NEUROSCIENTIFIC PSYCHAITRY: HOW DO WE GET THERE?

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INTRODUCTION

Neuroscience holds the potential for understanding the causes of mental disorders. In order to cure mental disorders we need neuroscientific psychiatry. What is neuroscientific psychiatry? And how can we achieve it? Here I will clarify the concept, identify the obstacles, focus on the target and trace the roadmap for neuroscientific psychiatry. I will argue that we can already begin using neuroscientific psychiatry today to accelerate progress in the years to come and shorten the time needed to achieve effective treatments for mental disorders.

CLARIFYING THE PROBLEM

There is a large body of knowledge in modern neuroscience, and the knowledge of neuroscience related to mental disorders is growing rapidly. In parallel for many years we have become acquainted with the phenomenology of mental disorders which has materialized over the last 4 decades into the descriptive format of the various editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM),

However the linkage between the neuroscience of mental disorders and the phenomenology of these disorders is nonexistent in clinical settings. First as a language, the terminology of the DSM does not relate to brain activity in any way, for example the term "depression" does not come close to describing a brain structure or function. Second as a conception, nothing in the suffering of the patient is conceptualized in terms of brain disturbance. Needless to say, that the clinician sees a patient who is suffering, and not neurotransmitters or neuronal networks. The taxonomy that should bridge the neuroscience of brain disorders with the clinical manifestations of psychiatric phenomenology is absolutely and totally absent.

The powerful therapeutic achievements of medicine are attributed directly to the ability to connect clinical suffering to its relevant etiopathological causes. For example curing a stomach ache by diagnosing appendicitis and having it treated or having the appendix removed. Without such clinical-organic linkage there is no cure. Without the ability to link mental disorders to their related brain-disorders we shall never cure psychiatric illnesses. Thus it must be agreed that such linkage between brain disturbances and mental disorders needs to be achieved.

IDENTIFYING THE OBSTCLES

Before we explain how such linkage is achieved we have to understand why it has not been achieved until now. One leading argument is that the brain is too complicated. It is true that the brain is the most complicated system known to man, but the understanding of complex-systems behavior is speedily progressing in neighboring scientific fields such as physics, mathematics and informatics. As complicated as it is, there is enough recent progress to begin to understand the disordered brain.

In effect it will be argued here that there is enough knowledge about brain-complexity to begin to formulate brain-related taxonomy for mental disorders. All that is necessary is to bring together these bodies of knowledge from physics, mathematics and informatics to bear on the clinical phenomenology in psychiatric settings.

How should the linkage between brain disturbances and mental disorders be achieved? To answer this question we need to examine the obstacles impeding such linkage. There are four general obstacles, the *i*) simple versus complex cause and effect obstacle, *ii*) the linear versus non-linear relationship obstacle, *iii*) the uni-level versus multiple-level obstacle and the *iv*) dynamic optimization obstacle.

i. Simple complex

In medicine we are accustomed to think in terms of "cause-and-effect" with direct linear relationships between them. For example, more antibiotics less infection, more diuretics lower blood pressure. These relationships hold if the system involved is simple or can become simplified for the purpose of the effect being controlled. The brain is complex thus between the cause (input) and the effect (output) there are multiple subsystems, and multiple channels of divergence and convergence, between these intervening subsystems, divergence and convergence junctions inevitably change and re-change input-output- relationships many times over and over again eliminating any simple cause-effect relationships.

ii. Linear non-linear

While in simple cause-effect relationships a linear graph can describe input-output relationships, e.g., the degree of infection reduces linearly as the amount of antibiotics increases, in nonlinear relationships U curve, inverse U curve and Sigmoid (S shape) graphs are the rule. Any psychiatrist knows the clinical "trigger" and "saturation" effects characteristic to mental phenomena, this is the Sigmoid (S shape) graph, yet when following the traditional medical approach psychiatrists still look for linear relationships where they do not and cannot exists.

iii. Few-level Multi-level and Emergent Properties

The input-output relationship in complex systems travel up,- and back down hierarchies of organization, or in other words it depends on interacting layered subsystems. Typical to complexity, lower-level simple processor subsystems interact at higher levels to form more complicated processing subsystems, these interact at an even higher level to form global complicated processing systems. These higher level formations influence lower level-processes via top-down effects thus creating a balanced ever-linked hierarchy of activity (Mesulam 1998). Regarding cause-and-effect relationships these are markedly altered from when a cause (input) travels all the way up a hierarchy and then all the way down to form the effect (the output), one can surely expect multiple phases at multiple level changes, in a way that the output

cannot be related to the input if the intervening characteristics of the system are unknown.

Additionally in such hierarchical systems each level of process and organization achieves characteristics and capabilities that are not available at the lower level, and that cannot be explained at the lower level because they are only explained by the integration that the higher level can achieve. These characteristics are called "Emergent Properties" and are of fundamental relevance to psychiatry because single neurons do not possess phenomena such as consciousness and personality while whole-brains do. Thus one cannot expect to understand such phenomena by researching single (or groups of) neurons and needs to consider whole brain dynamics to understand psychological phenomena such as consciousness and personality.

    iv. Dynamic Optimization

Dynamic systems are continually changing, such change over-time results from interactions between the composing subsystems. Do these interactions have an optimal pattern for effective change? In recent years the pattern of "Small World" has been found to be optimal for flexible effective dynamic change needed for any information processing system including the brain (Tang et al 2011). Small World organization entails high clustering of connections among near-by units and fewer path-length connections between far-away units, actually a certain balance between nearby and far-away connections is optimal and is given the title of "small worldedness (Sporns 2011). " If effective systems show small-worldedness organization, ineffective (broken disturbed) systems will show some altered small-world organization. Thus any study of brain pathology as a system disturbance should take this into account.

Overcoming these obstacles psychiatrists are facing a complex (compound of many elements), nonlinear, hierarchical and dynamically optimized system, in which none of these phenomena can be ignored, and all are relevant and need to be incorporated in any future psychiatric brain related taxonomy of mental disorders.

FOCUSING ON THE TRAGET

Facing the complexity described so far, how should research into the causes on mental disorders proceed? To answer this we first need to understand the currently applied research strategy and why it doesn't provide for the progress that we are looking for.

For many years, and even today, research proceeds along the line of simple linear one-to-one hypothesis trying to link DSM clinical entities to molecular genetic alterations, or to some physiological finding; this is the typical "Biological Marker" strategy. From the insights achieved to date it is clear that this strategy is not the way to go. It is simple, linear, it does not take into account hierarchy, as it tries to link molecular level directly to phenomenological level ignoring the entire complexity of intermediate multiple levels. Consequently it is understandable why more than a century of this type of research has not significantly advanced psychiatry.

Acknowledging both the complexity of the brain as well as the flawed DSM classification, the NIMH has recently come-up with an alternative strategy, called the

RDoC (Research Domain Criteria; Morris and Cuthbert 2012). First they created a clinical domain agnostic to the DSM which includes multiple psychological cognitive domains. These are: Negative Valence Systems (Active, Potential, Sustained threat, Loss Frustrate no reward) Positive Valence Systems, (Approach motivation, initial responsiveness to reward, sustained responsiveness to reward, reward learning Habit) Cognitive Systems Attention Perception (Working memory, declarative memory, language and behavior). Systems for Social Processes (Imitation, theory of mind, social dominance, Facial expression identification, Attachment/separation fear) Self-representation areas, Arousal/Regulatory Systems, Resting state activity. Secondly they formulated a matrix where each of these psychological-cognitive domains will be studied at multiple levels including "genetic," "molecular," "cellular," "circuit," "physiology," "behavior" and "self report." They presume that if numerous studies of all these domains within the matrix will be achieved, our understanding of all psychological-cognitive phenomena at all gene-to-behavior levels will increase, and the big-picture for a brain-related psychiatry will emerge.

While this approach acknowledges the complexity of the multi-level brain, and excludes the confounding DSM classificatory dimensions, it suffers from over-inclusiveness and introduces nothing new. This is because current research is just that - it studies multiple psycho-cognitive phenomena and disorders at all levels from genes to behavior and cognition. In effect the RDoC is a formulation of the existent current research approach, in other words it is a fancy name (or title) for the current state of the art.

More troubling, within each level of the studied phenomena (i.e., position within the RDoC matrix) a regular simple linear one-to-one hypothesis-driven research is performed though it is not better than the approach described above, that has not advanced us much.

In addition if one calculates how many studies and their resources and time, are required to these big picture, one realizes the enormity of the effort and that it will not be reached for thousands of years, if at all. The complexity of the brain poses so many directions and research trajectories that we are surely destined to get lost in this jungle of challenges for many, many years, if not forever.

To overcome this over inclusive unfocused strategy, we need a roadmap, a theoretical framework which will guide us directly to our target. As we cannot proceed in all possible directions and levels as proposed by the RDoC, we need to choose the critical level of the system (the brain organization) and link it to clinical phenomenology. The level to choose must 1) have the explanatory power for all other levels and 2) must be the point of intervention for effective therapy. This level is the neuronal circuitry, the neuronal network level. It is an intermediate level between the molecular genetics level and the whole brain organization level; as such it holds the explanatory power to bridge the levels of brain organization and function.

A good example is the DISC1 example, where genes responsible for the three-dimensional spatial formation of neurons impede the neuron from making the relevant connections with neighboring neurons resulting in a "disconnection" or "misconnection" dynamics which at the higher levels of brain organization impedes whole brain synchrony needed to achieve cognitive functions (Kamiya et al 2012).

The connectivity level of disturbance is explained by the genetic level and explains the cognitive disturbance.

More critically, the network level is a significant therapeutic target because regardless of the genetic damage, correction of connectivity will eliminate the synchrony disturbance at the higher levels, eradicating the cognitive insufficiency and curing the patient. It is thus understandable how schizophrenia involves many types of genetic alterations, any gene relevant to any molecule that has to do directly or indirectly with the cellular mechanisms relevant to connectivity will end up damaging connectivity, which in turn is the common pathway to the formation of the illness as a connectopathy (disturbance of connectivity) at whole brain integration.

Future therapy for this would involve brain-pacemakers, just as cardiac pacemakers eliminate cardiac insufficiency due to arrhythmias. The technology for brain-pacemakers in the form of Optogenetics (Boyden 2011) is already available.

TRACING THE ROADMAP: *CLINICAL BRAIN PROFILING*

Now, once we have chosen the promising neural network level of the brain which is presumed to be the best explanatory as well as best level for therapeutic intervention we need to trace the linkage between the clinical phenomenology of various mental disorders to their correlated neural-network disturbances. To do that, in many cases, we can rely on large available bodies of knowledge, in other cases, where we lack knowledge, we sneed to fill-in the traces with presumed correlations to be validated in the future. This is why the entire scheme needs to be formulated in a testable-prediction manner.

An appropriate name for such a roadmap is "Clinical Brain profiling"(CBP; Peled 2008; Peled 2009; Peled 2012) because linking phenomenology to brain disturbances involves identifying the brain profile that is clinically relevant to a mental disorder. CBP is also a good framework to start reconceptualizing mental-disorders as brain-disorders, thus initiating neuroscientific psychiatry.

The literature provides us with a large body of knowledge linking disconnection dynamics within neuronal networks with psychosis and psychotic-related phenomenology (Friston and Frith 1995; Jones 2010; Van der Heuvel 2010; Petterson et al 2011; Tang et al 2011; Yu et al 2011; Wang et al 2012). Thus it is a good starting point to reconceptualize the various psychoses as disconnection syndromes, indirectly over-connectivity maybe related to deficiency syndromes such as negative-signs schizophrenia (Geva and Peled 2000). Disturbances to hierarchal brain organizations in schizophrenia spectrum symptoms have also been described (Peled 1999). As such traces can be proposed also between bottom-up hierarchical insufficiency and deficient symptoms, and linkage can also be proposed between top-down control shifts and delusional ideations and perceptual biases (e.g., hallucinations) (Peled 1999). In general schizophrenia spectrum symptomatology can be related to different mixtures of connectivity disturbances involving also the hierarchical imbalance. It is predicted that these disturbances can be detected, measured and diagnosed as altered Small-World organizations or disturbances to the optimal small-wordiness of the brain (Yu et al 2011). Optogenetics will correct these by identifying targets of

network organization and appropriately intervening with their regulatory activity (Peled 2011).

We know from pharmacology of depression and from animal studies of depression and anxiety that depression and anxiety are related to reduced neuronal plasticity, while antidepressant effects correlate with neurognesis and synaptogenesis (Pettinger and Duman 2008; Cullen et al 2010; Christoffel et al 2011; vidal et al 2011; Zang et al 2011; McEwen et al 2012). Thus plasticity is directly relevant to the mood alterations we find in clinical settings.

From the neuronal network point of view, optimization can be linked directly to plasticity, it is intuitively understood that in order to adapt, change and become optimal, the brain must be plastic, ready to change with the changing demands from environment and internal conditions. Optimization is a type of brain dynamics and as such is expressed by emergent properties of which mood can be a global effect, or global emergent property (Peled 2012). These assumptions explain how plasticity (i.e., synaptogenesis) becomes relevant to mood. At this point we can begin to reconceptualize mood disorders as disorders of optimization dynamics that are influenced by the multiple processes involving neuronal plasticity (Peled 2012).

Personality is a developmental process where we internalize experiences that shape our perceptions of ourselves and others (Fairbairn 1944; Kerenberg 1978; Michael 1986; Fu and Zuo 2011). We know today that internal representations of memories are achieved via Hebbian dynamics of strengthening connections (Hebb 1949). We also know that the EGO as initially conceptualized by Meynert (1884) involves our resting-state default mode network organization (Ding et al 2011; wolf et al 2011; Peled 2012). All this together sets the stage for reconceptualizing mental disorders as disorders of the internal representations within the default mode network organization. Thus this most complicated realm of personality disorders can also be described in terms of neuronal network alterations and can be traced from phenomenology to brain disturbance of organization (Peled 2012).

Table 1 summarizes initially proposed correlates for Clinical Brain Profiling (Peled 2012).

Clinical manifestations	Presumed Brain dynamic disturbance
Personality disorders	Rudimental biased immature DMN
Symptoms and signs of anxiety Symptoms and signs of depression	Constraint frustration De-optimization dynamic shift
Symptoms and signs of mania	Hyper-optimization shift
Psychosis and positive signs schizophrenia	Disconnectivity dynamics
Repetitive poverty ideation perseverations	Over-connectivity dynamics
Avolition and negative signs schizophrenia	Hierarchical insufficiency
Systemized organized delusions	Hierarchical top-down dominance

SUMMARY

An old Chinese proverb declares that ""The beginning of wisdom is to call things by their right names"" if the diagnostic term of "depression" or "anxiety" is unrelated to the brain, then one cannot expect clinicians to think in terms of brain disturbances and thus cannot expect them to even come close to identifying any brain disturbance in their patients. Thus it is of no surprise that "wisdom' about the causes of mental disorders is lacking.

The DSM achieved reliability based on consensus, rather than valid evidence. The DSM cannot be validated because its taxonomy is descriptive not brain-related. Changing psychiatric diagnostic taxonomy into a brain-based taxonomy is inevitable in the search for valid psychiatric diagnoses. Any new taxonomy can become reliable due to consensus as has been achieved with the DSM terminology. It is time to choose a brain-related taxonomy that can be validated and make it reliable via consensus. At this time, any taxonomy that will be chosen can only be an APPROXIMATION for the true and correct neuroscientific psychiatry, but we must begin.

What taxonomy starting point should we choose? Clinical Brain Profiling qualifies as a distinguished starting point; it is focused and targeted, to the critical levels of brain organization (the network level).CBP overcomes the main obstacles posed by brain complexity, it takes into consideration such complexity by bringing complex-system sciences to bear on clinical psychiatry. At the same time CBP interacts with current knowledge based on available literature to predict future discoveries. It is relevant for future therapeutic strategies and technologies such as Optogenetic brain-pacemakers. In summary it is hard to conceive a better way to embark on the road for curing mental disorders.

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