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Brain "Globalopathies" cause mental disorders

Abraham Peled *

Sha'ar Menashe Mental Health Center, Hadera, Israel
Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

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ABSTRACT

"Consciousness" "mood," "identity" and "personality" are all emergent properties from whole-brain organizations; these are typically disturbed in psychiatric disorders. This work proposes that the underlying etiopathology of mental disorders originates from disturbances to global brain dynamics, or "Globalopathies" that are divided into three major interdependent types (1) "Resting-State Networkpathies," in personality disorders, (2) "Entropiathies" in mood disorders, and (3) "Connectopathies" in psychosis and schizophrenia spectrum disorders. Novel approaches of processing signals from the brain are beginning to reveal brain organization in health and disease. For example a "small world network" has been described for optimal brain functions and breakdown of that organization might underlie relevant psychiatric manifestations. A novel diagnostic reformulation can be generated based on pathologies of whole brain organizations, such new brain related diagnostic nosology is testable and thus can be validated. Once validated Globalopathies can provide for "Global-therapies" i.e., interventions that can reorganize the brain and cure psychiatric disorders. The technology for such interventions is becoming available.

Introduction

In this review I will argue that mental disorders are caused by "Globalopathies," meaning that the underlying etiopathology of mental disorders originates from disturbances to global brain dynamics. The current difficulty in revealing the underlying brain pathology of mental disorders is probably related to the fact that research has often concentrated on isolated brain targets rather than on the global picture. In addition the capability for revealing and deciphering global brain dynamics is in its infancy and does not yet provide full understanding of global brain organizations.

In recent years we have become aware of the Default Mode Network (DMN) a connectivity network organization of the brain at rest [1,2]. This is probably a developmental connectivity configuration developed by experience-dependent plasticity during the life time of the individual [3,4], we also know that optimal network organization entails "Small-World" organization involving an optimal balance between short path-length and longer distant connections [5–7], with clustering formations linked via "Hub" junctions capable of vast integration and information transfer.

We can now begin to reformulate mental disorders as disorders of such global brain organizations. For example "disconnection dynamics" spread in cortical networks and brain subsystems have been repeatedly related to fragmentation of brain organization causing neuronal activities to become statistically independent of each other, disintegrating conscious experience and causing psychosis [8,9].

In this focused review mental disorders are divided into three major interdependent types of "Globalopathies", (1) "Resting-State Networkpathies" (RSNs), (2) "Entropiathies" and (3) "Connectopathies".

This work is based on the premise that higher mental functions that are typically related to mental disorders are "Emergent Properties" of global brain functions, thus their related disturbances are unavoidably also disturbances to global brain dynamics. The review starts with exemplifying the relevance of global brain organization to the most fundamental higher brain phenomena, the emergence of consciousness; altered conscious experience is essentially involved in many mental disorders thus offering a useful guide to the relationships of global brain dynamics and mental disorders.

Globalotherapies entail controlling brain organization at the global whole-brain level, optimizing organization and correcting Globalopathies. This can be obtained by two types of intervention (1) global plasticity inducing interventions, or (2) localized interventions that induce global effects.

Globalopathies

"Consciousness", "mood," "identity" and "personality" are all emergent properties from whole-brain organizations. They cease to exist once brain functions become disintegrated into localized segregated functions. "Emergent Properties" are defined as "the

* Address: Sha'ar Menashe Mental Health Center, Mobile Post Hefer, 37806, Israel. Tel.: +972 522844050.
E-mail addresses: renak@lev-hasharon.co.il, neuroanalysis@gmail.com, av_peled@netvision.net.il

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sum is more than the elements" meaning that a single neuron or even a substantial group of neurons do not have properties such as consciousness, awareness and mood but the entire brain as a whole does. The physical system of the brain comprising of billions and billions of neurons each interacting with billions of other neurons creates infinite interactions with every millisecond of activity. This system generates these higher mental functions [10].

In the 1980's consciousness was described scientifically using the model of a Global Workspace [11–13]. This model assumes that consciousness correlates with integration of multiple partial processes. Partial processes are specialized, specific, and act in isolation and are thus uninterrupted by other specialized parallel processes. The brain requires effective specialized information processing computed by specialized partial processes, but the brain also integrates everything to generate a coherent consistent whole, one that dynamically integrates ongoing experience. The global workspace is the overall integration of participating partial processes, those processes that participate in the global workspace form global integrations. The global workspace is dynamic in the sense that partial processes can "join in," and "break away," from the global processes. Consciousness emerges from the global organization and the "content" of partial processes becomes conscious when integrated in the global process, i.e., the content of the partial process is "globally transmitted" becoming conscious. Partial processes that do achieve participation in the global process remain unconscious, or partially conscious, depending to what extent they contribute to the global formations.

Later on the ideas of global workspace were further developed and applied to the manner in which neuronal networks behave in the brain [14]. Both the global and partial processes can be conceptualized as neuronal ensembles that form neuronal networks that spread in the cortex and the entire brain. In this regard the brain is viewed as a huge network system in which every instant is dominated by one global neuronal network activation integrating multiple partial neuronal networks that are more localized or partially distributed. The next (next instant) global integration can integrate other partial processes, thus "including" and "secluding" other network formations as the process proceeds. This is also why conscious experience is serial, each moment we are conscious of one experience. This does not conflict with the brain parallel distributed processing that concomitantly goes on with the partial unconscious continuous processing. For example when driving, many complicated brain functions take place unconsciously while the driver is thinking (i.e., is conscious) about other unrelated contents.

The dynamics of vast brain integrations was also described using the concept of "Dynamic Core" [15] where reentrant connections form a dynamic changing "core" which is an activated neuronal organization selected out of all possible organizations of activated neuronal ensembles in the brain system. Numerical mathematical estimations of the vast global workspace, core or neuronal integration, were calculated using entropy measurement by Tononi [16]. Postulating that consciousness involves a unitary indivisible integrated complex, it is inevitable that it is one of many possible combinations; in effect it is one of all the other possible states which the brain can assume. Entropy is a measure of order, and if every instant is characterized by one unitary state out of numerous possible states, the brain maintains a high level of order at every instant, keeping the entropy measure of brain dynamics low. Once the unitary complex disintegrates into multiple changing elements it achieves many combinations of multiple states; at all times disorganization reigns and entropy values increase. By extracting an entropy measure "Phi" Tononi proposed a method for translating qualitative properties of experience into mathematics [17]. His postulation of Phi includes the quantity of consciousness associated with experience thus taking into consideration the constraint exerted on the brain by environmental occurrences via constraints of reality.

The idea of a globally organized system composed of partial processes lends itself very well to descriptions of brain organization as a hierarchical system as described by Fuster [18,19] and Mesulam [20]. They describe the brain as integrating partial (sensory motor) specialized and segregated functions into "multimodal" integrated processes, that are further integrated and finally at the top of the hierarchy, the global "transmodal" process occurs. The description of transmodal dynamics is very similar to that of Global Workspace lending itself to the idea that consciousness arises from higher level hierarchal organizations. For example Mesulam [20] argued that motivation and volition arise from the highest levels of sensory motor integration where the global motor dynamics "acts upon" the entire sensory experience. Thus we can see how motivated consciousness arises, motivation and volition are higher mental functions that are typically disturbed in severe mental disorders.

Once accepting the idea of global brain dynamics composed of multiple complex parallel distributions, the idea of "sub-consciousness" and "unconsciousness" receive their neurophysiological basis. The partial processes are unconscious as long as they do not participate in the global process explaining how we become aware of what is required for "pulling it up" from lower partial organizations to become included in the higher-level transmodal global conscious organization, or verse versa "repressing" it into unconsciousness, i.e., excluding from global transmodal configurations those partial processes that do not need to participate in the global organization and can function effectively as a partial process outside of global dynamics.

Resting-state networkpathies (RSNs)

The next question regarding whole brain dynamics is related to development. The newborn infant has to develop a stable organized dynamic brain that can accomplish the requirements off global organizations and high mental functions; these are not apparent immediately and go through a developmental organization. "Experience Dependent Plasticity" (EDP) is a term coined to describe how such a process occurs. According to insights by Donald Hebb from 1948 it is common to think that neurons that fire together wire together [21]. This has been repeatedly shown to occur between neurons both at fast chemical intra-synaptic processes as well as in long-term axon, spine and dendrite connections [22,23].

To understand this, one can imagine that experience expressed as activations of neuronal ensembles by sensory input. These are synchronous activated neurons, experience is coded into strengthened neuronal connections between the activated neuronal ensembles. Repeated experiences result in repeated activations. These generate gradual increment in the strength of the connections. In other words, once connections between neuronal ensembles representing an event, i.e., a memory, are strengthened, than neuronal ensembles representing this memory can be readily activated because the connections between the neurons of that ensemble readily excite each other generating a readily active-able neuronal ensemble.

Thus memories are embedded in the neuronal network structure of the brain in the form of strengthened connections among different neuronal ensembles [4,24]. A physicist would regard all possible states of a network (combinations of neuronal activations) as a "space" of the system, and every specific pattern of activation, as a "state" of the system, if the system attempts to activate a certain state (i.e., neuronal ensemble which is also a specific memory) than that state is said to be an "attractor" or in other words, it is a state too which the system is attracted to (because it tends to activate it) memories are embedded in the physical system of neuronal network of the brain in the form of attractors in state-space.

Over the period of development each individual experiences billions and billions of events many of them repeatedly. These events trigger a multitude of neuronal activations forming millions and billions of neuronal ensembles and aggregations embedding experiences in the brain system in the form of attractor-formations. Thus each individual in the course of his development creates a personal internal map of attractor configurations that represent his individual life experience [25]. This internal map is dynamic and changes according to the individual experiences which continue to occur throughout the life of the individual. These can strengthen past experiences or alter and reshape to form new representations.

In effect the internal map of representations has been well described for many years by "object relationship" psychologists [26] who described the internal representations of others, such as parents teachers friends as, "objects". In this case objects relate to memories and these are embedded in attractors. The individual also has a representation of himself in his brain that is composed of his experiences toward himself, and was termed "self-object" by object relationship psychologists. Thus one can see how even higher coding "maps" of social occurrences are represented in the brain as dynamic attractor formations in state-space. Object relationship theories have been useful in explaining why and how individuals experience adapt and react to the psychosocial surrounding, these individual adaptation behavioral reactions have been related to personality styles, showing that internal representations shape our personality. Additionally Rogers [27] described internal maps "organismic maps" as internal representations that determine the way we interpret experiences and react to psychosocial occurrences. These descriptions link internal representations and configurations to "personality" because personality is typically defined as the individual's set of interpretations, experiences and reactions to psychosocial occurrences.

Based on these insights the link between development of default mode network and the maturation of personality is created. The default mode network encodes internal representations as attractor configurations of state-space and these in turn determine and guide our psychosocial adaptation and psychological behavioral reactions, related to our experience-dependent individual style, i.e., personality traits.

A direct prediction from these insights is that individuals suffering from personality disorders will demonstrate altered default mode network development which will manifest as biased organization in terms of altered small-world network organization. Initial validation for such alterations is beginning to appear in the literature. Lei et al. [28] provide evidence for an association between individual differences in personality and scaling dynamics in default mode network. Default mode network of rsfMRI in 20 healthy individuals was significantly associated with the extraversion score of the revised Eysenck Personality Questionnaire. Specifically, longer memory in default mode network corresponded to lower extraversion. Wei et al. [29] explored brain disturbances underlying extraversion and neuroticism in 87 healthy individuals using fractional amplitude of low-frequency fluctuations on resting-state functional magnetic resonance imaging, they showed a positive correlation between low-frequency fluctuations amplitude at Slow-5 waves and extraversion in medial prefrontal cortex and precuneus, (important portions of the default mode network), thus suggesting a link between default network activity and personality traits. Overall, these findings suggest the important relationships between personality and low-frequency fluctuations, amplitude dynamics depend on specific frequency bands.

Wolf et al. [30] showed that patients with borderline personality disorder demonstrate an increase in functional connectivity in the left frontopolar cortex and the left insula, whereas decreased connectivity was found in the left cuneus. Within a network comprising predominantly right lateral prefrontal and bilateral parietal regions, patients with borderline personality disorder showed decreased connectivity of the left inferior parietal lobule and the right middle temporal cortex compared with healthy controls. Correlations between functional connectivity of the frontopolar cortex and measures of impulsivity as well as between connectivity of the insula/cuneus and dissociation tension were found. These data suggest that abnormal functional connectivity of temporally coherent resting-state networks may underlie certain symptom clusters in patients with borderline personality disorder.

Tang et al. [31] designed an exploratory data-driven classifier based on machine learning to investigate changes in functional connectivity in the brains of patients with antisocial personality disorder. They used resting state functional magnetic resonance imaging (fMRI) data for 32 subjects with antisocial personality disorder and 35 controls. The results showed that the classifier achieved satisfactory performance (86.57% accuracy, 77.14% sensitivity and 96.88% specificity) and could extract stable information regarding functional connectivity that could be used to discriminate antisocial personality disorder individuals from normal controls. More important, they found that the greatest change in the antisocial personality disorder subjects was uncoupling between the default mode network and the attention network. A voxel-based morphometry analysis showed that the gray matter volumes in the parietal lobule and white matter volumes in the precuneus were abnormal in antisocial personality disorder compared to controls. In summary this study used resting-state fMRI to identify abnormal functional connectivity in antisocial personality disorder patients. The authors suggest that their analysis can be used to improve the diagnosis of antisocial personality disorder, and elucidate the pathological mechanism of antisocial personality disorder from a resting-state functional integration viewpoint.

These findings together with the above insights have critical implications toward treatment of personality disorders, first they provide the neuro-scientific rationale for psychotherapy as an experience -dependent therapy. The therapist with repeated interpretations and guidance i.e., "corrective experience" gradually reshapes the internal configurations of network organization by activating new neuronal ensembles repeatedly strengthening connections for those new neuronal ensembles such new internal configurations increase the complexity of the internal formations augmenting adaptability by virtue of new more diverse repertoire of perceptions and reactions accompanied by better socially relevant coping organismic mapping, this "equips" the patient with new more adaptive sets of behavioral experience and reactions reducing his maladaptive consequences and suffering.

Entropiathies

One of the more replicated findings is the relationships between mood, depression and neuronal brain plasticity. According to the insights advanced so far we expect mood to be an emergent property of vast global brain dynamics. Plasticity changes can be spread and global and in effect the targets of antidepressant medications, the serotonin reuptake receptors, are vastly distributed in 60% of relevant neurons in the brain [32].

In the first section of this work we have seen how by extracting entropy measurement "Phi" proposed a way for translating qualitative properties of experience into mathematics [17]. In this postulation "Phi" includes the quantity of consciousness associated with the experience thus taking into consideration the constraint exerted on the brain by environmental occurrences via constraints of reality. The brain dynamically and continually adapts to environmental constraints by two concomitant mechanisms (1) adapting internal representations to the environmental constraints and (2) acting to change the environment (action and behavior) to suit the internal representations. Karl Friston [33] showed that he brain continually predicts the environmental occurrences extracted from its incoming stimuli, and adapts to it by reducing the "differences," between internal configurations and environmental events, i.e., reducing the "free Energy" which is a measurement of "difference" in term of entropy between brain organization and environmental constraints. These formulations are important as we can now visualize the mathematics of the adaptive ever-changing brain organizations in relationship to creating effective adaptive internal maps i.e., attractor formations. It is also important to realize how Hebbian dynamics and brain plasticity as an overall global process provides for the Bayesian Dynamics of the brain.

As mentioned above one of the more replicated findings is the relationships between mood, depression and neuronal brain plasticity [34–37], neuronal death and hampered plasticity (reduction of spines and dendrites)are associated with depression and antidepressant interventions are associated with synaptognesis, neurogenesis. Once plasticity dynamics is understood within the framework of free energy reduction and brain adaptation, mood related to plasticity can be associated to the Bayesian adaptive dynamics of the brain.

Depression is related to reduction of plasticity. Reduced plasticity hinders brain adaptability which increases free energy because maladaptation increases the differences between internal brain representations and changing environmental constraints, (i.e., changing occurrences). Thus increases of free energy entropy measurements could become a sort of "dynamic biomarker" for depressed mood. Antidepressant effect is related to increased plasticity which in turn, is related to better adaptability that reduces free energy (the entropy measurement of the difference between environmental constraints and internal representations).

These associations between neuronal brain plasticity and changing environmental constraint [25] offer a good model for the understanding of both "endogenic" and "reactive" depressions under one unified explanation. Anything that impairs plasticity, e.g., Alzheimer, metabolic-alteration brain damage, reduces plasticity and causes an increase of free energy due to the fact that the environmental constraints keep on changing to the extent that impaired plasticity cannot "catch up." Stress on the other hand typically entails abrupt large changes of environmental constraints (i.e., occurrences), thus such fast alterations supersede the speed of plasticity adaptations and inevitably free energy increases, explaining the depressed mood companying stressful rapid-changing events.

We know from clinical experience that the combination of both is sure to manifest as depression, for example when patients suffering from dementia are relocated (to foster home or other) the changing environmental conditions for a plasticity-hampered brain surely result in substantial increases of free-energy measurements expressed as an emergent property of depression. We also know from experience that plasticity-related recovery is necessary for reducing free energy and an antidepressant mood elevation effect. This is known as the bereavement period.

Connectopathies

As early as 1800 Meynert [38] described psychosis as resulting from weakness of connectivity among neuronal ensembles, Wernicke [39] also envisioned psychosis as disintegration of neuronal organizations, Bleuler coined the term "schizophrenia," "schizo" meaning 'split' considering that the disorders result from 'split-mind' or the splitting of mental functions.

In the 1990's the term 'disconnection syndrome' for schizophrenia was coined by Friston and Frith [8]. Since then many investigators have supported the notion of connectivity disturbances in psychosis and schizophrenia to the extent that many reviews are beginning to appear. Jones [40] summarized mounting empirical evidence for connectivity disturbances of neural network in the brains of schizophrenia and psychotic patients in his paper titled "Errant ensembles: dysfunctional neuronal network dynamics in schizophrenia".

In recent years disconnectivity in schizophrenia has been related to the small-world network organization and was found to alter and disturb small-worldliness optimal organization of the brain. For example Yu et al. [5] published a paper titled "Altered small-world brain networks in temporal lobe in patients with schizophrenia performing an auditory oddball task." Wang et al. [6] found that the topological properties of the patients' anatomical networks were altered, so that global efficiency decreased but local efficiency remained unchanged. The deleterious effects of schizophrenia on network performance appear to be localized as reduced regional efficiency in hubs such as the frontal associative cortices, the paralimbic/limbic regions and a subcortical structure (the left putamen). Using fMRI independent component analysis, Yu et al. [5] found significantly altered topological properties of functional network connectivity in schizophrenia patients compared to controls. In addition, topological measures of many independent components involving frontal, parietal, occipital and cerebellar areas were altered in schizophrenia patients relative to controls. Specifically, topological measures of whole network and specific components in schizophrenia patients correlated with scores on the negative symptom scale of the Positive and Negative Symptom Scale (PANSS). These findings suggest that aberrant architecture of small-world brain topology in schizophrenia patients consists of independent component analysis temporally coherent brain networks.

Auditory oddball task-related networks in schizophrenia patients provided further evidence for disconnectivity in brain function in schizophrenia [41]. Small-worldliness values were decreased in both hemispheres in schizophrenia patients. In addition, schizophrenia patients showed longer shortest path length and lower global efficiency only in the left task-related networks. These results suggested small-world attributes are altered during the auditory oddball task in schizophrenia.

Disconnectivity probably affects the brains of patients also in remission, Kasparek et al. [42] analyzed functional networks in schizophrenia patients in remission after the first episode; they found abnormal functional connectivity of several brain networks in remission after the first episode. Patients showed lower activation of the salience network during verbal fluency tasks. They also showed lower deactivation of the default mode network during verbal fluency tasks processing. Spectral analysis of the component time courses showed decreased power in slow frequencies of signal fluctuations in the salience and default mode networks and increased power in higher frequencies in the left frontoparietal cortex reflecting higher fluctuations of the network activity. Moreover, there was decreased similarity of component time courses in schizophrenia—the patients had smaller negative correlation between verbal fluency tasks activated and deactivated networks, and smaller positive correlations between default mode network subcomponents.

Supporting the idea of globalopathy in terms of connectopathy, Rish et al. [43] showed that schizophrenia is a disorder of the collective, "emergent" working of the brain. They showed that significant disruption of the topological and spatial structure of functional MRI networks in schizophrenia cannot be explained by a disruption to area-based task-dependent responses but rather relates to the emergent properties, is global in nature, most dramatically affects long-distance correlations, and can be leveraged to achieve high classification accuracy (93%) when discriminating between schizophrenic vs control subjects based on only a single fMRI experiment using a simple auditory task.

Connectivity is not random but shows small world organization (see below) thus organized in hubs that integrate information effectuating a hierarchal organization of connectivity in the brain. As early as 1881, Wernicke regarded the cerebral cortex as constituting, in its anatomical arrangement of fibers and cells, the organ of association [39]. Wernicke perceived a hierarchy of evermore-complex arrangement of reflexes in the brain. With this formulation he preceded later insights of brain organizations achieved by studying sensory and motor brain functions. According to Fuster [19] there is a hierarchy of perceptual memories that ranges from the sensorial concrete to the conceptually general [19]. At the bottom resides the information on elementary sensations; at the top, the abstract concepts that, although originally acquired by sensory experience, have become independent from it in cognitive operations [18]. This information process is most likely to develop, at least partially, by self-organization from the bottom up, that is, from sensory cortical areas towards areas of association. Memory networks, therefore, appear to be formed in the cortex by such processes as synchronous convergence and self-organization.

In the higher levels, the topography of information storage becomes obscure because of the wider distribution of memory networks that links scattered domains of the association cortex, representing separate qualities that however disparate, have been associated by experience. Because these higher memories are more diffuse than simple sensory memories, they are in some respects more robust. Only massive cortical damage leads to the inability to retrieve and use conceptual knowledge; the "loss of abstract attitude" described by Kurt Goldstein (Fuster [19]). Similar to sensory information, motor information on planning and deciding has also been hierarchically described. As first suggested by Hughlings Jackson [44], the cortex of the frontal lobe computes the highest levels of motor information. The primary motor cortex is the lowest cortical level and, represents and mediates elementary motor acts. The prefrontal cortex, conventionally considered the association cortex of the frontal lobe, represents the highest level of the motor hierarchy [44,45]. This position connotes a role not only in the representation of complex actions (concepts of action, plans and programs) but also in their enactment, including those such as working memory [46]. The prefrontal cortex develops late, both phylogenetically and ontogenetically, and receives fiber connections from numerous subcortical structures, as well as from other areas of the neocortex [47,48]. This extensive connectivity links reciprocally the perceptual and conceptual information networks of the posterior cortex with prefrontal motor networks, thus forming perceptual-motor associations at the highest level [19].

Mesulam [20] reviewed brain organization leading from sensation to cognition. Unimodal association areas comprise part of the lower hierarchical organization; they encode basic features of sensation such as colour, motion, and form. They process sensory experiences such as of objects, faces, word forms, spatial locations and sound sequences. More heteromodal areas in the midtemporal cortex, Wernicke's area, the hippocampal–entorhinal complex and the posterior parietal cortex provide critical gateways for transforming perception into recognition, word formation into meaning, scenes and events into experiences, and spatial locations into targets for exploration. The transmodal, paralimbic and limbic cortices that bind multiple unimodal and the higher more heteromodal areas into distributed but integrated multimodal representations occupy the highest connectionist levels of the hierarchy. The transmodal systems with their complex functional inter-connectivity actualize the highest mental functions (see emergent properties above).

Information is continuously sampled from the environment via the different sensory systems. Simultaneously, the environment is subject to continuous manipulations via the motor systems. This cycle of continuous sampling and intervention in the environment is governed by the ever more complex circuits which characterize the hierarchical organization of the brain. This hierarchy enables the associative transformations needed to support cognition that is typical of high mental functions, and is heavily dependent on neuronal connectivity.

The transmodal connectionist level of brain organization plays an important role in shaping the characteristics of high mental functions. If prior to establishing a connection two neuronal systems could act independently one from another, now that their activity is interdependent, the activity of one neural system or network will influence the activity of the other. This might explain the internal consistency we experience in our mental functions, and why reality is perceived as being coordinated audibly, visually and tactually. Planning, thinking and acting also have consistency; thoughts and reactions are goal-directed to the stimuli at hand, and match situational events. Finally, our entire conscious experience seems to be united in one complete logical and meaningful entity.

To summarize, the brain organizes with bottom-up processes of unimodal multimodal and transmodal integration [20] in which our conscious experience integrates into coherent experiences. Auditory stimuli and visual information are integrated to experience actual people who are talking as opposed to auditory hallucinations that are perceived regardless of the presence of real people. Top-down processes are responsible for higher-level schemata, representations, and ideations, which control, and sometimes bias, our incoming (bottom-up) experiences.

Connectivity imbalances in the bottom-up top-down dynamics can result in systemized delusions when top-down shifts result in overly-controlling schemata that bias the actual experiences. Bottom-up insufficiencies lead to impaired higher-level organization, curtailing higher-level phenomena such as motivation and volition [20] and resulting in the disastrous phenomenological manifestations of deficiency syndromes in schizophrenia patients [49].

Studying Globalopathies

One of the reasons why we have not yet identified the etiopathology of mental disorders is because we are still developing the signal-processing and mathematical tools that can detect and define the different types of Globalopathies.

Synchronization, among brain regions is still one of the most investigated methods for generating brain network assessments. In view of this work and the importance of detecting Globalopathies, it is vital to apply synchronization to global brain measures. In the literature [50], two levels of statistical analysis have been considered in comparing brain connectivity across groups and subjects: (1) the global comparison where a single measure that summarizes the information of each brain is used in a statistical test; (2) the local analysis where a single test is performed either for each node/connection. Meskaldji [50] comment on the different levels of analysis and present some methods that have been proposed at each scale.

Chen et al. [51] have developed a parallel nonlinear interdependence method with general-purpose computing on the graphics processing unit. They claim that their method can support real-time global synchronization measurement and used it to study epilepsy. The method allows for measuring the direction and strength of synchronization of activities of multiple brain regions, and adapts to the quickly increasing sizes and scales of neural signals. Ioannides [52] presented a quantitative study of dynamic reconfiguration of connectivity for event-related experiments. Their motivation is the development of a methodology that can be used for personalized monitoring of brain activity. In line with this motivation, they used data with visual stimuli from a typical subject that participated in different experiments that were previously analyzed with traditional methods. They tracked the event-related changes in network organization, at the source space level, thus providing a more global and complete view of the stages of processing associated with the regional changes in activity. Their results suggest the time evolving modularity as an additional brain code that is accessible with noninvasive means and hence available for personalized monitoring and clinical applications.

Regarding the study of connectomics concerns about the many sources of nuisance variations present and their impact on resting state fMRI measures continues to grow. Although substantial within-site variation can exist, efforts to aggregate data across multiple sites such as the 1000 Functional Connectomes Project and International Neuroimaging Data-sharing Initiative datasets amplify these concerns. The work of Yan et al. [53] draws upon standardization approaches commonly used in the microarray gene expression literature, and to a lesser extent recent imaging studies, and compares them with respect to their impact on relationships between common resting state fMRI measures and nuisance variables (e.g., imaging site, motion), as well as phenotypic variables of interest (age, sex). Standardization approaches differed with regard to whether they were applied post hoc vs. during pre-processing, and at the individual vs. group level. While all standardization approaches were effective at reducing undesirable relationships with nuisance variables, post hoc approaches were generally more effective than global signal regression.

Brain is a complex network optimized both for segregated and distributed information processing. To perform cognitive tasks, different areas of the brain must "cooperate," thereby forming complex networks of interactions also known as brain functional networks. In a recent paper Sporns [54] reviews current empirical efforts toward generating a network map of the human brain and explores new insights into the organization of the brain's structural connections and their role in shaping functional dynamics. Neuroimaging has revealed a number of highly nonrandom network attributes, including high clustering and modularity combined with high efficiency and short path length (small world organization). The combination of these attributes simultaneously promotes high specialization and high integration within modular small-world architecture. Structural and functional networks share some of the same characteristics, although their relationship is complex and nonlinear. Small world network organization seems to be an optimal form of brain organization that offers functional optimization, or in other words healthy mental functions [4,55]. In effect many studies that follow have shown that brain networks exhibit "small-world" characteristics. This is in relation to both anatomical connections in the brain and the synchronization networks of cortical neurons [56].

Using diffusion tensor imaging based fiber tractography Yap et al. [57] found that small-world architecture exists at birth and its efficiency increases in later stages of development. They found that the networks are broad scale in nature, signifying the existence of pivotal connection hubs and resilience of the brain network to random and targeted attacks. The brain network seems to evolve progressively from a local, predominantly proximity based, connectivity pattern to a more distributed, predominantly functional based, connectivity pattern.

In recent years, resting-state brain networks were described, as opposed to activated cognition-related networks. These are typically called "default-mode-networks." Ding [58] investigated the topological properties of the default-mode, dorsal attention, central-executive, somato-motor, visual and auditory networks derived from resting-state functional magnetic resonance imaging. They found small-world topology in each, resting-state network. Furthermore, small-world properties of cognitive networks were higher than those of perceptual networks. Thus they demonstrate a topological fractionation between perceptual and higher cognitive networks. This emphasizes the relevance of small-world organizations to higher mental functions. Vertes and Duke [59] found that small-world networks perform an order of magnitude better than random ones, enabling reliable discrimination between inputs even when prompted by increasingly incomplete recall cues. They showed that small-world architectures operate with significantly reduced energy and that their memory capacity scales favorably with network size.

The synchronized behaviors of a noisy small-world neuronal network with delay and diversity are numerically studied by calculating a synchronization measure and plotting firing pattern [60]. Delay in the information transmission can induce fruitful synchronization transitions, including transition from phase locking to antiphase synchronization, and transition from antiphase synchronization to complete synchronization. Furthermore, the delay-induced complete synchronization can be changed by diversity, which causes oscillatory-like transition between antiphase synchronization and complete synchronization. These are relevant functional dynamics when optimal versus disturbed functions are envisioned. Graph theoretic techniques can be utilized also for precise analysis of brain functional networks, as has been demonstrated by Kuchaiev [56] who described structural changes in brain functional networks in response to different stimuli or cognitive tasks.

Dimitriadis et al. [2] investigated the dynamic behavior of resting state functional connectivity using EEG signals. Employing a recently introduced methodology that considers the time variations of phase coupling among signals from different channels, a sequence of functional connectivity graphs was constructed for different frequency bands and analyzed based on graph theoretic tools. Hubs were spotted in the functional connectivity graphs based on local and global efficiency. They find a topographic role that showed widespread scattering with prominence over the frontal brain regions for both local and global efficiency. Hubs stable across time were identified via a summarization technique and found to locate over forehead. This conforms to the assumption that the frontal prefrontal brain regions act as a critical hub for widespread network activity of cortical brain regions.

As mentioned above "Entropy" is a measure of order, and if every instant of brain activity is characterized by one unitary state (out of numerous possible states) than the brain maintains a high level of order at every instant keeping the entropy measure of brain dynamics low. Thus entropy can be used to investigate brain organization levels. In this regard Dimitriadis et al. [2] in their EEG study found that the evolution of functional connectivity can be described via abrupt transitions between states, best described as short-lasting bimodal functional segregations. Based on a distance function that compares clustering, they discovered that these segregations are recurrent. Entropic measures further revealed that the apparent fluctuations are subject to intrinsic constraints and that order emerges from spatially extended interactions. According to Watanabe [61] pairwise maximum entropy model reflect anatomical connections more accurately than the conventional functional connectivity method. In a MEG study of resting-state networks they show that this model takes into account region-specific activity rates and pairwise interactions. These findings indicate that a relatively simple statistical model not only captures the structure of the resting state network but also provides a possible method to derive physiological information about various large-scale brain networks.

Graphing the theoretical estimations of small world network parameters and entropy measurements are useful methods for the analysis of brain organization levels. These methods can further contribute to the explanation of brain optimization by displaying development over time in the course of natural brain maturation. Boersma and his group [1] used graphs of theoretical concepts to examine changes in functional brain networks during normal development in young children. Resting-state eyes-closed electroencephalography (EEG) was recorded (14 channels) from 227 children twice at 5 and 7 years of age. Synchronization likelihood was calculated in three different frequency bands and between each pair of electrodes to find Synchronization likelihood-weighted graphs. Mean normalized clustering index, average path length and weight dispersion were calculated to describe network organization. Repeated measures examination of variance tested for time and gender effects. For all frequency bands mean synchronization likelihood decreased from 5 to 7 years. Clustering coefficient increased in the alpha band. Path length increased in all frequency bands. Mean normalized weight dispersion was reduced in beta band. The overall decrease in functional connectivity (Synchronization likelihood) might reflect pruning of unused synapses and preservation of strong connections resulting in more cost-effective networks. Accordingly, Boersma and his group found increases in average clustering and path length and decreased weight dispersion indicating that normal brain maturation is characterized by a shift from random to more organized small-world functional networks.

Measuring EEG activity in a large population-based sample Smit [62] investigated the development of the brain's functional connectivity throughout the life span (ages 5–71 years). Connectivity was established with Synchronization Likelihood. Relative randomness of the connectivity patterns was established with graph parameters of local clustering and global path length for alpha beta and theta oscillation networks. They found that from childhood to adolescence large increases in connectivity in alpha, theta and beta frequency bands and that this continued at a slower pace into adulthood (peaking at ~50 years). Connectivity changes were accompanied by increases in global path length and local clustering reflecting decreases in network randomness and increased order (peak levels reached at ~18 years). Connectivity was considerably correlated to cerebral white matter volume while path length was related to both white matter and gray matter volumes. In conclusion, Smit [62] showed that EEG connectivity and graph theoretical network analysis can be used to trace structural and functional development of the brain.

Diagnosing Globalopathies

Are we ready to re-conceptualize psychiatric disorders as Globalopathies? It seems that schizophrenia spectrum disorders can be reformulated as "Connectopathies," mood and anxiety disorders as "Entropiathies" and personality disorders as "Resting-State Networkpathies" (RSNs). Naturally patients will typically suffer from a combination of these disturbances. For example, a patient suffering from resting-state networkpathies will inevitably become exposed to entropiathies because the development of his internal representations and brain organization will have difficulty adapting to altered changing psychosocial environment. Under increased computational demands from stressful complicated events his network may "fragment" causing "connectompaty" with psychotic symptoms. On the other hand if connectompaty transpires, the network cannot adapt to reduce free energy resulting in "entropiaty" explaining why many schizophrenia patents also suffer from mood alterations and why schizoaffective phenomenology exists. In effect each patient is likely to suffer from the interrelationships that global brain disturbances naturally have, thus demonstrating the spectrum of clinical psychiatric phenomenology.

"Connectopathies" are actually disturbances to the delicate balance between integration segregation and over-segregation dynamics. 'Cs' connectivity segregation is the typical disconnection syndrome repeatedly documented with psychosis. Opponent disturbances can be over-integration dynamics ('Ci' connectivity integration), which has been found to relate to reduced dynamics and repeated activations (poverty of thought and perseverations [3,63], as is typical to negative signs schizophrenia and the deficiency post-psychotic syndrome of these patients. The course of the disorder alternating between repeated psychotic episodes and increased deficiency symptoms can indicate oscillations between these two dynamic extremes of connectivity segregation and connectivity integration.

Connectivity dynamics also involve the hierarchical organization of the brain. Mesulam [20] and Fuster [18,19] described how the brain is hierarchically organized with higher mental functions achieved by higher levels of brain organizations (e.g., transmodal systems, prefrontal cortex). Connectivity imbalance in such hierarchy can perturb bottom-up and top-down processes typical to brain organization. In such cases deficient bottom-up organization can lead to deficient higher-level organizations such as hypofrontality with phenomena such as avolition, as well as exaggerated top-down control with biased information processing (e.g., biased schemata leading to delusional ideation. Let us denominate brain hierarchal imbalance as hierarchical bottom-up (Hbu) insufficiency and hierarchical top-down (Htd) shift, each defining an opposing disturbance to overall normal hierarchal brain dynamics.

As explained, disorders of plasticity relate to mood disorders. We shall assume that reduced neural plasticity causes increase of discrepancy between the internal representations of default contextual networks and the environmental occurrences. This "Deoptimization Dynamics" increases Free Energy resulting in an emergence of depressed mood. We shall use the symbol 'D' to signify brain Deoptimization dynamics and 'O' to signify hyper-optimization dynamics. Optimization reduces free energy by increasing adaptability and thus emerges as an antidepressant mood elevating effect.

Based on the general neural-network literature we can assume that during optimization disturbances, frustration of constraints between the units of these networks occur [3,4,25]. 'Constraint frustration' means that there are inconsistencies between the values of neuronal activity and the values of their synaptic transfer functions [3,4,25]. Moderate inconsistency is normal in active (dynamic) neural networks, however there is a considerable increase of inconsistencies in perturbed neural networks such as in hyper, or deoptimized network dynamics. An increase, if high enough, may threaten network organization and even lead to more serious disturbances such as previously described hierarchical and connectivity disturbances. Similar to the assumption of mood shift arising from altered optimization dynamics, let us assume that anxiety arises from an increase in 'constraint frustration' dynamics. When such dynamics are related to a trigger stimulus as in phobias, we shall refer to it as a 'stimulus-bound constraint frustration' dynamics. Thus 'CF' and 'CFb' are the symbols chosen to represent these anxiety-related brain dynamics. Finally Resting-State Networkpathies, which are disturbances to the development of the default mode network result clinically in a phenomenology of personality disorders (as explained above).

Table 1 summarizes our clinical brain profiling (CBP) hypothesis. "Resting-State Networkpathies" are represented in the first

Table 1
Clinical brain profiling – diagnoses.

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

row as DMN, "Connectopathies" occupy the next four rows and finally "entropiathies" occupy the last four rows.

"Globalotherapies" future treatment of mental disorders

As mentioned above Globalotherapies entail controlling brain organization at the global whole-brain level, optimizing organization and correcting Globalopathies. This can be obtained by two types of intervention (1) global plasticity inducing interventions, or (2) localized intervention that induce global corrective effects, i.e., directly on relevant hubs of that have well-known global network effects.

There are two major types of global plasticity inducing interventions: (1) plasticity-inducing medications (e.g., similar to SSRIs) for example Morag et al. [64] discovered that genome-wide transcriptional profiling of in vitro phenotyped LCLs identified CHL1 and additional genes implicated in synaptogenesis and brain circuitry as putative SSRI response biomarkers and experience dependent therapies (such as the various psychotherapies training and rehabilitation exercises). In effect, a combination of both these interventions targeted to the relevant globalopathy is warranted to achieve global plasticity inducing interventions. If for example one can reverse the brain to plasticity conditions that are similar to those of a young child, reorganization and corrective developmental processes can be achieved to optimize the development of the default mode network in order to eliminate personality disorders. Psychotherapy which entails psychological maturation via experience dependent plasticity will be extremely effective if plasticity of the brain of the patient is reversed to that of a small child or even infant. Experience dependent therapies for example the various training and rehabilitation psychotherapies, can be augmented and more focused using computer multimedia technology such as Virtual Reality [65,66] and virtual worlds. These can use Avatars or humanoids, virtual people to create virtual controlled psychosocial situations that can deliver corrective experiences that are therapeutic. The technology is already in use for desensitization therapies for phobias and PTSD treatments [65–67].

Technology that can provide for localized intervention to induce global corrective effects has become available. One example is the use of deep brain stimulation for depression. Deep brain stimulation of the subcallosal cingulate white matter is an experimental therapy for major depressive disorder and there have been cases in which it had an effective antidepressant effect for patients with resistant depression [68]. A first estimation of the connectivity related to the location of stimulation and the fact that it involves white matter, suggests that a wide spread activation of connected networks occurs, an activation which spreads out to distance networks far away from the location of stimulus. This can be one example for a localized intervention (stimulation) with global consequences.

Another promising technology is that of "Optogenetics." Optogenetics is a new technology offering control over neuronal activity by turning on and off distinct neuronal populations using cell-type specific, optically sensitive, molecular neuronal activity "switches." These "switches" are microbial, light-sensitive ion conductance-regulating proteins, e.g., channelrhodopsin-2 (ChR2) and halorhodopsin (NpHR). They are genetically engineered to become part of the cellular machinery and introduced individually to target neurons relevant for activating or inhibiting pre-chosen neuronal circuits [66]. A few interesting brain hubs can be identified in controlling brain networks especially if these have been found to relate to schizophrenia. For example the prefrontal cortex is most frequently indicated in the psychopathology of schizophrenia. It has massive efferent afferent interconnectivity with most of the cortical systems and thus is probably best suited to be involved in connectivity balance spread in the brain. Due to the massive efferent afferent interconnectivity of the prefrontal circuitry it can (at least in part) act as a relay to whole brain connectivity organization. In other words input–output activity of the prefrontal pyramidal neurons can associate, or dissociate signals arriving by efferents from vast cortical regions with efferent signals from the prefrontal cortex to vast spread-out cortical areas. With this assumption the input–output transmission relationships of the pyramidal neurons of the prefrontal cortex become connectivity organizers in vast cortical brain regions if not for the entire brain. If the input–output transmission is inhibited a disconnectivity dynamics will ensue in the brain and if inversely the input–output transmission is enhanced thus efferents readily excite afferents overly connecting vast spread-out brain circuits, and overconnectivity dynamics develops. The pyramidal neurons of the prefrontal cortex receive connections from inhibitory neurons, the "Wide-arbor" and "Chandelier" cells. These have inhibitory effects both on the dendrites (Wide-arbor) and the axons (Chandelier) of the pyramidal neurons and are in an ideal position to control input–output relationships of the pyramidal neurons. Wide-arbor inhibitory activity on dendrites will reduce effects of incoming afferent signals to the pyramidal neuron, and Chandelier inhibitory activity on the axons will inhibit pyramidal outputs reducing efferent signals from the pyramidal neurons. In other words the control over the input–output relationships of the pyramidal neuronal activity is directly regulated by the activity of these interneurons. Based on the hypothesis advanced so far, optogenetic control over the activity of the Wide-arbor and Chandelier interneurons readily controls the connectivity-organizing effects of the prefrontal cortex on the brain.

The subthalamic nucleus and lateral pallidum are both fast-firing pacemakers (Surmeier et al., 2005). The pallido-subthalamic connection is inhibitory; the subthalamo–pallidal is excitatory. The lateral pallidum receives mainly converging striatal axons, while the subthalamic nucleus receives mainly cortical axons, it is assumed (Peled, 2011) that having converging striatal inputs, the globus pallidus monitors cortical integration while the subthalamic nucleus, with its direct cortical afferents, monitors cortical segregation. Together they are coupled autonomous oscillators presumably acting as coupled regulators sensitive to the cortical connectivity changes and in a position to output a "corrective signal" whenever the connectivity balance is disrupted, shifted extensively or abruptly. Such a corrective signal if forwarded to the substantia nigra reticulate (SNr) via excitatory connections in the form of fast spiking activity. Convergence into slow spiking activity occurs in the substantia nigra compacta (SNc) efferent of the Dopaminergic activity. In total it seems there is a feedback system inputting from the cortex via the Straium GP and STN, and outputting through the SNr and SNc, signals relevant to the ongoing conditions of brain organization.

To conclude Optogenetics hold the promise for intervention at the level of very focused and sophisticated brain hubs, which offers the promise to be able to control whole brain activity and cure Globalopathies.

Conflict of interest

None.

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