Nano-Brain-Pacing: Curing Mental Disorders

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Abstract

This is a proposal, a general outline for treatment of serious mental disorders using a microelectromechanical device and nano-technology. To this end we need to know the algorithm and location of the disturbance causing the serious mental disorders, and we need to apply “corrective” interventions targeting the disturbances, i.e., a feedback loop mechanism. Here I argue that the targeted disturbances are disturbances to the small-world organization of prefrontal cortical neural networks. I propose that by using voltage-imaging sensing nano-technology, large-scale neural networks with millisecond-scale temporal resolution can be achieved to detect small-world disturbances in the frontal cortex. Corrective efforts should use fully biologically-compatible remotely-controlled non-invasive neural excitation techniques; for example through the activation of the heat-sensitive capsaicin receptor TRPV1 by magnetic nanoparticles. These should target polarization and hyperpolarization, excitatory and inhibitory activity that is relevant to reestablish small-world brain activity in the prefrontal cortex. To close the sensing-stimulating loop, two thin skin-mounted micro-electro-mechanical devices (stickers) that are precisely matched to the human epidermis will be bilaterally attached to the forehead. At their micromechanical level these devices will embed signal-analysis detection translatable to controlled radio-magnetic stimulation. The magnetic stimulation causes heat-sensitive capsaicin receptor to activate related-neurons remotely non-invasively. This sensing-stimulating loop is continuously iterative thus any correction achieved to the small-word organization is still monitored for additional correction if needed, thus a feedback homeostatic regulatory process is installed. With that a complete nano-frontal brain-pacing is achieved, which is predicted to eliminate symptoms and cure serious mental disorders.
Introduction

To cure mental disorders we need 1) to know the exact algorithm of the brain disturbances causing them and 2) we need to intervene and correct these disturbances by controlling relevant neuronal activity. The brain acts “globally” i.e., global brain disturbances cause mental disorders, “healthy” global organizations seem to comprise small-world-network organizations while mental disorders seem to involve disturbances to the small-worldiness of brain organizations (Peled 2013). The most serious mental disorders are those of psychosis, schizophrenia and autism. These are assumed to involve fast millisecond range plasticity. Mood disorders are related to slower plasticity and adaptability of brain circuits and personality disorders are caused by relatively permanent plasticity of basic experience-dependent acquired internal representations (memories). For detailed explanation see Peled (2013) and Peled Geva (2014) publications. It is thus clear that the road for curing mental disorders is through controlling neuronal plasticity at the global algorithmic level. Most important, by controlling the fast plasticity processes because 1) they are responsible for the more serious incurable mental disorders such as schizophrenia, and 2) because controlling fast plasticity will lead to control over other plasticity modalities, as these are consequences of fast-plasticity (Hebbian algorithm Lopes-dos-Santos et al 2013). Recently the neuro-technology of ‘sensing’ and “intervening” in the brain is developing fast and the most promising technology for remote, non-invasive brain-intervention is that of nano-technology. Thin, skin-mounted electrophysiological sensors are being developed (Jang et al 2015) these may one day support microelectromechanical devices for signal-analysis detection translatable to controlled radio-magnetic stimulation which in turn activates neurons engineered with nano-particles to respond to magnetic fields. Here I will describe the logical steps to cure mental disorders by first finding the algorithm and location for intervention, and then by setting the intervention in the form of sensing-stimulating loop at a nano-brain-pacing scale.
Algorithm and location for intervention.

While in the past psychiatrists researched correlations between disease entities of mental disorders and molecular biomarkers such as genes and neurotransmitters, in recent years the Connectom (Bullmore and sporns 2012) level of endophenotypes is researched. Terms such as Connectopathies (Martin 2012; Peled 2013) and Pathoconnectomics (Woebe 2015) have been invented.

It is becoming apparent that serious mental disorders such as schizophrenia, psychosis and other similar clinical manifestations are related to disturbances of connectivity in the brain (Ordóñez et al 2015) and that such disturbances can be characterized with Graph-theory analysis as disturbances to small-world brain organization (Yan et al 2015; Ottet et al 2013). Small-world topology is characterized by dense local clustering or cliquishness of connections between neighboring nodes (i.e., neurons, brain regions) yet a short path length between any (distant) pair of nodes due to the existence of relatively few long-range connections. Anatomically and functionally small-world topology can support segregated / specialized and distributed / integrated information processing. Moreover, small-world networks are economical, tending to minimize wiring costs while supporting high dynamical complexity. Disturbances to the small-world organization of the brain with instability and damage to neuronal integration causes fragmentation of consciousness (hallucinations and delusions) and unstable cognition (loosening of association altered logic). These are typical to psychosis and schizophrenia. In summary. Schizophrenia-spectrum disturbances are thought to be caused by disturbances to Small-World-Network organization of the Connectom (Li et al 2012 Rubinov et al 2009).

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, hubs in their own right Figure 1. The dopaminergic and serotonergic influences on prefrontal hubs seem to be regulatory as (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 1).
The cellular, molecular level of prefrontal “machinery” is detailed by 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-worldliness 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 colleagues in an article in Nature (Yizhar et al., 2011) intervening with the 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.

**Stimulating neuronal networks with nano-technology**

It is obvious that any brain intervention stimulation or inhibition will have to be remotely controlled non-invasively and should be fully biologically compatible. One of the more promising techniques recently developed is from Anikeeva’s lab (Chen et al 2015). They demonstrate minimally invasive and remote neural excitation through the activation of the heat-sensitive capsaicin receptor TRPV1 by magnetic nanoparticles. The nanoparticles dissipate heat generated by hysteresis, triggering widespread and reversible firing of TRPV1(+) neurons, when exposed to alternating magnetic fields. Wireless magneto-thermal stimulation in the ventral tegmental area of mice evoked excitation in subpopulations of neurons in the targeted brain region and in structures receiving excitatory projections. The nanoparticles persisted in the brain for over a month, allowing for chronic stimulation without the need for implants and connectors. To make the approach feasible in humans, researchers will need to design nanoparticles that are very selective in their ability to target specific brain structures and neurons. TRPV1 channels are widely distributed throughout the human brain, so another major challenge is figuring out how to deliver stimulation only to the cells researchers want to target. Moreover in the case of the prefrontal circuits there will be a need for targeting polarization and hyperpolarization, excitatory and inhibitory activity that is relevant to re-establish small-world brain activity (Figure1).

**Sensing-stimulating loop at a nano-brain-pacing scale.**

As any intervention in a dynamic regulatory system, there is a consensus that any brain-pacing intervention should be implemented using a feedback (loop) mechanism, one that couples “sensing” and “acting”. In this case therapeutic intervention is directed by, and synchronized with, the detected disturbance. It is also a consensus that any such brain-machine interface will have to be interactive with the neuronal tissue, thus it will have to be miniaturized to sub-neuronal dimension, and safe enough,
meaning that any interaction with that device is remote and non-invasive (or at most minimally invasive). Thus the technological solution we are searching for is that of nano-technology, the only technology relevant for sub-neuronal dimensions.

Thus we are interested in nano-technology for sensing and stimulating and we also need the technology that will loop them together. Naturally any such technology should be safe regarding cytotoxicity and has to have full bio-compatibility (Raffa et al 2010). With voltage-imaging sensing nano-technology we are looking at imaging of large-scale neural networks with millisecond-scale temporal resolution. Sensing and reporting changes in membrane potential is crucial for understanding voltage-imaging signaling. Quantum dots (Marshall and Schnitzer 2013) are great candidates for voltage-sensitive probes because their physical size is comparable to the thickness of the cell membrane and because their electronic properties make them potentially tunable to the external electromagnetic field. This would require the structure of nanoparticles to be engineered in a way that allows changes in the electric field to be transduced into changes in quantum dot emission. To sense membrane potential changes with maximum efficiency, quantum dots must be in, or very near, the cell membrane, within the highest transmembrane electrical field gradient. Ensuring intramembrane positioning may require specialized, novel coating.

The sensors that detect, collect, register and analyze nano-related voltage-imaging must be technologically non-invasive and minimally demanding for patients. Recently a group from Rogers lab in Illinois (Jang et al 2015) has developed thin, skin-mounted electrophysiological sensors with mechanics precisely matched to the human epidermis. These can be tailored to precisely match the non-linear properties of biological tissues, with application opportunities that range from soft biomedical devices to constructs for tissue engineering. These bio-inspired bio-integrated sensors in the form of thin lightweight stickers should have microelectromechanical systems that both sense voltage-related imaging and also deliver radio-magnetic controlled stimulating energy. At their micromechanical level they should also embed signal-analysis detection translatable to controlled radio-magnetic stimulation, thus closing the loop on sensing-stimulating capabilities.
Nano-brain pacing and serious mental disorders.

The aim is to correct abnormal biased small-world-network organization in the brain. The target of intervention is the prefrontal circuits as these relate to a critical hub of the more general whole-brain network organization. To correct dynamic ongoing disturbances to the small-word-network of the prefrontal cortex a sensing-stimulating apparatus should be mounted in-place. This apparatus device should have a non-invasive remotely controlled technology. 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-worldiness of prefrontal neuronal systems. In response to spotting any altered changes in small-worldiness 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 to the small-word organization is still monitored for additional correction if needed, thus a feedback homeostatic regulatory process is installed.

In all the technology is composed of sensing-stimulating nano-particle devices and a microelectromechanical-equipped sticker on the forehead (figure 2), one that “detects-corrects” small-world organization. Thus, people suffering from serious psychiatric disorders could come 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. Additional delivery to consider for the nanoparticles is via nasal influx, having the patient inhale nanoparticle liquid immersed in the olfactory bulb and then absorbed in the brain going up to the prefrontal cortex.
References


