

# Clinical Brain Profiling. Brief and simplified

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In this short manuscript I will attempt a brief explanation of a novel method for the diagnosis of mental disorders that is called Clinical Brain Profiling (CBP). I will begin with a short neuro-scientific background, continue by translating phenomenology of mental disorders to pathology of brain organization with an explanation of CBP, and conclude by exemplifying some of the work of the psychiatrist of the future.

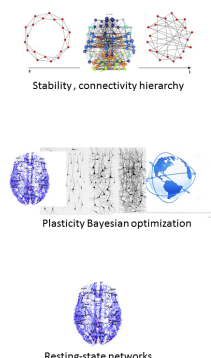
## 1) Neuro-scientific Background

Today we know enough about the workings of the brain to begin to formulate a brain-related diagnosis for mental disorders.

We know that the brain develops from infancy to adulthood, and beyond, by a process of "experience dependent plasticity". Such a process enables synapses to form connections among neurons based on their activations by the experience of incoming stimuli. Such activity enables experience to shape neuronal networks organizations spread in the brain.

Each one of us is basically a representation of the experiences perceived and accumulated throughout life. The networks of each and every one of us are thus different and unique encodings of the personal experience. This basic connectivity neural network structure of the brain was coined by Meynert in 1895 as "Ego." Such a network was revealed recently in imaging research and is typically called "Resting-state" (RS) or "Default mode network" (DMN) as it has been revealed in brain imaging of subjects at rest, or in non-task conations (figure 1 bottom).

Fig 1



Encoding life experiences - this network actually represents the way we envision ourselves and others, it holds in memory all experiences and thus obtains an internal model (or representation) of the outer world, including its psychosocial occurrences. Such internal representations, or "object Relationships" as psychologists term them, are used as internal maps (e.g., "Organismic maps" as Rogers (1) called them) which govern the way we feel and react to environmental psychosocial and other occurrences. In other words our personality traits are governed by such internal representations, and are thus dependent on the maturity and integrity of the resting state DMN (or Ego if you will). We can now begin and refer to personality disorders as disturbances to the resting state RS (figure 2 bottom).

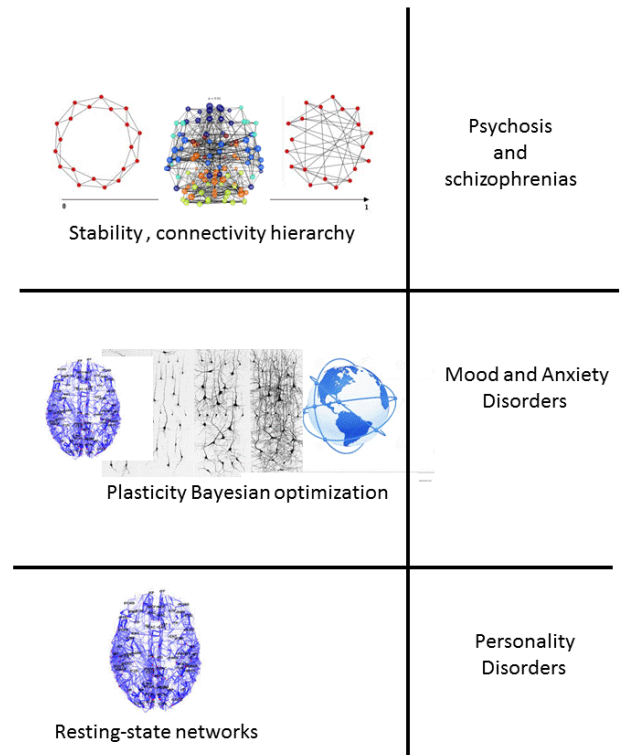
We have already mentioned that the RS network develops by strengthening connections among neurons thus creating a basic neuronal network structure for brain organization, the process of making connections depends on the ability of neurons to generate dendrites and spines forming the physical infrastructure that allows the development of the RS network. Such a process is termed "Plasticity" and it enables whole brain organization to adapt, encode and process incoming experiences (figure 1 middle). It is at the basis of offering optimal match between the internal representations and the actual occurrences. It allows the brain to generate internal constructs and adapt, predict, and project them to external occurrences, to generate an adaptive optimal predictive model which will guide us to effective productive and adaptive behaviors and achievements (Bayesian Brain discovered by Karl Friston 2). Optimization is when internal predictions match real

occurrences (e.g., the expectation of passing a test, matches actually passing it) will be accompanied by an emergent property of elevated mood. Emergent meaning a property that is of the entire system and not of the isolated events, or processes. Mood is not a characteristic of single neurons but it emerges as a characteristic of whole brain dynamics (i.e., optimization and reduction of predictive errors, free energy see Friston (2). Inversely in de-optimization, when there is a mismatch between internal expectation and actual occurrences, depressed mood emerges. Thus any reduction in plasticity will hamper optimization dynamics and cause depression. This is evident in dementia and diseases that afflict neuronal plasticity. Antidepressant medications are known to have plasticity inducing effects, and that explains how they might increase optimization and have antidepressant consequences. Plasticity also stabilizes the brain system (reduced frustration of constraints, see below) thus emerging with a calm tranquil sensation as opposed to anxious sensations that emerge from perturbed unstable neuronal networks. Middle of figure 1 and 2 symbolizes the plasticity, adaptability and optimization characteristics of the brain.

Finally the brain has to function and maintain optimization in the face of continued perturbations and instability generated by the computational activity and stimuli processing challenges. As a result, the RS network and its plasticity capabilities must be continually maintained, in other words the brain connectivity must be balanced impeding interferences from disconnection dynamics or over-connection activity (figure 1 upper part). In addition the connectivity maintains hierarchy. We know from graph theory that the connectivity configuration involves "hubs" of higher-level integrations, which integrate primary lower-level processes and allow for higher level integration of transmodal processes. The higher level hub networks integrate whole brain organizations into "Global Workspace" (3) constructs that carry the conscious content, an emerging property of conscious experience. Thus connectivity is balanced not only between disconnection and over-

connection but also hierarchically between top-down predictions and bottom-up prediction-errors (2), balance critical for optimal and correct interpretations of environmental occurrences (upper part of figure 2).

Fig 2



2) Translating phenomenology to pathology.

When translating clinical phenomenology to brain disturbances we assign schizophrenia and psychosis to instability and connectivity perturbations of the brain. We assign mood and anxiety disorders to disturbances of brain plasticity resulting in disturbed optimization dynamics. Finally we assign the phenomenology of personality disorders to immature, biased unstable RS network (figure 2) Disturbances to connectivity is either general, hierarchal or both, typically both relate to psychotic manifestations such as loosening of association, thought disorders, delusions and hallucinations, all intuitively conceived as resulting from disintegration of the connectivity hierarchical organization of the brain. Deficiency and negative symptoms result from over-connectivity of a consequently "fixated" brain which is

dynamically limited in the number of activations i.e., poverty of thoughts. Motivations hampered by bottom-up insufficiency and the lack of higher-level brain organization (4).

Disturbances to plasticity reduce optimization dynamics and hamper free-energy reductions resulting in the emergent property of depressed mood. Hyper-optimization will emerge as mania and oscillation of optimization dynamics will result in optimization instability and bipolar phenomenology. Conflicting signals between network neurons (constraint frustration) will destabilize brain networks with the outcome of an emergent property of anxious sensation of anxiety.

Patterns of non-adaptive, biased non-productive reactions and behavior within psychosocial context, is the mainstay of the definition for personality disorders, these are related to biased mismatching internal representations embedded within the structures of the resting state networks, thus the phenomenology of personality disorders can be attributed to altered biased diseased RS networks of the brain(4).

Capitalizing on these insights we can now begin and draft a set of brain-related disturbances presumably associated with the different psychiatric phenomenology that we encounter in the clinic. This can be defined as "Clinical Brain Profiling", an attempt to draft a "profile" of brain disturbances associated with the clinical findings.

### 3) Clinical Brain Profiling

Figure 3 defines how clinical brain profiling can be constructed.

First regarding the disturbances to connectivity balance, the hierarchal brain disturbances are divided into hierarchal bottom-up insufficiency (Hbu) and hierarchal top-down shift (Htd), the connectivity disturbances are disconnections, i.e., connectivity segregation (Cs) and over-connectivity, i.e., connectivity integration (Ci).

As for disturbances of plasticity, they can be divided into de-optimization (D) and hyper-optimization (O) dynamics, each with its related emergent property of "depression" and "mania" respectively. In bipolar conditions the brain

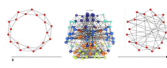
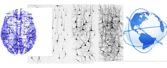

dynamics oscillate between these extremes of optimization dynamics. Neuronal network "strained" by computational demand from incoming stressor signals are perturbed and thus "constraint frustration" emerges within synaptic connectivity formations. A connection is considered "frustrated" when the waited value of connectivity is in discrepancy with the value of neuronal activation. In other words within neuronal ensembles when the value of connection weights are incompatible with that of values of neuronal activation. the emergent property of that condition is defined as anxious sensation, thus Constrain Frustration (CF) is a general form of disturbance while a more limited form is "bound" to specific stimuli (phobias) thus titled CF bound (CF<sub>(b)</sub>).

Finally, as already explained above the altered RS network presumably explains personality disorders.

The set of disturbances listed here, i.e., Htd, Hbu, Cs Ci CF, CF(b), O, D, and RS, construct a set of vector entries which will become the Clinical Brain Profile of the patient being assessed (Figure 4 top). The psychiatrist will evaluate the patients phenomenology (depression psychosis and so on) thereafter he will formulate the presumed brain disturbances afflicting the patient's brain and finally use those generated assumption to construct the clinical brain profile (vector) of that patient. The deduced profile will be personalized for the specific patient, thus CBP is in accordance with the current progression towards personalized medicine.

Furthermore the new CBP taxonomy is brain related and thus testable (4) and subject to validation, something that the older descriptive non-brain-related taxonomy cannot achieve. Descriptive DSM taxonomy cannot be validated, because it is not related to the brain.

Fig 3

Type of disturbances	Globalopathies	Clinical Phenomenology
Htd = Hierarchal top down Hbu = Hierarchal bottom up Ci = overconnectivity Cs = disconnectivity	 <p>Stability, connectivity hierarchy</p>	Psychosis and schizophrenias
D = De-optimization O = hyper-optimization CF = Constraint frustration CF = CF bound to stimuli	 <p>Plasticity Bayesian optimization</p>	Mood and Anxiety Disorders
RS = Disturbances of development of the resting state network	 <p>Resting-state networks</p>	Personality Disorders

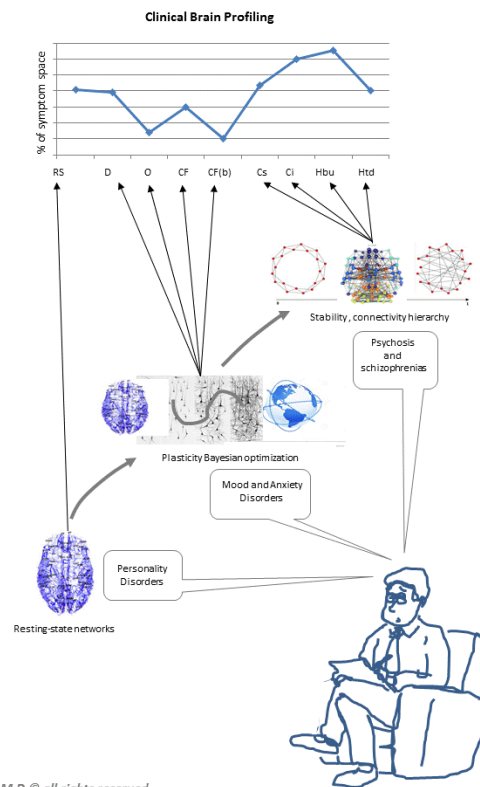
4) Psychiatrist of the future.

The psychiatrist of the future, when diagnosing patients will begin with the assessment of the phenomenology (complaints and observation) of the patient, just as he/she does today. The future psychiatrist will then generate the set of presumed disturbances to the patients' clinical manifestation. He/she will generate a personalized profile of brain disturbances for the patient's problems, i.e., Clinical Brain Profiling, and thus form a testable prediction for the causes of the patient's illness (figure 4). The patient will then be ready for the diagnostic imaging procedure that will follow. The next step, treatment, depends on technology of brain control, such technology involves Optogenetics (5), Focused Ultrasound, and DBS (deep brain stimulation). Technologies that can be designed to re-optimize, stabilize and correct the brain disturbances and as a consequence eliminate symptoms and signs and cure mental disorders.

The assessment procedure achieved by the psychiatrist of the future will be comprehensive and address the comorbidity and spectrum phenomenology which is the rule (not the exception) of clinical manifestations in patients. For example: a good assessment of the developmental trace of the individual can provide insights into the resilience and robustness of the RS network. A RS network which is rudimental biased or malformed will inevitably mismatch with occurrences in real life, thus generating de-optimization

confirm the brain disturbance generated by the CBP. Hopefully in the near future signal processing of brain-imaging will advance to the extent that effective validation of CBP can be obtained.

Fig 4



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dynamics, with the emergent property of depression. No wonder that those suffering from personality disorders typically complain of depression and anxiety. If stress of any sort (psychosocial or chemical drugs), perturbs the brain network organization further, then disconnection dynamics may arise with the patient exhibiting psychosis. This example shows how a variety of concomitant clinical manifestations can become established in one patient, currently typically diagnosed as Borderline Personality Disorder.

As for treating these patients, future medications, or stem-cell neuronal transplants, will increase brain plasticity tenfold and offer the ability to conduct "plasticity altering therapies" that can reshape brain developmental organization and correct aberrant RS networks thus easing

substantially the clinical manifestations of personality disorders. Optimizing the RS networks will also increase adaptability and reduce mismatch and free energy, thus eliminating depression and anxiety symptoms. In addition, an optimized stable connectivity balanced network will prevent psychotic symptoms, but if they occur "brain pacer" devices can reconnect and re-optimize connectivity balances thus eliminating psychotic symptoms.

We can now envision how the psychiatry of the future will be conducted to effectively cure patients. This can all start by adopting the CBP format for psychiatric diagnosis.

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