

the computational load and the information processing in the network increases, in conditions like stress, that anxiety is the natural sensation that accompanies hyper-demands on the network. This is intuitively a good explanation for a type of continuous existential anxious sensation owing to network load and activity (existential anxiety).

If the plasticity is increased, and spread-out across whole brain networks, it can absorb this type of perturbation. This can explain why SSRIs are as effective for anxiety as they are for depression. In anxiety the flexibility of the system absorbs and relaxes the perturbation spread in the brain, while the same plasticity also helps adaptability, reducing free energy and the delta, adapting to the perturbations of the environment, thus creating an anti-depressant effect.

Regarding depression, to date data suggests (Kekic et al., 2016) that tDCS interventions comprising multiple sessions can ameliorate symptoms of several major psychiatric disorders, both acutely and in the long-term. Three independent tDCS trials conducted on 171 depressed patients suggest that “Cognitive disturbance”, “Retardation”, and “Anxiety/Somatization”, are potential clinical predictors of response to tDCS in depression (D’Urso et al 2017). A meta-analysis that evaluated therapeutic effects of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) in major depression showed efficacy in treating depression. In addition, it showed that increasing HF-rTMS sessions was associated

with increased efficacy of HF-rTMS in reducing depressed patients' symptom severity. A total number of pulses of 1200-1500 per day appeared to have the optimal antidepressant effect of HF-rTMS (Teng et al., 2017).

PERSONALITY AND NEUROMODULATION

Before discussing neuromodulation and personality, the definition of the transition from physical system to psychological phenomena such as personality warrants an explanation. Personality has two important elements: first, personality is a developmental process that evolves in a time frame of years, from birth to adulthood. Second, personality is the sum of psychological traits of the person which govern the psycho-social interactions and inter-personal relationships that the individual manifests. Personality, then, is a developmental process related to interpersonal relationships in which the biological underlying process is typically defined as "Experience Dependent Plasticity". Experience Dependent Plasticity means, the changes in the interactions among neural ensembles in response to experiences. When an individual has an experience, there is a set of incoming stimuli that activate neurons in the brain. These activated neurons represent the stimulus and actually become a representational internal state configuration of the encoded experience. Throughout a lifetime, an individual experiences multiple events and occurrences which are translated into internal representations or internal configurations; These ensembles of activated neurons are representatives of the specific experiences (Peled, 2013).

According to the well-known Hebbian algorithm (Lopes-dos-Santos et al., 2011), if neurons fire together, they wire together. Internal representations are created from repeated experiences and are

sometimes also called ‘Memories’ (Hélie et al 2008). Thus, if one repeats a process, for example, in order to memorize something, then it is embedded in the connectivity structure of the brain and creates an internal representation. These internal representations generate a map or a model in the brain. The brain represents multiple maps and models such as the Humanculus which is a representation of our body in the brain (Muret and Makin, 2021). It is thus hypothesized that the brain as a whole-brain system can actually represent all experiences that we have from birth to adulthood including the dominant figures (i.e., people that we interacted with, such as family, teachers and so on, The types of interactions that we have experienced with these persons are also represented. For example, if we had supportive, encouraging experiences at a young age, we will probably generate an internal representation of being capable and effective. In contrast, if we grew up in an unstable environment in very unfavorable conditions, with unstable interpersonal-reactions we would probably develop negative attitudes towards ourselves and towards the people around us.

Object relationship psychology has been very effective in explaining such manifestations by talking about object relationships where objects have internal maps and representations of self and others. Thus, there is also a self-object in the sense that we ourselves are also represented in the brain. We can intuitively think about our reactions with others in our minds and can actually do offline simulations in the brain of our responses to certain conditions and

situations. The brain constantly checks for how adaptive it could be in interpersonal relationships, using these internal maps. Thus, if you have internal maps of others and yourself which are adaptive and which identify with the actual and/or psycho-social events, then there is a good possibility that you will act effectively and adaptively in the environment. But if there is a mismatch between the internal representations, the internal maps, and the actual occurrences, then this mismatch causes one to malfunction in the environment, which will reduce adaptability and efficacy in inter-personal relationships. Once these biases cause erroneous or maladaptive behaviors, they will manifest as failures in inter-personal relationships, which are a hallmark of personality disorders.

The relevance of adaptability of internal representations to their environment and to the psycho-social occurrences is evident. and illustrates that the adaptive brain which reduces free energy is also a brain that has good and optimal internal representations. This is also relevant to mood, because as explained in the previous chapter the increase of free energy and non-adaptability of a Bayesian brain, causes depression. A major complaint of patients that suffer from personality disorders is depression, which is currently explained by the fact that if the internal representations are not optimized and de-optimized, there is an increase in free energy and the emergent property as explained in the previous chapter would be depressed mood. Thus, the manifestation of personality disorders is anxiety and depression which can now be understood as a result of maladaptive internal representations.

When attempting neuromodulatory intervention for personality disorders, we must consider increasing plasticity. If we can increase plasticity over long periods of time, we can actually push the brain into a plasticity condition of a younger child's brain and then we can achieve a corrective intervention. After generating increased plasticity, it is crucial to control experiences which can be called an "experience control intervention". Psychotherapy is actually an experience control intervention. In psychotherapy, there are corrective experiences which change the internal representations into more adaptive and effective internal representations. An external intervention aside from an increase in plasticity, should be one of experience. Another option is to control experiences artificially, by using 'Virtual Reality' technology. Virtual reality technology can actually control the experience one is having and at the same time, with an increase in plasticity, one can change non-adaptive experience- dependent configurations into more effective and adaptive ones. Thus, a better internal configuration together with optimized conditions, will treat the emergent property which is a depressed mood.

In the discussion of neural-modulation of personality disorders, the time frame is lifelong and requires administration of stimulation sets which are relevant to whole brain plasticity. However, in order to succeed, there must also be a corrective, experience-dependent process to reformulate internal representations, their complexity, adaptability, and their efficacy in controlling and guiding the

interpersonal relationships that the patient experiences.

CONCLUDING REMARKS

As explained in the introduction, this handbook is not intended to give an in-depth overview of the technology and of the findings in the field to date. It is limited to an attempt to generate an initial preliminary guideline for neuromodulation in order to promote an understanding of the need for a future neuromodulation intervention in psychiatry.

As for neuromodulation technologies, there are non-invasive technologies that apply electrical current from outside the brain and outside the skull such as 'Transcranial Current Stimulations' that could be direct or alternating currents. The direct current stimulation does not exert any stimulus effect on the neurons, rather, it alters the gradient of a membrane potential, causing the neurons to fire more easily and thus perhaps fire more effectively and repeatedly resulting in an increase of neuronal plasticity (neuroplasticity). This is because re-activation of neurons generates new synapses and dendrites. Thus, direct current stimulation actually facilitates on-going activity (which is already activated) and thus does not have a direct algorithmic-alternating effect on the networks computational task-related activity.

Alternating current stimulation differs in the sense that it can cause entrenchment of the activity of networks. For example, if networks oscillate at alfa frequency, then alfa synchronized alternating current can entrench, increase or constrain the activity of alfa oscillations. The exact meaning of the rhythms is not yet known

however it has been reported that they correlate with some major cognitive conditions such as sleep or alertness (Rundo and Downey, 2019). Thus, it is possible that the alternating current can influence these conditions by either enhancing or reducing them, for example, activity relating to attention or alertness versus sleepiness. Clearly, if these oscillations indeed influence these types of networks, they will influence the plasticity of these networks. In line with the findings and theories presented in this booklet regarding the time frames, locations and activities related to psychiatric phenomenology, interventions can be designed accordingly.

Direct activation, is a different type of technology that can be either invasive, (which requires implanting electrodes into the brain) or non-invasive. In this case as well, one should consider the idea of time frames and spread-out diffuse cortical activation that may be required for this kind of neuromodulation. Once there is a location and a time frame of activity, a decision must be made as to where to implant the electrode and when to activate it. Multiple electrodes, which may complicate the algorithmic activations should also be considered. Considerations regarding the activation of various locations synchronously or a-synchronously, and whether the current to be injected is inhibitory or exhibitory must also be taken into account. Additionally, stimulation patterns must consider the networks being perturbated and whether they have inhibitory or excitatory effects. Thus, it becomes very complicated to use local deep brain activation and the precise location of the disturbance in the brain of the specific patient must be determined.

The presentation thus far supports a proposal to attempt to target (if one is targeting a very localized region) hubs of connectivity in order to activate wide-spread diffused cortical networks when dealing with the whole brain dynamics of mood and experience. Deep brain stimulation has both advantages and disadvantages and becomes more challenging with the technology for excitation of multiple hub locations.

Other types of interventions would be similar. For example, focused ultrasound (Krishna et al., 2018) is a technology that can actually stimulate regions near and deep inside the cortex. However, this intervention poses the same challenges of trying to understand what to stimulate and then create an algorithm of stimulations. In the future, nano-technology (Roet et al., 2019) will putatively enable simultaneous stimulation or measurement of various brain regions. The psychiatrist will then also face the same problem of identifying the algorithm of pathology as etiology. Thus, it is clear that regardless of the technology, the same common problem of understanding the etiology of mental disorders will emerge.

It then seems that the attempts at brain stimulation that are being investigated and experimented today, suggest that we are putting the 'cart in front of the horse' meaning that we need to identify the etiology of the mental disorders before designing the intervention, rather than experimenting with various interventions without full understanding of their side effects, or relevance to the pathology and etiology of the specific mental disorder that requires

intervention. Thus, it is first necessary to connect the etiology to the proposed intervention.

To summarize, a protocol should be designed wherein neuromodulation is a clinical application in terms of the theoretical construct of the etiology of the patient. Thus, putting the cart back behind the horses, mental disorders first need to be reformulated as brain disorders. On that basis, general outlines of neural-modulation can be designed, regardless of what type of technology will evolve in the future as an effective dominant intervention, using neuromodulatory technology.

Assuming that a patient is on a spectrum of phenomenology ranging from psychosis, with negative symptoms, anxiety, mood and personality disorders. which could be a polymorphic mixture of phenomenology. If the patient is psychotic than his condition can be reformulated as a disturbance in the millisecond range of small-world-network very fast plasticity. Interventions that target hubs that are related to spread out activity can be considered as the general method for re-optimizing and re-stabilizing the small world network functionality of the brain via interventions in hubs, (such as the pre-frontal cortex). The target is actually the executive central networks which have to do with the decision-making, thinking, acting, perception and the entire range of very fast plasticity changes in the brain. The hierarchical dynamics must also be considered when dealing with patients who predominantly have delusions or patients who have negative-symptoms due to

hierarchical insufficiency, specifically avolition. Ultimately these patients are considered to have a disturbance in the hierarchical bottom-up-top-down processes. Indeed, over-connectivity dynamics will constrain brain activity and is thus is also relevant for negative symptoms.

A patient, who has depression or a mood disturbance is in a different time frame, that may require weeks or months of interventions. Depression also has different dynamics in that it is a whole-brain dynamic moving from one condition to another condition and each condition more or less optimizes and adapts to external occurrences (Peled 2013). A patient with depression may require interventions that will massively increase plasticity, and that are not localized but rather spread out in the cortex. In addition, there is a need for absorption of perturbations (reducing anxiety (Peled 2013). The increase of adaptability and reduction of 'Free-Energy 'in mood disorders such as depression should be considered.

Regardless of the technology to be developed, in the case of mood disturbances, widespread cortical intervention, which could be achieved with multiple stimulations, or by targeting the connectivity hubs that will activate wide spread cortical activity, will be considered.

Regarding personality disorders, diagnoses will be with the accepted phenomenology of maladaptive psychosocial interactions and faulty-reactions, disturbances to functionality within psycho-social contexts. Once personality disorder is diagnosed, the focus is

on long-term developmental plasticity in the time range of the life span. In such cases it is necessary to reverse brain plasticity to childhood-like plasticity conditions that will allow effective changeability. Once achieved there is a need for an external 'corrective experience' designed to specifically correct the faulty, biased internal representations (typical to personality disorders) in order to create more adaptive and effective internal representations that will offer better functionality and less symptoms.

The re-formulation of mental disorders as brain disorders (Peled 2013) is crucial, and will form the basis for various novel interventional technologies. Once this re-formulation succeeds, neuromodulation interventions will follow, and the etiology of mental disorders will be validated.

Table 1 offers hypothetical example options to consider for neuromodulation in mental disorders.

Table 2

Psychosis	Slightly desynchronized gamma stimulation delivered to dorsolateral prefrontal cortex
Negative signs	Increased synchronized gamma stimulation delivered to dorsolateral prefrontal cortex
Delusions	Slightly desynchronized gamma stimulation. This is to disconnect the overly connected networks and offset them dissolving erroneous biased configurations to allow for newly adaptive

	network configuration to take place.
Avolition	Increased synchronized gamma stimulation intended to induce neuronal plastic evolution of personalized higher-level lost network-configurations, and return of adaptive higher-level transmodal brain systems.
Depression	Frontal parietal intense random and direct stimulations (tRCS tDCS) to induce massive plasticity induction to be combined with CBT sessions. high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) 1200-1500 per day deliver the best antidepressant effects.
Mania	High–frequency high-voltage inhibiting currents to frontal parietal regions to induce massive plasticity inhibition to brain networks. To reduce plasticity and generate an anti-manic depressing effect.
Anxiety	Frontal parietal intense random and direct stimulations (tRCS tDCS) and HF-rTMS) 1200-1500 per day, to induce massive plasticity induction to be combined with relaxation

	techniques sessions
Personality disorders	Frontal parietal intense Random and direct stimulations (tRCS tDCS) and HF-rTMS) 1200-1500 per day to induce massive plasticity induction to be combined with intense focused dynamically oriented psychotherapy

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