Towards a new model of understanding – The triple network, psychopathology and the structure of the mind

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ABSTRACT

With progress in neurosciences, neuroimaging and brain stimulation techniques, mental illnesses are now being seen as development anomalies at the molecular-structural level of synapses, resulting in abnormal cross wiring in areas responsible for complex cognitive and emotional processing. These include the multimodal association cortices situated in the prefrontal lobes, the insula in the temporal lobes, midline cortical structures, and their connections to the thalamus, amygdala and the basal ganglia. Three key networks have been identified which are considered the brain hubs for complex perceptual, emotional and behavioral processing as well as introspection, theory of mind and self-awareness; namely the salience network (SN), the central executive network (CEN) and the default mode network (DMN). They function in an interconnected manner and involve in higher information processing of the entire internal and external milieu of the organism to determine the behavior strategies to be adopted. A triple network model of aberrant saliency mapping and cognitive dysfunction in psychopathology has been put forward recently and an attempt is being made to understand core cognitive networks and their dysfunction across multiple disorders including schizophrenia, depression, anxiety, autism and dementia. Against this background, the author would like to take the triple network dysfunction model a step further to hypothesize the following. 1. All or some of the three core networks (CEN, SN & DMN) are affected variably in psychiatric disorders, the severity and the nature of the clinical symptoms depending upon the degree of damage and the number of networks that are dysfunctional and whether that dysfunction is reversible or permanent. For example, in a condition like schizophrenia, all three networks would more or less be affected giving rise to plethora of symptoms like executive deficits, negative symptoms, abnormal salience and mood states. In milder conditions like anxiety and depressive disorders, on the other hand, the dysfunction is of a lesser degree and reversible. 2. These networks are the final common pathway through which a variety of internal or environment insults to the brain may act, the degree of damage and reversibility being determined by the critical period of brain development in which these occur. 3. The harmonious functioning of these core networks is what gives rise to the complex phenomenon of the mind in the brain.

Introduction

Psychiatry is still in its infancy as compared to the rest of the medical sciences, its development having been considerably hampered by two key factors: 1 – the difficulty in conceptualizing mental disorders as diseases of the brain, and 2 – the primitiveness of our measuring instruments which limit our ability to actually see and understand the living, functioning human brain. The latter has been mitigated to a small extent by advances in cognitive neurosciences, neuro-imaging, genetics and molecular biology but the former still remains a subject for acrimonious debate with biologists being accused of being too reductionist [1]. In the recent times, there is mounting evidence that most mental disorders may have their origin in brain pathology [2]. This is not to underestimate the effects of the social environment. In fact early childhood trauma has often led to drastic and lasting effects on the later brain functioning [3]. Similarly there is evidence that good influences like a role model, a mentor or even psychotherapeutic interventions can influence synaptic connectivity [4,5].

The human brain is after all a dynamic and plastic organ. It responds to and changes according to the external environment, takes internal cues from the body and decides on how to act, react or respond. It therefore seems almost a truism to make a statement that an abnormal brain will lead to abnormality in perception, integration and interpretation of stimuli as well as behavioral responses to these stimuli. Clinically, this will manifest as abnormal sensory perception, abnormal salience, misinterpretation in social processing, cognitive distortions, deficits and maladaptive behavior – symptoms of mental illness in short.

Corroborative evidence for this has come from various sources – from psychopharmacology, neuropathology and in recent times, functional brain scans [6–9].

In the fifties, the serendipitous discovery of chlorpromazine and imipramine revolutionized psychopharmacology [10]. The fact that drugs could relieve key symptoms of the mind like disordered thinking, low mood or hallucinations was revealing in itself of the so called ‘organic’ etiology of mental illness. This was the impetus for research focusing on chemical neurotransmission, synapses receptors and second messenger systems. Many neurotransmitter systems – norepinephrine, serotonin, dopamine and glutamate have been the targets of
investigation. The problem is that these neurotransmitter systems are distributed all over the brain. However certain key pathways for serotonin, dopamine and glutamate were identified as abnormal in major mental disorders [11–13].

The next quest was for the locus of abnormality or the lesion in the brain. Unlike lesions in simpler and relatively closed systems like the motor system or sensory system lesions which are very well defined, it would be simplistic to assume that there is one single site or locus for complex constructs like emotion, memory and learning. Multiple brain regions throughout the brain have been identified as problem areas in psychiatric disorders – the frontal cortex, temporal cortex, thalamus, hippocampus, even the cerebellum but none of these regions appear specific to any category of illness. There are no typical findings like neuro fibrillary tangles or plaques indicative of any obvious neuronal degenerative process [9]. This suggests that the pathology may involve neuronal circuits, neurotransmitter systems or even molecular or subcellular structures.

Understanding psychiatric illness has never been easy. With lack of solid grounding in pathogenesis, attempts have been made to understand them from a purely clinical viewpoint as a cluster of signs and symptoms. Nosological classification, while practically useful for the clinician does throw up several puzzles on other fronts. Psychiatric diseases do not always breed true [14–18]. Overlapping symptoms and borderline conditions seem to exist which have to be put into a categorical no man’s land. Diagnostic classifications have had to be revised and revamped as new findings come to light [19]. The ongoing NIMH R Doc project which began in 2009 is such an attempt to identify links between brain and behavior based on neuropsychological and neurophysiological dimensions of behavioral constructs bypassing categorical classifications. Another point to note is that delusions, hallucinations, mood instability, anxiety and such other symptoms are not limited to mental illness [21]. Any insult to the brain, congenital or acquired, can result in psychotic or mood symptoms. Transient psychotic experiences also seem to occur in the general population, all those identified not necessarily going on to develop mental illnesses [22].

Is there a final common pathway through which these different etiologies can act to produce symptoms seen mostly in mental illness but which are not exclusive to them?

Current understanding of mental illness from neuroimaging

The structural neuroimaging technique of voxel based morphometry (VBM) which developed in the late nineties, has been of great help in localizing brain pathology in neuropsychiatry [2]. A wealth of information has emerged from this data identifying certain common neural substrates across diagnostic categories. Grey matter reductions were seen consistently in the insula, the left and right striatum and the pregenual cingulate cortex even in drug naive patients with psychiatric disorders.

A recent study comparing 193 studies of mood, anxiety, substance abuse and psychotic disorder in more than 7000 patients showed a pattern of gray matter loss extending across medial frontal regions, insula, thalamus, hippocampus and amygdala with increase in gray matter in the striatum [2]. A common substrate occurring across every category was the anterior insula (AI) and dorsal anterior cingulate cortex (dACC) also now named the ‘Salience Network’ (SN). This has led to great deal of interest in this area which is now regarded as the ‘psychiatric core’ for brain stimulation studies [23]. Its subcortical components include the ventral striatum, ventral tegmentum, and amygdala. The AI receives convergent input from multiple sensory modalities. The subcortical nodes provide access to emotional and reward saliency of the sensory input. In addition, the insula is also sensitive to internal signals associated with autonomic processes like respiration, cardiac activity and interoceptors. It therefore detects behaviorally salient stimuli or processes. This process is important for all cognitive tasks so that appropriate resources can be allocated to respond to important stimuli. The dACC node on the other hand is responsible for response selection and conflict monitoring. Through its connections with the dorsolateral prefrontal cortex (DLFPC), it facilitates access to the central executive network (CEN), working memory and attentional systems once a salient event has been detected. The SN; the right AI node in particular also functions as a switch between the CEN and the default mode network (DMN) suppressing the latter and activating the former when a salient stimulus or cognitive task is at hand. Failure of this switch leads to inefficient cognitive control and weaker cognitive performance due to inadequate DMN suppression or CEN activation [24,25].

A second area of interest is the DMN, where structural and dynamic abnormalities have been described in a variety of neuropsychiatric conditions. The components of this network include the medial prefrontal cortex, posterior cingulate cortex, precuneus and lateral parietal cortex. The DMN has is a hub for self-referential thinking, recollection, prospection and ‘mind wandering.’ DMN also seems to play a central role in level of consciousness [26,27].

The third network of interest is the so-called task positive network (TPN) of which the central executive (CEN) and fronto-parietal (FPN) are sub-networks. These are active during cognitive tasks of attention and working memory in contrast to the introspective functions of DMN [20–27]. Besides, FPN has been recently linked to lucid dreams, in which dreamers gain awareness that they are dreaming during the dream (Baird et al., 2019). Researchers in Stanford University have put forth a triple network dysfunction model based on analysis of large scale brain networks. They have narrowed down on three networks, namely the SN, DMN and CEN. They theorize that network approaches will provide insight into aberrant brain organization in many psychiatric and neurological conditions across multiple clinical categories [28–30].

The unique feature of this triple network is that together they seem to be brain hubs where all sensory, affective and cognitive information, past and present converge (SN), are interpreted and integrated into a unique stream of consciousness (DMN); where consistent emotional reaction and/or other goal directed activity is planned and executed (CEN) – the sentinel, the strategist and the Do-er, in short. Dare we say that this is the holy trinity, the mind in the brain?

Hypothesis

The author agrees that the triple network dysfunction model seems the most plausible explanation for complex brain disorders. However, she would like to go a step forward to state the following:

The triple network is the final pathway where multiple etiological factors converge to produce the clinical picture in neuro-psychiatric disorders.

The number of networks involved, the degree of damage, and the potential for reversibility will determine the clinical symptoms and explain why some disorders like depression improve without leaving behind major deficits, unlike schizophrenia where complete recovery may not occur.

Conversely, the harmonious functioning of the three core networks is responsible for the complex phenomenon that we understand as the ‘mind’ in the brain.

An overview of major mental disorders based on the hypothesis

The author believes that most clinical syndromes in Psychiatry can
be explained by this triple network hypothesis. In the following discussion, an attempt is being made to understand how the phenomenology of illness matches the current advances in neurobiology as regards neuropsychiatric syndromes as well as link it to dysfunctions in the previously mentioned triple network (see Table 1).

**Schizophrenia**

Psychosis is characterized by disorders of thinking in the form of delusions and formal thought disorder, perception (e.g. hallucinations), self-experience (e.g. the experience of being controlled by an outside force), loss of motivation, inappropriate emotional regulation and behavioral disorganization. A diagnosis of schizophrenia is made if core symptoms like persistent delusions, persistent hallucinations, thought disorder, and experiences of passivity, which have been present for more than one month and there is no other brain condition like head injury, tumor, drugs of abuse etc. that can account for it.

ICD 10 and 11 as well as the DSM 5 rely heavily upon so-called first rank symptoms of thought alienation phenomena to diagnose schizophrenia, however the validity of this has often been questioned [19,31–35].

Schizophrenia clinically affects multiple domains of an individual functioning: affective, social, cognitive and psycho-motor. A bewildering array of symptoms are found in schizophrenia or any primary psychosis. An attempt can be made to deconstruct individual symptoms and explain them on the basis of brain networks.

**The so-called core symptoms of delusions, hallucinations and fragmented self**

**Early psychosis and delusional mood**

Jaspers has described early delusion formation from his elegant and painstaking work with patients [36]. Typically patients describe perplexity and a feeling of something indescribable of a threatening nature (abnormal salience and activation of amygdala) happening in the environment. It is almost as if it is with great relief that the individual seizes upon an explanation for the delusional mood with a full-fledged delusion.

Delusions can be understood as misinterpretation of otherwise unimportant or irrelevant stimuli induced by an aberrant or dysfunctional SN. This includes internal or bodily stimuli or external and social stimuli. For example, aberrant social salience and negative affect will lead a delusion of persecution where neutral stimuli in the social environment are misconstrued as threatening [37,38]. Probably this is reinforced by autonomic sensations from the subcortical connections of the SN. The delusional explanation following abnormal salience is provided by the introspective functions of the DMN [39].

Hallucinations similarly maybe a failure of gating of irrelevant sensory stimuli and/or a wrongful attribution on part of the dACC and the CEN to internal self talk laden with an affective component. The DMN which is said to be involved in self-talk, introspection and mind wandering (Posterior Cingulate Cortex) may be responsible for generating such talk [39–42].

**Self pathology and first rank symptoms**

Phenomenologists have often described schizophrenia as a disorder of consciousness. Patients describe a loss of ego boundaries, characterized by unpleasant referential thinking, thought broadcast and hyper-reflexivity, where the normal seamless temporal continuity of self and actions are lost [42]. The loss of integrity of boundaries of the self is responsible for thought alienation phenomena – thought withdrawal, insertion and broadcast. Patients typically describe a fragmentation of self and thought process, which had been believed by Kraepelin and Bleuler to be the core morbid process in schizophrenia [43,44]. A temporal fragmentation in the stream of consciousness has been described by patients with schizophrenia, which has been attributed to abnormal resting state connectivity in the midline structures (DMN) of the brain [40].

Other conditions where self-awareness and autobiographical continuity of memory are lost, as in dissociative or mystic meditative states, dissociative anesthesia with ketamine and other drug induced states and epilepsy may also logically inferred to involve DMN pathology.

**Social behavior and affective regulation in schizophrenia**

Social behavior and real life social functioning are affected in most chronic and severe schizophrénics. Some of it is attributed to negative symptoms like apathy, alogia and lack of motivation and some to actual deficits in social cognition [45,46]. These symptoms overlap with autism spectrum disorders and the same brain areas could be affected – the social brain (dACC and amygdala), the mentalizing network (DMN), the areas involved in mirroring or empathy and ‘theory of mind’, which broadly overlaps with meta cognition [47].

Recent studies in macaques have studied the social network size of the individual which seems to correlate with the connectivity between the DMN and ACC [48]. Emotional control depends upon the dynamic interplay between affect generation and affect regulation. Affect regulation involves strategies like affect suppression or cognitive reappraisal, which depends upon the integrity of the DLPPC (cognitive reappraisal), VLPFC (selection/inhibition of reappraisal) and the dorso medial PFC (semantic self-reflective process). Studies in schizophrenia indicate that the patients tend to use suppressive strategies over reappraisal strategies [49–51].

**Cognitive dysfunction in schizophrenia**

Executive functions like working memory, attention, and planning have been consistently found to be abnormal in schizophrenia [52]. Neuro-psychological testing in first degree relatives have often shown abnormalities as well indicating that these are heritable abnormalities or endophenotypes of the disorder [53].

Hence schizophrenia, in keeping with its status as the most severe of mental illnesses, seems to have dysfunctions affecting the entire triple network. This can explain the seeming heterogeneity in the clinical symptoms as well.

Patients who have predominantly salience mode dysfunction (positive symptoms like delusions and hallucinations) seem to do better than those with deficit or negative symptoms (CEN) and social function deficits (DMN + CEN). The latter seem to be associated with early onset and poor prognosis. Perhaps the dysfunction is the result of irreversible structural brain processes.

Acute and other psychotic disorders of varying etiology could also be explained as predominant and reversible SN dysfunctions with milder disturbances in the other networks.

**Mood disorders**

Abnormally depressed or elevated mood are said to be the core diagnostic clinical symptoms in mood disorders. Some aspects of social cognition are also impaired along with the abnormal self-talk being either overly negative and critical or unduly optimistic in nature. This could therefore involve DMN pathology primarily.
The salience node involvement is indicated as evidenced by the abnormal importance being given to negative stimuli in the social environment and the feeling of ‘social pain’ in depression involving the amygdala and dACC [54–56]. It is also possible that the mood is secondary to these phenomena and not vice versa.

The involvement of the orbitomedial and ventrolateral PFC could explain lack of error monitoring and judgment seen both in depression and in mania. The subgenual area of the ACC though said to be not a node of the DMN, is a target for deep brain stimulation (DBS) in depression. It is possible that the dACC is indirectly stimulated [57].

A number of depression spectrum disorders like dysthymia, somatisation, social anxiety and other neurotic conditions could be explained by DMN + mild SN pathology. Dissociative conditions could also be explained by DMN pathology which profoundly but reversibly alters the sense of self (trance), its continuity (dissociative identity disorders) and autobiographical memory (fugue/amnesia).

Mystic experience, drug induced altered states of mind with profound disruption of the self with a feeling of merging into and oneness with the universe, could involve temporary DMN connectivity alterations [41]. When the SN is secondarily involved, the emotional states of bliss or terror may be experienced along with the perceptual and thought disturbances.

Executive function impairment and psychotic symptoms (even first rank symptoms) are often seen in patients with bipolar disorders bringing them closer to the schizophrenia family of disorders. In such cases, a reversible pathology may be said to involve the CEN as well. This may well be responsible for the genetic overlap seen in schizophrenia and some individuals with bipolar disorders.

It can also explain why psychological treatments like cognitive behavior therapies work in mild to moderate depression where the CEN can be harnessed for a top down change in self-talk, whereas they are not useful in severe depression where the CEN is also dysfunctional.

Obessive compulsive disorder

Though clinically classified as an anxiety disorder, OCD has been investigated as a psycho-motor disorder involving rigidity in set shift and goal directed behavior. Reduced connectivity in fronto-striatal circuits specifically the dorsal PFC (CEN) to the dorsal caudate and the VLPFC with the putamen respectively have emerged in functional circuitry specifically the dorsolateral PFC (DLPFC) to the dorsal caudate and the putamen (fugue/anxiety disorder) and autobiographical memory (fugue/amnesia).

The primalsense of the uniqueness of self as distinct from the rest of the mind in the brain, both balanced or disordered, is the virtual philosophy of any kind. Most etiological agents probably act on one or more nodes of the triple network producing symptoms like psychosis with perceptual and cognitive or behavioral disturbances. The entire network may not be involved resulting in partial psychiatric syndromes. For example, an injury to the temporal lobe may damage the insula in the SN explaining the aggression, irritability or even psychosis in such conditions but the complete picture of schizophrenia is not seen as the other networks are spared.

The mind in the brain

Self-awareness, continuity of self and the ‘hard’ problems of consciousness have always puzzled mankind for centuries. Based upon an intuitive understanding, we have always assumed that the mind is a thing apart from the brain, which is just a material organ. All important religions apply this distinction. Psychology and Psychiatry too have been unable to shed this ideological baggage successfully. Analysis of large-scale networks in the brain have given an unexpected insight into what might be the mind in the brain.

What is the common understanding of the mind? That is it is a subjective, lived experience, it can give rise to analytical thinking and reasoning, it can feel emotions like anger, sadness and love and it gives one a unique identity.

The primal sense of the uniqueness of self as distinct from the rest of the world, being conscious of one’s self and one’s boundaries, both mental and physical and the subjective phenomenon called ipseity [42] by neuro philosophers can be assessment of one’s social and material environment and drawing conclusions based on past experience and present requirements seem to involve the SN and the DMN. Finally, planning, making decisions and deciding how to act upon these constructs involve the CEN as well. All put together, the mind would seem like a well-orchestrated symphony of the triple network acting harmoniously together. At each step, things can go wrong, beginning from altered state of consciousness or permeable ego boundaries, to altered self-talk to abnormal saliency. All these could result in making erroneous judgments, dysfunctional mood or behavior leading to psychopathology. Based on all these, the author would like to say that the seat of the mind in the brain, both balanced or disordered, is the virtual complex interconnected working of the triple network.
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<td><strong>Main Networks involved (SN/CEN/DMN)</strong></td>
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Discussion

The triple network hypothesis seems to elegantly integrate all the available evidence on the neural basis of most important mental disorders. It explains why we may have to rework the current evidences from dynamic neuro-imaging into the diagnostic classification. It also explains the heterogeneity in the clinical presentation in illnesses like schizophrenia. Overlap in symptoms and borderline conditions can be now understood in the light of this hypothesis. Lesions in any of the nodes of the network can give rise to symptoms of psychiatric disorder without the full-fledged illness explaining 'organic' psychosis and other neuro-psychiatric disorders.

Why disorders do not completely ‘breed true’ also can be understood from this stand point.

The structure of the mind can at long last be elucidated as the synchronous functioning of the triple network and disorders of the mind as their dysfunction. This is not however a reiteration of the unitary theory of mental disorder or of the spectrum concept of mental mind as their dysfunction. This is not however a reiteration of the unitary theory of mental disorder or of the spectrum concept of mental disorder [63]. All that has been said is that the clinical symptoms would depend upon the site, severity and the reversibility of dysfunction in either the networks as a whole or their constituent nodes.

The author however fully understands that her hypothesis is based upon theories that have not been fully elucidated and on as yet unproved theories of the mind and mental disorders. Disorders like OCD or the tenacity to which delusions are held still cannot be understood completely but as new findings come to light, these mysteries too may be solved. However, the hypothesis may help to narrow down our search and focus upon these three important networks to get valuable and rewarding new insights. We have been groping in the dark for centuries searching for the neural basis of psychiatric disorders. This hypothesis may be a humble step towards some glimmer of understanding into the mind and its abnormalities.

References


