

Returning to basic principles to develop more effective treatments for central nervous system disorders

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Impact Statement

This work is important because central nervous system (CNS) disorders are a major health burden world-wide, current treatments have limited effect, and huge investments of time and resources have produced very few new treatments. The work advances the field by identifying that a root cause of the limited development of effective treatments for CNS disorders is conceptual rather than technological. It does so by supplying new ideas about how the function of the brain and mind arises from physical matter, what constitutes CNS disease, and the need to align treatment interventions with the nature and structure of functional systems that support cognitive and emotion-related function. It aims to impact the field by making research efforts more productive and identifying as an example a new class of treatments, digital neurotherapies (DNTs), that have the potential to have greater efficacy and fewer side effects because they align with brain structural organization.

Abstract

Development of new treatments for diseases of the central nervous system (CNS) is stalled. Of candidate drugs developed through costly preclinical research, 93% fail clinical trials. Hoped-for improvements in diagnosis or treatment from decades of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) imaging have yet to materialize. To understand what we are doing wrong, I begin with recognition that all aspects of life, including the brain and mind, are physical phenomena consistent with processes described by physicists. Two processes, emergence and entropy, are of particular relevance in complex arrangements of matter that constitute life in general and the brain in particular. The human brain functions through dynamically reconfiguring and hierarchically organized neural functional systems with emergent properties of cognition, emotion, and conscious experience. These systems are shaped and maintained by nentropic environmental input transformed by sensory receptors into neural signals that trigger epigenetic neuroplastic processes. CNS diseases produce clinical disorders by disrupting these systems. As researchers seek appropriate levels of system organization at which to characterize and treat illness, focus has been on medications that impact processes at lower levels or transcranial electric or magnetic stimulation that impact broad contiguous swaths of tissue. Neither align with the brain's neurosystem organization and therefore lack specificity necessary to be effective and to limit side effects. Digital neurotherapies (DNTs), in contrast, align with neurosystem organization and achieve the needed specificity using the same input pathways and neuroplastic processes that created the neural systems

organization to repair it. The omission of DNTs from major systems-based initiatives represents powerful residua of dualist thinking. Interventions based on perceptual and cognitive processes are not thought of as being as physical as drugs or electric or magnetic stimulation through the skull. In fact, they are examples of the most basic processes that create and support life itself.

Keywords: Central nervous system disorders, treatment, entropy, emergence, neurosystems, digital neurotherapy

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Introduction

Development of new treatments for diseases of the central nervous system (CNS) is stalled, even as disorders like depression and dementia constitute an increasing share of the burden of disease world-wide and the international research community spends many billions of dollars and thousands of research careers applying powerful new technologies to the problem. A recent Director of the US NIMH said, "There are very few new molecular entities, very few novel ideas, and almost nothing that gives any hope for a transformation in the treatment of mental illness."¹ Of candidate new drugs,

each developed in preclinical animal studies at a cost of approximately \$500 million,² 93% fail human clinical trials.³ Of those that are approved, nearly all are only partially effective and have problematic side effects. Something is wrong about the ways we are thinking about and approaching the problem. This article steps back to basic principles and processes to suggest new ways to understand and treat CNS disorders.

All aspects of life – including the brain, mind, and their linked functionalities – are phenomena of the physical world consistent with and shaped by laws and processes described by physicists. Two of these processes, emergence and entropy,

are of particular relevance in the highly complex arrangements of matter that constitute life in general and the brain in particular. Emergence is evident, for example, in the properties of water absent in the hydrogen and oxygen atoms of which it is constituted. Entropy is the grinding process of reducing more complex organizations to simpler ones, eliminating emergent properties. Life represents temporary victories of emergence, and in complex organisms brain function is most fundamentally directed toward meeting this existential challenge. General systems theory describes processes and principles in this competition. The goal of this review is to ground the development of next generation treatments for CNS disorders in these basic principles.

Emergence

Functions made possible by combinations of basic units into multicomponent structures are “emergent properties.” Astrophysical measurements show that the young universe was homogeneous, with matter apparent only in the forms of hydrogen and helium atoms and temperature the same everywhere within 1/100th of a degree.⁴ But when random motion produced clusters of atoms close enough to one another, gravity pulled them closer, and over billions of years a dizzying array of structures emerged as randomly generated clumps of matter varying in mass, gravity, and proximity altered one another’s movement and structure. Stars were formed in which extreme pressure and heat altered and combined the hydrogen and helium atoms of which the stars were constituted to produce new elements; an example of downward causality through the hierarchical organization of matter that much later made life possible. Water is made in part of one of these new elements.

Conditions on earth created many chemically stable combinations of elements that proved essential for life; amino acids of which proteins are made and chemical bases of which RNA and DNA are made. Living single-cell organisms evolved with cell walls defining an interior space including millions of large and small molecules interacting in controlled chemical reactions that maintained internal structures. The cells could reproduce and actively seek and absorb energy from external sources. Over billions more years, the single-cell organisms formed multicellular life forms with still more emergent properties. The soil-dwelling amoebae *Dictyostelium discoideum*, for example, exist as unicellular organisms that when food supplies are low combine into 100,000 cell, 2–4 mm long organisms with differentiated body parts and able to move large distances.

Each of the estimated 86 billion neuronal cells in the human brain is directly connected on average to 1000 others. Complexity and functional organization are built beginning with local ensembles of interconnected cells, each with distinctive anatomic and physiological features, like letters in an alphabet. These ensembles are integrated into ever wider and changing interconnected systems in which cognitive, emotional, and behavioral functions emerge. The same structural units contribute to different functions when arranged differently (e.g. tea, eat, and ate). Functional systems can be incorporated into larger systems, giving up their original function as they contribute to the new function (e.g. team,

meat, and mate). And as in all other instances of emergence, you cannot predict the nature of the emergent function by knowledge only of the parts. If you knew the number of times each letter was used in this paper, you would not know what words were used. If you had a list of all the words in the paper, you would not know the ideas in the paper. In order to create and express simple ideas, words are combined into sentences, and so on.

Entropy

When a warm object is put in contact with a colder one, the warmer one invariably becomes cooler and the cooler one warmer until the temperature is uniform across them. There is a loss of the orderliness associated with differentiation and structure, and an increase in the sameness associated with randomness. Entropy refers to the degree of random sameness. For both statistical and energy reasons, entropy is thought to continuously increase toward more sameness unless energy is provided to create differentiation. At any moment, for all 100 randomly moving gas molecules to be on the left side of a container is like getting 100 “heads” in a row when flipping a coin in that instant, 0.1 with 29 zeros after the decimal point. It is much more likely that between 45 and 55 are on each side. With a starting point of imbalance, the system will move to balance as more molecules will randomly move to the side with fewer than the reverse just because there are more on that side to begin with. Local asymmetries of distributions can be achieved by expending energy, as in magnetic resonance imaging (MRI) where application of a magnetic field produces a distribution bias in orientation of the protons in hydrogen atoms in water molecules. Entropic rebalancing is rapid after removal of the energy-dependent perturbation. But the energy generating the temporary imbalance has been expended and translated into heat energy contributing to an increase in entropy outside of the local MRI field. Many physicists consider the universe to be an isolated system with a fixed amount of energy. Energy like that used in MRI, or by living things, is drawn from breaking down and releasing energy stored in molecular structures. Inherent inefficiencies in these energy-related decreases in entropy in local systems add to the heat energy that speeds the increase in entropy in the universe as a whole. Codified in the first and second laws of thermodynamics, these notions are widely adopted and of demonstrated value in design of mechanical systems and understanding gases. However, the theory remains incomplete as, for example, with regard to how to deal with the nature and effects of gravity.

Life itself has been seen as posing additional challenges to the laws of thermodynamics. In “What is Life?,” the Nobel Prize winning physicist Erwin Schrodinger wrote,

we know all atoms to perform all the time a completely disorderly heat motion, which, so to speak, opposes itself to their orderly behavior . . . only in the cooperation of an enormously large number of atoms do statistical laws begin to operate and control the behavior of these *assemblies* with an accuracy increasing as the number of atoms involved increases . . .

It is in relation to the statistical point of view that the structure of the vital parts of living organisms differs so entirely from that of any piece of matter we physicists and chemists have ever handled in our laboratories or mentally at our writing desks . . . (moreover) what we call thought (1) is itself an orderly thing and (2) can only be applied to material, i.e., to perceptions or experiences, which have a certain degree of orderliness.⁵

Schrodinger added that "any other kind of lawfulness and orderliness (non-statistical) is being perpetually disturbed and made inoperative by the unceasing heat motion of the atoms."⁵ In related expressions of wonder and uncertainty, the Harvard and IBM physicist Leon Brillouin wrote in 1946: a living organism,

has special properties which enable it to resist destruction, to heal its wounds, and to cure occasional sickness. This is very strange behavior, and nothing similar can be observed about inert matter . . . is there not, in living organisms, some power that prevents the action of the second principle (of thermodynamics)?⁶

He went on,

The adult individual is a most extraordinary example of a chemical system in unstable equilibrium. The system is unstable, undoubtedly, since it represents a very elaborate organization, a most improbable structure (hence a system with a very low entropy . . .). (which is) further shown when death occurs . . .⁶

General systems theory developed to describe features of non-statistical orderliness in both mechanical and biological processes, including brain function and thought, based on processes other than statistical. In systems models, order and stability are themselves emergent.

General systems theory and cybernetics

"The fundamental problem of today is that of organized complexity"⁷ wrote Ludwig von Bertalanffy, the developer of general systems theory in the first half of the 20th century:

It is necessary to study not only parts and processes in isolation, but also to solve the decisive problems found in the organization and order unifying them, resulting from dynamic interaction of parts and making the behavior of parts different when studied in isolation or within the whole;⁷ in other words, to describe the rules and processes of interactions that lead to emergence and stability in entities with multiple interacting components.

Norbert Weiner, Harvard mathematics prodigy and founder of Cybernetics, described how as an organization becomes more complex it is increasingly the patterns of organization that characterize it, and more and more energy is needed to maintain the organization against entropy and disorganization. "We are not stuff that abides, but patterns that perpetuate themselves,"⁸ he wrote, and, in an important

additional step, "a pattern is a message, and may be transmitted as a message."⁸

The models and rules of interaction were applied to machines in which feedback loops dynamically adjusted states and interactions of components to achieve common fixed outcomes through variable means. The English psychiatrist W.R. Ashby in 1948 built mobile machines called "Homeostats" from four interconnected Royal Air Force bomb control units in order to model brain function. Feedback loops among functional components enabled a Homeostat to automatically adapt its configuration to maintain function despite external perturbations. Ashby's Homeostats demonstrated general principles relevant to living things and the brain: (1) "In a large polystable system the whole reaction will be based on activations that are both numerous and widely scattered . . . a reaction based on numerous and widely scattered elements will tend to have more immunity to localized injury than one whose elements are few and compact."⁹ (2) In the Homeostat, as in living things, all units have a "physiological" range of acceptable states. If other units perturb them outside this range, they act so as to reduce those effects. This then results in changes in multiple other components and systems within the "organism" to which the unit is connected and of which it is part. (3) When there is too much interconnection within the system, these interunit perturbations reverberate and delay new equilibrium. (4) Units that remain stable through a range of inputs before making discrete changes create "step functions" valuable in balancing adaptability and stability. (5) Two internal components can be functionally connected by each registering the action of the other on the environment even when they are not connected within the Homeostat. (6) When the Homeostat is connected to the environment through sensors and effectors, it becomes part of a much larger system as it can be impacted by all components of the environment that impact the environmental factors that affect it.⁹ Homeostats could achieve states of inactivity following external perturbation following a variety of internal dynamic routes and settling into a variety of equilibria unknown even to its designer. A brain with only 1000 ensembles of interconnected neurons would have $10^{300,000}$ possible states. Ashby concludes in *Design for a Brain* (1952) that,

the complexity of actual organisms . . . is greater by many orders of size than that considered here . . . in the real the same principles work in a complexity that is of an altogether higher order, one that may well prove to be forever beyond the *detailed* comprehension of the human scientist.⁹

Entropy, systems theory, living things, and human brain functional organization

The second law of thermodynamics has been reconciled with the phenomena of life through the distinction among open, closed, and isolated systems. Living things are open systems that exchange matter and energy with their environments. This is most commonly discussed in terms of breaking the bonds of ingested complex molecules (food) to make energy available to counter entropy and maintain internal order and structure. Closed systems can exchange energy but

not matter with their environments, as an ice cube absorbs energy from the sun or heater. Isolated systems exchange neither matter nor energy with their environments and only in isolated systems do the "Laws" of thermodynamics fully apply. The only system that scientists suggest might actually be an isolated system is the Universe itself. The significance of the second law for understanding function and dysfunction of the brain and other organic entities is appreciation of the challenge in creating and maintaining the organization and structures on which their function depends.

Schrodinger and Brillouin used the terms negative entropy or negentropy for environmental input that countered entropy to maintain internal organization in open systems including life forms. While abstract and multipotential terms, they have generally been used to refer to importing energy, and in animals in reference to food from which energy in chemical bonds is extracted to fuel structure-maintaining processes in the body and brain, including obtaining more food. The information and structure already exist in the organism; energy and raw materials are imported. However, two additional types of negentropic processes are of particular relevance in living systems. One are enzymes and other aspects of intracellular synthetic processes that reduce the energy needed to build and maintain structure,¹⁰ sometimes called Maxwell's Demons after a hypothetical device Maxwell suggested that could reduce entropy and even violate the second law.¹¹ Living things have evolved to resist entropic disorder with lower and lower energy expenditure, demonstrating the power of this selective force in Darwinian evolution. The other set of processes are those that directly import structure or organization from the environment. While evident in simple life forms that construct an internal representation of features of their environments, directly importing structure or organization from the environment has evolved to be a dominant mode of shaping both the structure and function of the human brain. It is a distinguishing feature of human beings and their brains and culture. In this case, the raw materials exist in the brain and it is the information and structure that are imported.

The information in a signal depends both on qualities of the sender and receiver. Television broadcast and cell phone signals are each only intelligible to appropriate receiving units. The remarkable thing about these processes in humans and many other animals is that the structural and functional organization of the receiving systems themselves are altered by the signals they receive. In the absence of stimulation, cells along sensory input pathways from receptor to cortex are smaller, misshapen, and die in increased numbers.¹² When input from the eyes was surgically rerouted to what is naturally auditory cortex in new born ferrets, the ferrets could see, and the cells in the auditory cortex organized themselves into retinal maps with ocular dominance columns rather than assuming the tonotopic cellular architecture of auditory cortex.¹³ By similar processes, visual cortex in humans born blind becomes an auditory processing area,¹⁴ and blind adults can learn to "see" through somatosensory input when cameras mounted on eye glasses send electrical signals to a small metal grid placed on their tongues.¹⁵ The structural and functional organization of neural systems necessary for our perception of the world, for the languages we speak

and understand, and for the categories and concepts we use to think are negentropic organizations imported from the environment. In this regard, the absorption of negentropy by the eyes and ears differs fundamentally from that by the stomach. The stomach breaks down the structures it imports in order to extract energy and raw materials to support new structures created by the organism. The eyes and ears maintain the organization of environmental input and the brain shapes itself to that organization.

But what is still more remarkable in the negentropic exchanges with the environment is that humans uniquely alter the environment that shapes their brains. The dynamic cross-generational process thus created is called cultural evolution and it has altered human brain-based capabilities over the past 40,000 years much more quickly and through different mechanisms than has Darwinian biological evolution.^{12,16} As Schrodinger elegantly argued, and Watson and Crick soon after discovered, in order for life forms to reproduce reliably in the face of entropic threat, the relatively small number of atoms in the genetic blue print must be organized in highly stable molecular arrangements that can also be copied with minimal entropic disruption. Stability was the goal. Darwin then showed how in the context of the species/environment system, entropic irregularities in the reproduction of the genetic blue print created population variability that was turned to life's advantage in adapting itself to chaotic change in the environment. Cultural evolution creates a much higher degree of population variability and uses new methods of storage and transmission to ensure transgenerational reproducibility of highly distinctive features of brain structure and function.

Of genes that had been unchanged in over 80 million years in the evolution of chimpanzees from rodents, and then changed from chimpanzees to humans, a large majority served to turn other genes on and off.¹⁷⁻¹⁹ While the distinction created by Darwinian evolution between humans and chimpanzees is manifest in a 1.3% difference in genes, the differences in gene expression in the brain, largely environment-induced, are an order of magnitude greater.^{19,20} The structural and functional organization that constitute the human brain's hierarchical systems organization and associated emergent properties are negentropic imports from the environment that are made possible by regulation of gene expression by patterns of light and sound waves reaching the eyes and ears from environmental sources. The sources of these inputs are increasingly human-made, creating a life form that uses its environment to develop, stabilize, and reproduce highly complex internal organizational states across generations. One might even say that in works of art and literature, and accomplishments in science, law, and ethics, the complex organization of the individuals who produce them survives their physical demise, a marker that heretofore had proved ultimate susceptibility of biological organization to entropy. From birch bark, turtle shells and papyrus to paper bound between hard covers, reproduced in millions of copies and stored in fire-secure and humidity controlled libraries, to current electronic storage devices automatically reproduced and consisting of material closer and closer to the most basic elements of matter and even capitalizing on their random and quantum features, the

order created by humans persists with less and less energy cost and for longer and longer times. Only if the species as a whole were to die, would the external structures created by human beings cease to be meaningful, complex structures.

Cultural evolution creates population variability that is greater in extent and with more incremental differences between individuals because of variation among individuals in brain-shaping environmental input. Psychologists and psychiatrists have long recognized processes by which repeated interactions with the more fully developed brain systems of adults shape those in children. Lev Vygotsky wrote that

“In the early stages of development the complex psychological function *was shared between two persons,*” but as the child develops,

The function which hitherto was shared between two people now becomes a method of *internal organization.*^{21,22}

Freud described identification as

the assimilation of one ego to another one, as a result of which the first ego behaves like the second in certain respects, imitates it and in a sense takes it up into itself.²³

Greenson stated that

“identification with an object (person) means that . . . a transformation of the self has occurred . . . one can observe behavior, attitudes, feelings, posture, etc., which are now identical to those characteristics belonging to the external object.”²⁴

In recent human history, input from sources outside of small family and kindred groups has markedly increased, including in public schools, through books, works of art, radio and television, the Internet and transformation of the physical environment – all creating a range of small-to-large differences in brain-shaping experiences across the population.

Cultural evolution and biological evolution also differ in the way information is stored so as to provide continuing influence on brain organization. In biological evolution, information is stored in the largely stable base sequence of DNA molecules. In cultural evolution, the information is stored in the minds and behavior of adult members of society; in cultural artifacts such as books, architecture, and works of art, and in social institutions including laws, customs, and schools. In biological evolution, the information is stored in complete and nearly identical form in each individual. In cultural evolution, the information is distributed in different and incomplete form across many individuals and artifacts. Energy efficiency in storage and distribution of information on mass scale, and the relative ease and systematic nature of modification of that information also change the energy costs of resisting entropic disorganization.

Approaching human brain pathology and treatment from these perspectives

A.R. Luria’s work with Russian soldiers who had suffered localized brain injuries demonstrated that human brain

function is based on emergent functions resulting from integrating activity of multiple anatomic areas distributed across the brain in dynamically reconfiguring systems. His work refuted 19th century phrenology that divided the brain into discrete anatomic regions each dedicated to a specific cognitive or moral function. Luria observed,

that a disturbance of a particular complex function does not in fact arise in association [only] with a narrowly circumscribed lesion of one part of the cortex, but is observed as a rule . . . with lesions of several different parts of the brain. Disorders of writing . . . may appear in lesions of temporal, post central, premotor and occipitoparietal regions . . . and so on.²²

He concluded that the regions were part of a system necessary for the behavior. Moreover, “a lesion of a narrowly circumscribed area of the cortex practically never leads to the loss of any single isolated mental function, but always to the disturbance of a large group of mental processes . . .”²² This led him to conclude that each region contributes to multiple behaviors, like letters in alphabet. He further noted that the same function could be carried out by a different collection of neuronal modules in different individuals, or in the same individual at different times (like synonyms). He wrote,

mental functions, as complex functional systems, cannot be localized in narrow zones of the cortex or in isolated cell groups, but must be organized in systems of concertedly working zones, each of which performs its role in a complex functional system, and which may be located in far distant areas of the brain.²²

Since different complex functional systems are constituted by integration of different sets of specific “working zones,” lesions in different parts of the brain lead to different behavioral deficits and associated clinical syndromes. But the fact that a lesion in a specific place disrupts a function does not mean that that place can constitute the function, that it is specialized for the overall function or that the function resides therein; the fact that a broken starter motor prevents a car from driving does not mean that the driving function is localized in the starter motor.

Early brain imaging studies in animals provided further confirmation that even simple functions are based on integration of activity in large numbers of neurons spread across the brain. For example, a 1986 PET study²⁵ in cats found that after training, five million cells distributed throughout the brain showed learned responses to simple geometric forms. A more recent study found that water-predicting olfactory cues modulated activity in over one-half of 24,000 neurons in 34 brain regions when mice were thirsty. This global representation of the thirst motivation state gated brain-wide response to sensory information and related behavior.²⁶ Turning to the much more complex human brain, data from 241 patients with focal brain damage revealed widely distributed areas and white matter tracks associated with a general intelligence factor (“g”) that shares performance variance across multiple tasks (Figure 1).²⁷ Data from 120 functional imaging studies during semantic processing revealed 1135 activation foci.²⁸ Even using subtraction methods to “isolate” semantic

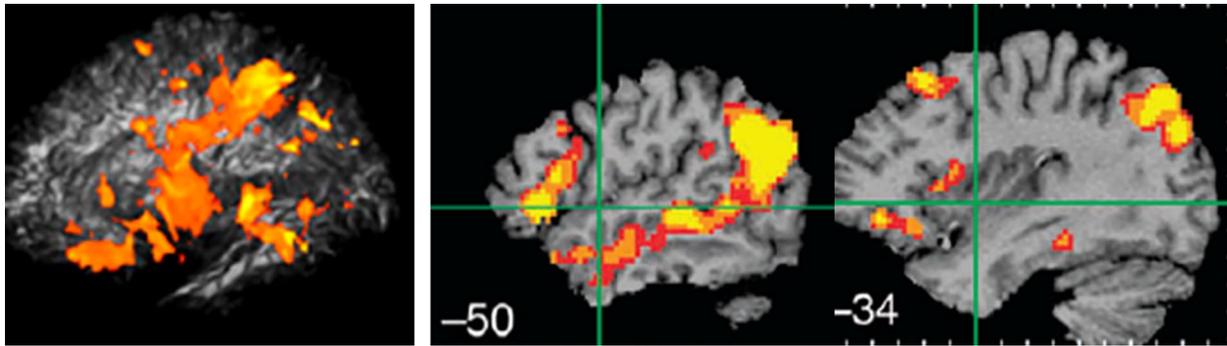


Figure 1. Activation associated with the general intelligence factor “ g ”²⁷ (left) and semantic processing. (A color version of this figure is available in the online journal.)²⁸

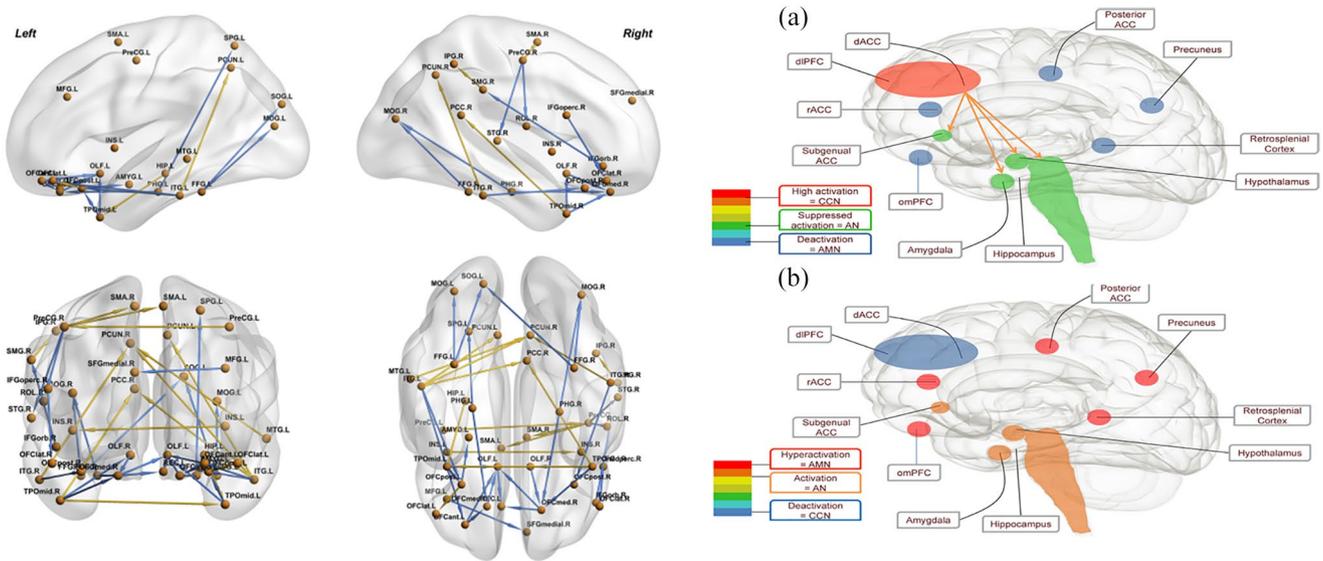


Figure 2. Depression: resting state connectivity abnormalities³⁰ and neurosystems model.³¹ (a) Healthy controls and (b) depressed individuals.

processing (e.g. subtraction of activation during phonological processing from activation during semantic processing of the same stimuli), activation was widespread (Figure 1).²⁸ And when people actually do read for semantic meaning, phonological processing is often part of the process.

Not surprisingly then, multiple studies have shown neurosystems dysfunctions distributed across multiple brain regions in psychiatric and other CNS disorders. A meta-analysis of MRI studies in Major Depressive Disorder, for example, showed gray matter structural abnormalities in the anterior cingulate cortex, hippocampus, middle frontal gyrus, orbitofrontal gyrus, inferior temporal gyrus, insula, thalamus; white matter abnormalities in prefrontal regions, right solitary fasciculus, corpus callosum, inferior fronto-occipital fasciculus, left superior longitudinal fasciculus, and anterior cingulate-limbic areas; and resting state fMRI abnormalities in postcingulate cortex, medial prefrontal cortex (mPFC), precuneus, temporo-parietal gyri, dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), amygdala, subgenual and pregenual cingulate, dorsal mPFC, and cerebellum.²⁹ The authors concluded: “MDD is a disorder with dysfunctional neural networks in numerous areas rather than a disease of a single impaired region.”²⁹ Figure 2 shows the resting state connectivity links that are stronger

(yellow) and weaker (blue) in 336 patients with MDD compared to 350 healthy controls³⁰ and a widely used model of depression highlighting depression-related alterations in activation balances among interconnected brain regions.³¹ As Mayberg concluded: “depression is unlikely a disease of a single gene, brain region, or neurotransmitter system. Rather, the syndrome is conceptualized as a systems disorder . . .”³²

Neurosystem abnormalities have been similarly documented in essentially all CNS disorders.^{33–37} Even when pathology has been identified at more microlevels, pathophysiological elaboration and symptom generation are usually associated with broad and higher level systems dysfunctions that can predict treatment response.^{38–49} All diseases of the CNS produce clinical symptoms and behavioral limitations by disrupting the constitution, function, and/or interaction of neural functional systems. The brain responds to illness through system-level reconfigurations aimed at compensatory restoration of function. Clinical illness results when these efforts at compensation fail, and symptoms result from both illness and compensation. Loss of negentropic structure and information⁴¹ are fundamental.

While the cognitive and other functions that emerge from a functional system may be seen as localized in that system, the wide variability across individuals in the regions

constituting systems associated with the same cognitive function, for example, right hemisphere systems supporting language when the left hemisphere is removed early in life for otherwise intractable seizures, and the variability within individuals doing the same action under different situations, for example, a baseball player throwing a ball when in different postures and movement trajectories as a result of how the ball was approached and picked up, would constitute a “family” of different multipart locations for the same function. And since individual anatomic components participate in multiple functional systems, a nosology of cognitive and behavioral functions mapped onto the brain would show multiple different cognitions and behaviors overlapping at many locations. Still, it might be useful to represent the location of cognitive or behavioral functions as a range of possible neural system configurations with limits and probability weightings, and illness resulting when configurations fall outside the range.

How can you treat neurosystems dysfunctions?

Psychiatry has yet to determine the appropriate levels of system organization at which to characterize illness and direct treatment. Disease processes can originate and operate at any level of hierarchical organization and effect function at higher and lower levels to promote entropic disarray. For example, phenylketonuria results from a genetic variant that causes low levels of the enzyme that metabolizes an amino acid present in many foods, leading to levels of phenylalanine toxic for development and function of higher level systems, seizures, widespread intellectual limitations, and disorders of emotion result. Efforts are being made to intervene with gene therapy, but the treatment for the last 70 years has been at the individual/environment behavior interface – alterations of diet. In the case of depression, there is evidence for proximal and perhaps fundamental causative factors originating in the psychosocial environment and operating on the symbolic level, including loss of jobs, loved ones, homes, and status. Compromise of uniquely human prefrontal cortical systems and associated cognitive functions are prominent features of the illness, predict relapse, and are associated with lower system dysfunctions including emotion and cortisol dysregulation that sustain exacerbating cycles of higher and lower system dysfunctions. Other organ systems are also impacted, increasing the incidence of cancer and cardiovascular disease. Excessive focus on one or another level of organization has led to psychiatry being called “brainless” at some times and “mindless” at others.^{42,43} Stress diathesis and biopsychosocial models have been adopted as more wholistic approaches. Although not yet widely applied in psychiatric research, Shannon’s information theory provides quantitative models of relations among information, entropy, and communication widely used in other disciplines and potentially of high value for measuring effects of CNS disease within and across levels of organization.⁴¹

Depression is also of interest because pharmacotherapy and psychotherapy, treatments aimed at different levels of neurosystem organization, are both effective. Numerous fMRI studies have shown changes in function and interconnectivity throughout the brain following pharmacotherapy,

both while processing emotion-related stimuli and at rest (see meta-analyses and reviews).^{44,45} Some of the changes normalize identified pretreatment abnormalities and some correlate with the degree of symptom improvement. They demonstrate that widespread neurosystem re-organization is associated with recovery. However, that attribution of the changes to pharmacotherapy is problematic because of high response to placebo in drug studies. Meta-analyses including data from thousands of patients found 53.5% response to active medication versus 37.7% response to placebo.⁴⁶ A recent review of clinical studies concluded: “If 10 patients with moderate to severe depression take an antidepressant for two months, five (50%) will report being “better” but in four of them the response will not be because of the drug.”⁴⁷ fMRI studies of drug effects uniformly lack control groups of patients on placebo, making it impossible to know how many of the observed changes should be attributed to placebo-associated recovery. Moreover, meta-analysis of changes in brain activation following ingestion of antidepressant medication or placebo in clinical and non-clinical groups (including data from one unpublished study in depressed individuals) could not find drug effects.⁴⁸ Although limited sensitivity of current imaging methods, especially when combined across subjects and studies, must account for the inability to differentiate drug from placebo, the same methods were able to distinguish whether people were looking at pictures of other people who were happy or fearful. Patterns of light waves coming into the eye from features of the external human environment to which we and our nervous systems are linked produced bigger changes in brain activation patterns than did putting a chemical designed to alter brain function into the mouth that then circulated through the blood into the brain. And the robust placebo effect itself is mediated by symbolic higher level systems.

Multiple studies have also shown changes in brain activity and connectivity patterns in depression following cognitive behavioral therapies (CBTs). Several of these included groups of depressed patients in control conditions minimizing contributions of spontaneous recovery and placebo effects. Changes following treatment and associations with the degree of symptom reduction have been reported, for examples, in connectivity between the posterior cingulate (PCC) and inferior temporal and inferior frontal gyri;⁴⁹ connectivity between ACC and mPFC;⁵⁰ activity in subgenual anterior cingulate (sgACC), mPFC, and sublingual areas;⁵¹ and both within the ventral attention system (regions in the temporal, parietal, and frontal lobes) and between this network and others.⁵² A study comparing CBT and pharmacotherapy found both associated with decreased activation in amygdala and insula during face recognition and emotion regulation tasks, with the degree of change correlated with the degree of symptom reduction independent of the type of treatment.⁵³ A comparison of CBT and medication to medication alone found greater decreases in spontaneous sgACC activity with combined treatment, again with the degree of decrease correlated with decrease in symptoms.⁵⁴ The clinical response to CBT and associated neurosystem changes provide concrete examples of how specific types of interpersonal interactions mediated by patterns of sound waves impacting the brain through auditory afferents and patterns



Figure 3. Drug therapies digital neurotherapies.

of light waves impacting the brain through photoreceptors in the eye can treat CNS disorders. These are the same neigentropic pathways of existential importance.

The NIH BRAIN Initiative⁵⁵ and NIMH Non-invasive Neuromodulation Experimental Therapeutics Unit⁵⁶ are important parts of growing efforts to develop and compare assessment and treatment tools aimed at different levels of human brain organization:

The BRAIN Initiative is inspired to understand how our brains make us uniquely human and distinct individuals . . . individual neuroscientists have chosen to work at specific spatial scales, ranging from the nanometer or even atomic scale of ion channels and transmitter receptors, to the intracellular level of molecular pathways, to the intercellular level of synaptic activity an its modulation, or to the systems level of transmission across the brain . . . spanning these scales is crucial to explain how the human brain actually works.⁵⁵

The initiative's seven pillars range from studying different brain cell types to developing circuit maps in scale from synapses to whole brain. The aim is developing invasive and non-invasive tools to interrogate and modulate circuits to create patterns of behavior that cause complex behaviors. "Advancing understanding of what gives rise to human characteristics and experiences (language, thoughts, and actions)"⁵⁵ is a critical component of the BRAIN initiative. The Non-invasive Neuromodulation unit employs "strategies for enhancing the precision and efficacy of neuromodulatory techniques" with current "focus on circuits at the meso- and macroscale" but anticipates next generation devices "to enable circuit manipulation at the microscale."⁵⁶ The "experimental therapeutics framework" is central to the effort – identify a neurosystems abnormality, demonstrate ability to measure and impact it, and show the degree of impact is associated with clinical impact.⁵⁶

DNTs are missing from these two important initiatives. DNT is a set of device-based neuromodulatory interventions that send highly specific patterns of light waves to the eyes and sound waves to the ears to produce activity-dependent enhancement of targeted, dysfunctional neurosystems. These are the processes and pathways that provided the neigentropic environmental input that created the neurosystems that make possible and distinguish the human brain,

and are compromised in CNS disorders. DNTs are neurosystem modulators directed at important levels of organization with unique sensitivity and specificity to target and shape those systems. The inclination to modulate neural systems by sending electrical current or magnetic fields through the skull rather than by light and sound waves through the eyes and ears can only be understood as residual dualism that sees the former and not the latter as related to the brain.

DNT

When a person walks around a corner and sees either a small delivery van or a large bear, the distinction is made on the basis of differences in light waves that reflect off the truck or bear and enter the eye. The light waves generate electrical signals in the retina that propagate along afferent pathways and activate very different neural systems based on whether it is a van or a bear. By controlling the stimuli sent to the eyes or ears, and the information processing then required, DNT creates specific patterns of neuronal firing and neural system activation. DNTs use highly repetitive and specific visual and auditory stimulation and information processing demands to repetitively activate neurofunctional systems compromised by disease. They harness the brain's neuroplastic potential to produce activity-dependent enhancement of the targeted systems with associated changes in connectivity (Figure 3). Like CBT, they use eye and ear input channels to engage and modify neurosystems at high levels of organization unique to the human brain. However, DNT targets system dysfunctions first identified in groups of patients by brain imaging and then individualized by functional probes, automatically adjusts stimulation and processing demands to maintain balance of challenge and success in each individual optimal to promote neuroplastic change, automatically reassesses and updates targets over the course of treatment, and does all over the Internet at low cost. Easy data capture supports rapid low cost cycles of evaluation and improvement of the intervention. DNT is just as physical an intervention as are medications that are ingested by mouth and distributed throughout the brain through the blood (Figure 3).

Schizophrenia is a CNS disorder for which medications are a mainstay of treatment but are largely ineffective in addressing cognitive deficits which limit function and quality of life. Meta-analyses of studies including over 2000 patients demonstrate that adding DNT to pharmacotherapy

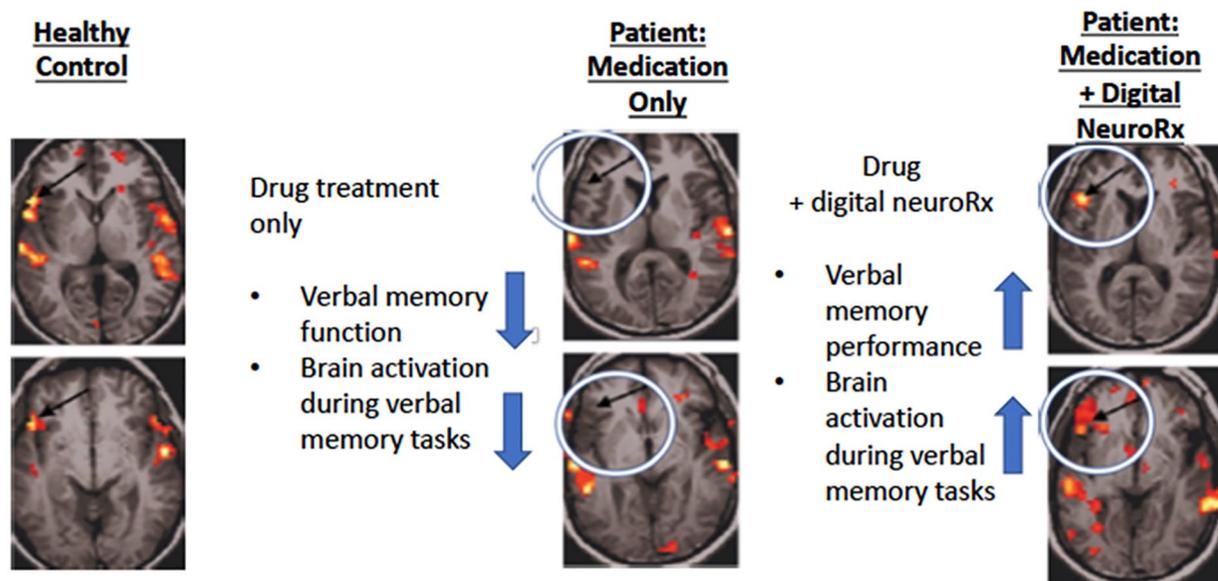


Figure 4. Working memory deficits and associated failure of task-related brain activation in people with schizophrenia receiving medication are improved when digital neurotherapy is added. (A color version of this figure is available in the online journal.)⁶²

(often called computerized cognitive remediation) improves sustained attention, speed of information processing, working memory, verbal learning, reasoning, and social cognition.^{57–59} Effects are durable at six- and twelve-month follow-up,^{58,60,61} and show far transfer to improved community function^{57,58} with, for example, improved employment outcomes.⁶¹ MRI before and after DNTs has demonstrated normalization of task-related brain activation in multiple areas of the dorsolateral prefrontal cortex, frontopolar cortex, inferior parietal lobe, and anterior cingulate cortex^{62–64} (e.g. Figure 4), increased connectivity between the thalamus and both the middle frontal gyrus and anterior cingulate⁶⁵ and increased volume of the right hippocampus.⁶⁶ In most studies, the degree of brain imaging changes significantly correlated with the degree of improvement in cognition.

In attention deficit hyperactivity disorder (ADHD), DNT offers an alternative to medication with similar benefit.⁶⁷ Consistent with the experimental therapeutics approach highlighted in the NIH device-based neuromodulation initiative, symptom reduction was predicted by the degree to which targeted cognitive functions improved. Changes in electroencephalogram (EEG) evoked-responses⁶⁸ and fMRI⁶⁹ have been reported following the same intervention.

In geriatric depression, addition of DNT to pharmacotherapy led to rapid recovery of patients who had completely failed to respond to two or three months of supervised medication.⁷⁰ The DNT was designed to target an executive cognitive dysfunction and associated brain structure and connectivity abnormalities previously associated with failure of pharmacotherapy. Meta-analysis of nine older and generally small-sample randomized controlled trials showed reduction of symptoms and improvement in both cognition and daily function with DNT,⁷¹ with similar results again found in a subsequent study.⁷²

Studies in patients with Multiple Sclerosis demonstrate effectiveness of DNT where basic neuroanatomic pathology has been identified. Meta-analysis of randomized controlled

trials including 982 patients found consistent improvement in attention/processing speed, executive functions, and verbal and visuospatial memory,⁷³ including increases in working memory-related activation in prefrontal cortex and temporo-parietal regions (Figure 5).⁷⁴ Additional studies in Multiple Sclerosis found improvements in cognition and reductions in depression, fatigue, psychosocial function, and quality of life,^{75,76} with improvements maintained at six-month follow-up.⁷⁶

Conclusions

Creation and maintenance of structure in the face of entropic challenges are the *sine qua non* of all living entities. From early in evolution, negentropic imports from the environment have been essential in these processes, and they play a fundamental role in creating and maintaining the anatomic and functional organization of the human brain. “We are not stuff that abides, but patterns that perpetuate themselves.”⁷⁸ Input channels originating in the eyes and ears have evolved to translate structure from light and sound waves into neuronal activity that through epigenetic and neuroplastic processes create the immensely complex functional and structural organization of the human brain. Brain functions of individuals raised with major restrictions in this input – whether kept in isolation in locked rooms or left as infants in understaffed orphanages – are profoundly compromised. Input from these channels is also necessary to maintain structure and function throughout life. Individuals who volunteer for relaxation in sensory isolation chambers soon seek ways to stimulate themselves, those in quiet rooms for extended periods choose to listen to meaningless reports of long lists of stock prices, and those in solitary confinement have high risk of going mad.

Illness can originate at any level of brain organization with impact upon function at both higher and lower levels of organization. Clinical disease is usually experienced and

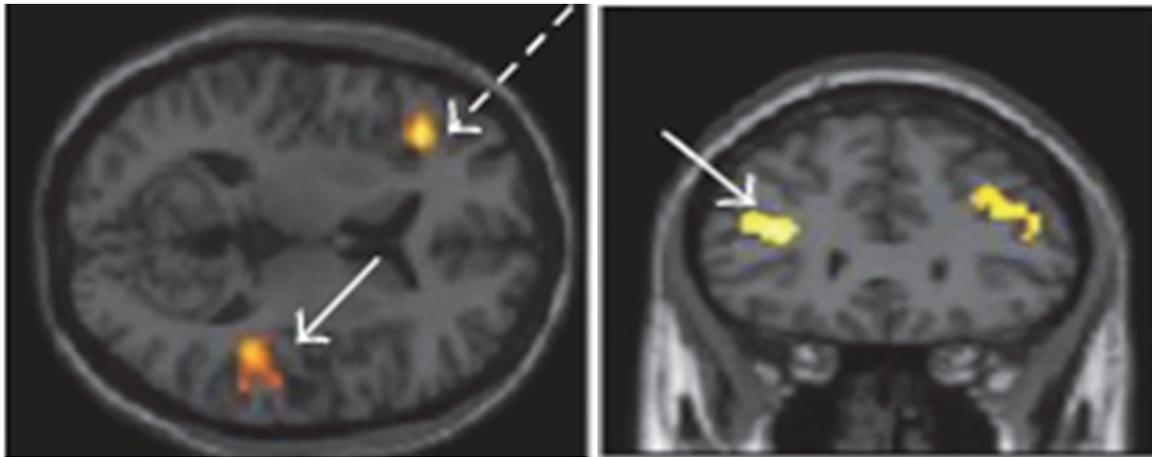


Figure 5. Greater activation on fMRI during n-back task in patients with multiple sclerosis at 12 weeks follow-up after 6 weeks of digital neurotherapy intervention compared to control group. On axial slice (left), solid arrow points to right temporo-parietal activations, and dashed arrow points to left prefrontal region. On coronal slice (right), arrow points to right prefrontal activation. (A color version of this figure is available in the online journal.)⁷⁴

defined as dysfunction of higher level systems that support cognition, mood, and emotional responsivity, whether from pathological processes originating at those levels or from the upward effects of pathology at lower levels. Intervention can also be aimed at any level. Psychiatry is currently confronting the failed promises of decades of pharmacologic research and new research tools to advance treatment. In the context of huge investment in new drug development based on highly sophisticated animal studies, the Director of the NIH asked “what about the prefrontal cortex, a complex amalgam of regions in humans that clearly plays a crucial role in psychiatric dysfunction, yet is ridiculously simplified and comparatively miniscule in mice?”⁷⁷ He further noted “the lack of specificity in available somatic treatments, be they drugs that bind widely distributed targets or stimulation-based therapies that at best target large swaths of brain tissue,” and referred to “pie-in-the-sky dreams” of being able to manipulate neural systems with higher specificity.⁷⁷ DNT has the requisite specificity because it uses the physical highways to the brain through the eyes and ears that have evolved to create the highly differentiated neural functional systems in the first place. Despite this, DNT is not considered in the NIH Brain Initiative or the NIMH neuromodulation device initiative; omissions likely representing powerful residua of dualist thinking that interventions based on perceptual and cognitive processes are not as physical as drugs or electric or magnetic stimulation through the skull. DNT holds promise to provide much-needed next generation treatments. It deserves a seat at the table – and perhaps at the head.

AUTHORS' CONTRIBUTIONS

B.E.W. reviewed the literature, developed the ideas, and did all the writing for this paper.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Professor Wexler and Yale University hold equity in the Yale Start-Up company C8Sciences which sells and supports use of Digital Neurotherapy interventions based

on Professor Wexler's research at Yale. If C8Sciences becomes profitable, Professor Wexler and Yale University could benefit financially.

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