Brain-pacing Sticker [BpS]

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*"The ones who are crazy enough to think they
can change the world are the ones who do"*
Steve Jobs

Introduction

To cure mental disorders, we shall have to know what causes them and correct it by having control over brain activity

Here an attempt is made to capitalize on existing and predicted science / technology, and try to envision the therapy for mental disorders in a practical testable manner that may constitute a roadmap, an instruction-toolbox, for researchers wanting to reach this overwhelming achievement of curing psychiatric illness.

The basic assumption is that psychiatric disorders are brain disorders, different psychiatric illnesses are caused by different patterns of brain "optimizations breakdowns." Mental functions are "Emergent Properties," thus emanate from global-brain disturbances, or in other words disturbances to whole brain optimization (Peled 2013).

"Brain-Pacing" to resume brain-optimization is the general premise for future direction in psychiatry. Looking beyond the horizon of current science, it is predicted that brain-pacing technology will involve miniaturization of devices and nano-level brain interface. In fact one can envision a "Sticker-device" carrying a sensing, organizing, feedback loop apparatus placed on the forehead, acting remotely and non-invasively on nasally-pre-inhaled bio-nano-particles positioned on prefrontal cortical interneurons.

See Figure 1

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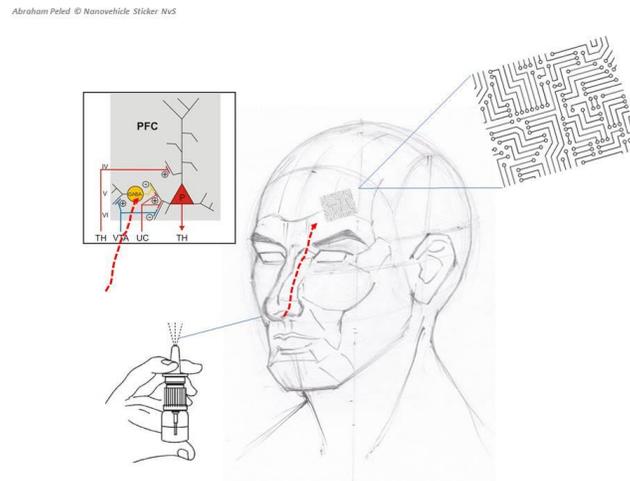
Patients will place two stickers bilaterally on the sides of their forehead, and then (nasally) inhale specially designed nanoparticles. These can be Dynamic Viral Capsids DNA Nanorobots, or inorganic fabricates hybrid system interfaces with relevant neurons (Alivisatos et al 2013). These will be guided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

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

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

thus optimizing brain organization via network prefrontal hub control, eliminating related psychiatric phenomenology and curing the patient.

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

Additionally, this task is so daunting that it requires the establishment of a new discipline integrating science-technology in seemingly disparate fields such as physics mathematics and clinical psychology and psychiatry. More-over it requires simultaneous understanding of nanoscience, neuroscience, neural-computation, signal-processing and self-organizing AI dynamics, all in one team.

In this document I will try to outline the needed science, and team, including some suggestions to overcome some of the obstacles, hopefully this paper can offer a preliminary roadmap to those taking on this enormous challenge. This is in no way a comprehensive detailed program, as much of the knowledge is missing in general and for me in particular (as I am a clinician with very little familiarity with Nanotechnology). This is also why a team-building proposal is included in this paper.

Clinical Brain Profiling: Understanding psychiatric phenomenology in terms of brain disturbances:

In their extensive review Alivisatos et al (2013) state "Equally important for achieving a deeper understanding of brain function is the comparable development of a conceptual framework and mathematical theory for brain activity in high-dimensional spaces." This relates to 'Clinical Brain Profiling" a theoretical testable construct reformulating mental disorders as brain disorders.
A first step is to predict and validate the causes for psychiatric illness, the optimization breakdowns that emerge (as emergent properties) in the form of psychiatric phenomenology known to every clinician. In the past I have written abundantly on this topic and even came-up with a computer-program translating clinical findings (mental status, symptoms and history) into a set of (vector) predicted brain disturbances which I titled Clinical Brain Profiling (CBP). Here I will summarize CBP concisely and in general terms, for in-depth understanding of CBP the reader is referred to the literature as follows Peled Geva 1999; Peled 1999; 2000; 2004a; 2004b; 2005; 2006; 2009; 2008; 2010a; 2010b; 2012a; 2012b; 2012c; 2012d; 2013; Peled Geva 2014.

As for dynamic optimization of brain organization criticality optimizes connectivity (Peled 2013) and small-world hub organizations optimizes hierarchy (Peled 2013). Over-connectivity versus disconnectivity dynamics are balanced by criticality, hub organization offers hierarchy where unimodal processing multimodal processing and transmodal processing offer a bottom-up top-down balance helping create an internal model of reality governed by Dynamic Causal Modeling (Moran et al 2013) Bayesian predictive principles. Fast, millisecond-range plasticity is supported, but also effects, slower (days to weeks) plasticity dynamics stabilizing long-lasting memories and internal representations that in themselves have an organizing stabilizing effect (Peled 2005; 2012).

Table 1 summarizes predicted CBP

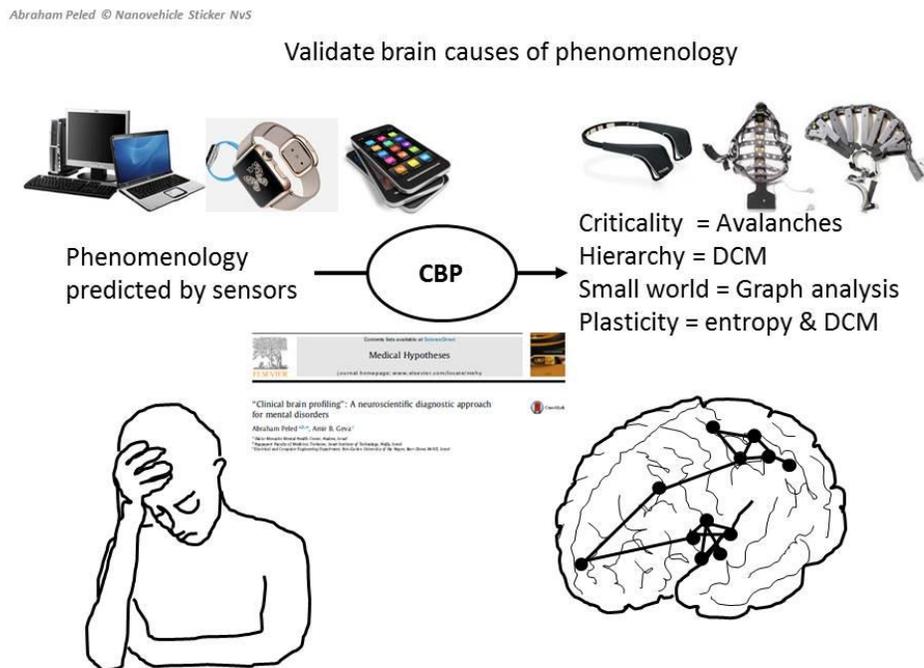| Type of Brain Disturbance	Psychiatric phenomenology
Criticality Fast millisecond range plasticity	
Segregation and Disconnectivity	Psychosis and disorganization
Integration and Over-connectivity	Poverty of thought and perseverations
Hierarchy small world network and hubs	
Bottom-Up insufficiency	Negative signs schizophrenia
Top-Down shift	Systemized delusions
Slow plasticity and Internal representations (IR)	
Optimization of IR	Mania
De-Optimization of IR	Depression
IR Default mode network Configuration	Personality disorders

CBP has been studied for reliability (Peled 2014) and has a working computer program at:

http://neuroanalysis.org.il/?page_id=114 that generates testable CBP's for validation. Validation of CBP prediction would require multiple (a battery of) signal processing methods because each method is sensitive to a different predicted brain disturbances, one that is sensitive to specific signal processing method and not to others. Table 2 exemplifies this

Table 2:

Criticality Fast millisecond range plasticity	Correlations, Synchrony, Granger causality Mutual information, Dimension estimation Bayesian statistics Dynamic Causal Modeling Independent components analysis, Neural complexity (Correlation matrix) Graph assessment of overall Small Wordiness criticality assessment of Avalanches
Hierarchy small world network and hubs	Estimating hierarchy with hub composition K-shell decomposition, Fractal geometry estimations, Integrated information theory estimations
Slow plasticity and Internal representations (IR)	Whole brain Matching complexity, estimations. Free energy estimations. Entropy measurements. Age-related changes of all the above

The CBP entries are constructed to accommodate traditional psychiatric evaluation involving signs of mental status examination, complaints of symptoms and medical history, see http://neuroanalysis.org.il/cbp/index.php however these entries in part can be sampled using sensor technology of behavior and more sophisticated sensor processing such as face and speech recognitions. Sensors activity coupled with synchronized brain-imaging sensors of wireless (dry-electrode) EEG can begin an online large-data generation that will ultimately lead to validation of CBP

Figure 2 illustrates such phenomenology-brain coupled sensing

For complementary information about predicting brain disturbances of psychiatric patients based on their phenomenology read the related references specially. Peled A. Brain "Globalopathies" cause mental disorders. Med Hypotheses 2013 Dec:81(6):1046-55 and Peled A, Geva A. Clinical brain profiling: a neuroscientific diagnostic approach for mental disorders. Med Hypotheses 2014 Aug 8.

Also watch this set of Webinar talks: 1) <u>Diagnosis & Phenomenology</u>, 2)<u>Neurosystems</u>, 3)<u>Personality & DMN,</u> 4)<u>Mood & Plasticity</u>, 5)<u>Psychosis & Connectivity</u>, 6)<u>CBP Summary</u> and see the following Summery Lectures <u>Part 1,</u> <u>Part 2a,</u> <u>Part 2b,</u> <u>Part 3.</u>

The Brain-pacing Sticker application and Nanoparticles

This section is divided to "**site of action**," "**mode of action**" and the "**Pacing Sticker**" integrating explanations of the device and its biological action on the brain.

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

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

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

1. Remote signal
2. Nanoparticle action on calcium channel receptors and action potential

3. Regulatory action on layer IV pyramidal neurons, executing Network Hub effects.

4. Network Hub activity optimizing whole-brain connectivity stabilizing perturbed brain.

Figure 3 illustrates this regulatory effect:
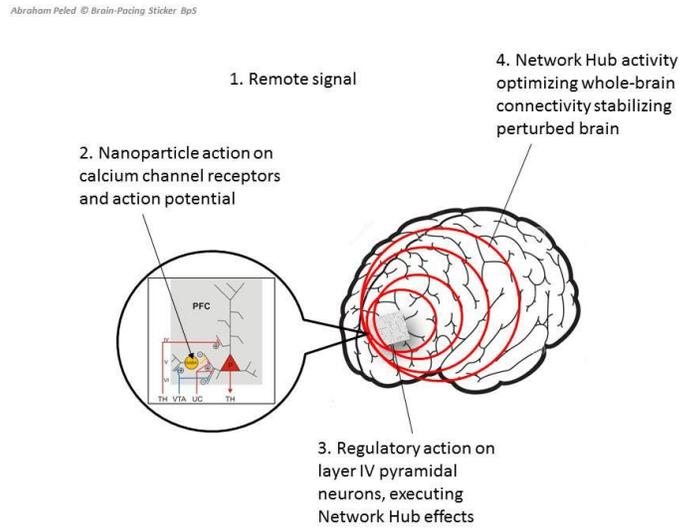
The Pacing Sticker: The Brain-pacing Sticker has a sensing arm of input, a controlling arm of output and a self-organizing module see Figure 4:
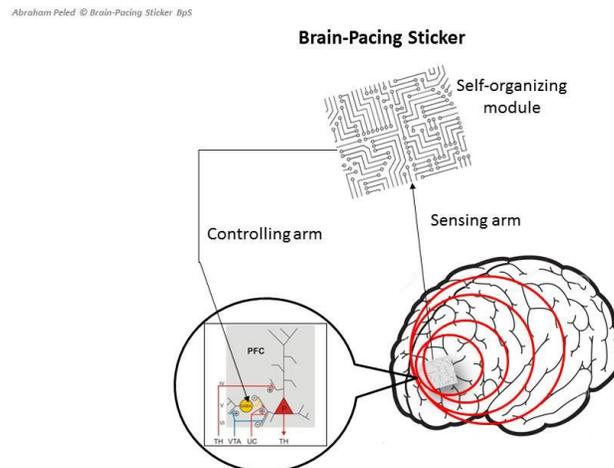
The sensing arm collects the EEG signals from the prefrontal cortical regions located underneath the sticker. Regular EEG will probably not suffice and some more accurate imaging technology will be needed, this may include "quantum dots" "optical sensing-like' devices, probably Ca^+ imaging but such that will have negligible adverse interactions with surrounding neural tissue as to offer longevity sampling activity (Alivistos et al 2013). It must then calculate whole-brain organization sensing using signal processing methods that can extract whole-brain activity from localized PFC activity. The sensing input arm must convey whole-brain organization to a "self-organizing" module in the sticker, in a manner that allows for that module to simulate both the actual brain-organization and an optimal brain-organization. The optimal brain organization is the one that will be conveyed by controlled signal via the controlling-output arm. A "Delta" calculated between actual brain-organization and desired optimal brain-organization (e.g., hamming distance measuring apparatus) monitors the online feedback-loop of this Brain-pacing system. A gradient-descent dynamics between actual and desired brain-optimization characterizes a well-functioning brain-pacing device.

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

Figure 5 schematizes the Brain pacing Sticker activity
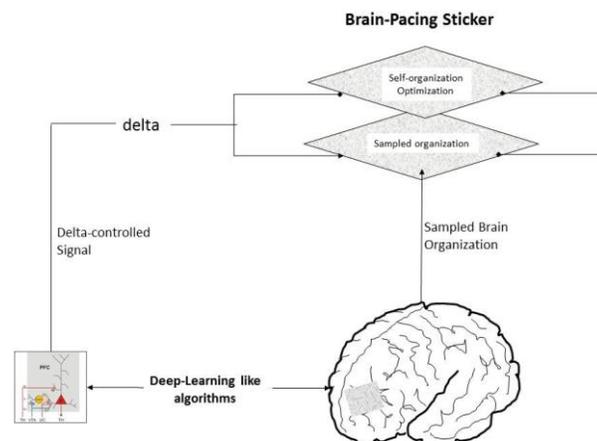
Required Team and Profession (future psychiatrists).

Brain-pacing for psychiatric disorders will require a totally new psychiatrist of the future, diagnosing patients in a totally new manner. "NeuroAnalysis" conceptually relates phenomenology of psychiatric illness to predicted brain disturbances, the Clinical Brain Profiling CBP Neuroanalytic approach has been studied for reliability (Peled 2014) thus ready to substitute the DSM approach which has been instituted for the purpose of reliability. The advantage of CBP over the DSM approach is that CBP conceptualizes psychiatric phenomenology in terms of specific brain disturbances thus can be validated, actually CBP is formulated as testable-predictions, naturally lending themselves to validation.

To be able to understand "Neuroanalysis" and develop a brain-pacing sticker cure for psychiatric illness the psychiatrist of the future will have to be trained mastering not only neuroscience, medicine neurology and psychiatry but also complex-systems physics, neural-computation, bioengineering, nanotechnology and signal processing. Thus it seems that a curriculum for the psychiatrist of the future will have to be as shown in table 3. (See also appendix for book chapter of "Optimizers 2050." (Peled A, Brand D. Saga Books 2005).

Table 3:

Schedule	Topics
3 years	Premedical studies
2 years	Basic bio-engineering
3 years	Medical studies and pharmacology emphasize on internal medicine related to brain diseases
3 years	Neurology and Psychiatry including practical clerkship training
2 years	Courses in Complex-systems physics, neural-computation, nanotechnology and signal processing.

Brain-pacing Sticker Taskforce:

The taskforce for the realization of Brain-pacing Sticker will need to organize based on the 3 major challenges posed by this ambitious project.

1. Developing the sticker, hardware and implementing nanotechnology for sticker apparatus.

2. Developing and testing nano-bio-vehicles to control interneurons in PFC

3. Developing and computing the sensing-signaling self-organizing loop device.

Thus three sub-taskforces should be placed to work, both specifically on each challenge, but also jointly on the whole project. As evident each group will require multidisciplinary team and effort, ranging from hardware nanotechnology to complex subsystems physics, neural computation and beyond, involving also clinicians. Likewise the project can be broken down to subprojects according to the above topics.

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Appendix :

The following chapter below is a first chapter from the book titled "**Optimizers 2050**" (Peled A, Brand D.. Saga Books 2005), specifying what psychiatrists will be trained for in 2050.

"Dan Moor drove into the parking lot at University Hospital and pulled into an empty space facing the building. He switched off the engine and sat behind the wheel, staring at the psychiatric wing. Of average height and build, Dan's sandy colored hair bordered on unruly. He ran his fingers through it now, feelings of anticipation and apprehension making his stomach churn.

The year is 2050 and Dan has just graduated from the Optimizers Pre-residency Program for psychiatry. The Optimizers program was developed some three decades ago as a special training program for those wanting to become psychiatrists. Only the top students can compete for the optimizers program after graduating from medical school.

The scientific leap forward in brain research over the last four decades has put psychiatry in the forefront of medical disciplines. Brain medicine involves mastering advanced knowledge from mathematics and physics of complex systems, so it was inevitable that a special training program would be developed to keep pace with advances in the field.

Dan reached into the back seat and picked up his briefcase. In an effort to calm himself as he left the car, he focused on the elements that constituted the basic sciences of the four-year pre-psychiatry program—neural computation, neuroscience and computer-generated signal analysis of imaging devices. Non-linear higher-level mathematics had become indispensable in psychiatry.

Unlike other medical doctors, psychiatrists are now called optimizers. This is partly because they were required to graduate from the optimizers program but more because curing mental disorders involves optimizing brain functions, especially those functions of higher levels.

Approaching the psychiatric department, Dan could see Dr O'Connor through the glass doors. Tall, dark and immaculate with piercing grey eyes, he was an imposing figure. He was also Dan's appointed supervisor for the first twelve months of his residency. Beside him was Professor Krauss, whose white hair and twinkling eyes made him appear more like a benevolent grandfather than a professor with more than forty years experience in psychiatry. Although retired, he still visited the department regularly, offering his wealth of experience in clinical supervision. Professor Krauss had heard lectures from great psychiatry authors dating back to the pre-optimizers era, even before the introduction of Theoretical Psychiatry[1], having graduated from what was then called a biological psychiatry residency. The professor's presence reassured Dan and dispelled the last of his anxiety. After they exchanged greetings, Dr O'Connor informed him that he would receive his first patients soon. 'In the meantime,' advised Dr O'Connor, 'you might like to go over your IVI procedures.'

Professor Krauss accompanied Dan to the staff lounge. There were a number of small offices adjoining the lounge and one had Dan's name in the slot on the door. Dan put his briefcase away and rejoined the professor in the lounge, where they discussed the three basic phases for optimization in the treatment of mental disorders—Investigation, Validation and Intervention. They both looked up when Dr O'Connor appeared in the doorway.

'Dr Moor, we will see three new admissions now,' he said.

Dan looked at the professor who nodded and said, 'We will talk again.'

'I look forward to it,' smiled Dan and walked briskly to the ward with Dr O'Connor.

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[1] Peled 2004

'They were admitted last night,' said the doctor as he increased his speed. 'You will be able to start the Investigation phase for these patients right away.'"