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Paving the way for new research strategies in mental disorders. Second part: The light at the end of the tunnel

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Abstract. Following we consider strategies to overcome the situation described in a previous article (López-Ibor JJ, López-Ibor MI. Paving the Way for New Research Strategies in Mental Disorders. First part: the recurring crisis of psychiatry. *Actas Esp Psiquiatr*. 2013;41(1):33-43), by putting emphasis on psychopathology instead than in classification, in functions rather than in diagnostic criteria, to be aware in the progress in neuroscientific monistic perspectives and by importing the methods of the emerging connectomics. Medicine is undergoing deep changes. Networking is becoming the new paradigm and we consider that it should be the turning point of the future psychiatry, both in research and in practice.

Key words: Classification, Mental disorders, Dualism, Connectomics, Network medicine

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Hacia nuevas estrategias de investigación en los trastornos mentales. Segunda parte: La luz al final del túnel

Resumen. A continuación consideraremos las estrategias a seguir para superar la situación descrita en un artículo previo (López-Ibor JJ, López-Ibor MI. Hacia nuevas estrategias de investigación en los trastornos mentales. Primera parte: La crisis recurrente de la psiquiatría. *Actas Esp Psiquiatr*. 2013;41(1):33-43.) centrándonos en la psicopatología en lugar de en la clasificación, en las funciones más que en los criterios diagnósticos, teniendo en cuenta en el progreso de las perspectivas monistas neurocientíficas e importando los métodos de las conectómicas emergentes. La medicina está sufriendo profundos cambios. La creación de redes se está convirtiendo en el nuevo paradigma y consideramos que este debería ser el punto de inflexión de la futura psiquiatría, tanto en investigación como en la práctica.

Palabras clave: Clasificación, Trastornos mentales, Dualismo, Conectómicas, Creación de redes

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INTRODUCTION

In a previous article, we have gone the present although old crisis of psychiatry around three paradigmatic areas: classification, dualism and localizacionism.¹ Following we will consider possible ways to rise above the present impasse. We will group them according the three elements described above. Of course, they are not the only ones, they overlap among themselves, and most of them are in need of much research efforts.

THE RENAISSANCE OF PSYCHOPATHOLOGY

It has been suggested that a "renaissance of psychopathology" might be necessary.² Which psychopathology? For sure a different one, beyond dualism and associated to new perspectives such as adaptation and endophenotypes. Lopez Ibor Sr. reported his last conversation with K. Schneider.³ At a certain moment Schneider confesses that psychopathology has come to an end and that there are no new avenues to explore. López Ibor contradicted by saying the psychopathology that you have so successfully fostered. There must be new ways. Then the conversation went on other directions.

Let's put forward an example. In a research project⁴ of the perception of faces of unknown people, with an emotion free expression, we decided to select a sample of highly delusional patients with low scores in hallucinations. The aim was to investigate the attribution of meanings to a relatively non-significant but complex sensory experience in patients suffering from delusions. Actually all the patients fulfilled criteria for first episode psychosis. The method was an evoked potential paradigm explored with MEG. In essence we found that the activity generated by the stimuli went progressively along several brain structures each one performing a different task which we presumed to be related to a specific trait of delusional activity. The main differences with controls were:

1. BA17 (visual primary areas) at < 100ms: no difference with controls, therefore the visual stimulus is normally recognized.

2. BA 37 (*gyrusfusiformis*, Kanswisher fusiform face area) at 200ms: no difference with controls: a face is recognized as a face.
3. BA 21, 41 & 42 (auditory cortex) at 100-700ms: significantly higher activity than controls. BA areas 41 and 42 perform the basics of hearing (pitch and volume) and have connections both to higher and lower centres. BA21 is a region believed to play a part in auditory processing and language, and has abundant connections with the Wernicke's auditory cortex (BA 22, 39 and 40). The fact that a visual stimulus, once reconstructed in the primary visual areas and recognized in as a face in the *gyrusfusiformis* merits an explanation. We will come to it latter.
4. BA 38 (temporopolar area) right hemisphere: 300-400ms: significantly higher activity than controls (8.3 vs 0.4, $p < 0.5$)
5. BA 38 (temporopolar area) left hemisphere: 300-400ms: significantly lower activity than controls (71.5 vs 7.7, $p < 0.5$). We analyse following the interpretation of this results.
6. We could not record any activity of the amygdala, which cannot be detected by MEG due to the architecture of this centre, nor any from the frontal lobe, may be to the small size of the sample.

What do "auditory" areas really do

At this point we have to delve into philosophical concepts which are essential in psychopathology.⁵ Psychopathology is one of the humanities, perhaps the uppermost in rank because it deals with one of the confines of human nature.

In a previous paper on the etymology of the word anxiety we have included reflections on the origin of the Greek word *logos*.⁶ Although the word survives mainly as a suffix (i.e., psycho-logy) and is kept in some languages mainly as a cultism, we have lost its original meaning. The Greek word *Logos*, derives from the substantive *lego* and this one from the verb *légein* 'to choose', 'to put together', 'to count', 'to calculate', 'to say about', and 'to speak'. The original meaning has split into two or even three (the third one appears in the Oxford Dictionary and in the Webster Dictionary, but not in others of different languages):

1. Word, speech.
2. Reason, thought, proportion, measure, calculation.
3. The divine wisdom manifested in the creation, government, and redemption of the world and often identified with the second person of the Trinity.

Logos in philosophy is the rational principle that developed and governs the universe. For the pre-Socratic philosophers is the principle that governs the cosmos. The neo-Platonic

philosophers used this term in metaphysical and theological sense, *logos* is the intermediary between God and the cosmos. In the Johannine gospel *logos* is the word of God become flesh, as the supreme way of alliance between God, nature and human beings. In Goethe's *Faust* John's *logos* is translated as 'will'.

We also considered in the quoted paper the meaning of Proto-Indo-European and Nostratic two roots which had in common a third and older one:

1. *Legh-* 'to lie down' 'sediment', 'deposit' (which derived into *lie*).
2. *Legh-* 'to pick up', 'to collect', 'to put together', 'to count' (which derived into *eclectic*, *to collect*, *legend*, *legion*, *intelligence*, *law*, *colleague*, *college*).

Heidegger in his commentary to Fragment B 50 of Heraclitus known as "Logos"⁷ writes: "O *Lógos*, *tó Legein*, is the laying that gathers". But at the same time *légein* always means for the Greeks to lie before, to exhibit, to tell, to say. O *Lógos* then would be the Greek name for speaking, saying, and language. Furthermore, *Lógos* is also what is said, the legend, the myth. "Myth means the telling word. For the Greeks, to tell is to lay bare and make appear -both the appearance and that which has its essence in the appearance, its epiphany. Mythos is what has its essence in its telling-what is apparent in the unconcealedness of its appeal. The mythos is that appeal of foremost and radical concern to all human beings which makes man think of what appears, what is in being. *Logos* says the same; mythos and *logos* are not, as our current historians of philosophy claim, placed into opposition by philosophy as such; on the contrary, the early Greek thinkers (Parmenides, fragment 8) are precisely the ones to use mythos and *logos* in the same sense". The *legein* of *logos* is interpreted by Heidegger in a transitive way (way lie in front of others in order to communicate), we prefer the intransitive way (things are laid in front of us before we collect them) but this is secondary to the fact that *Logos* is at the same time thought and speech.

Our hypothesis is that as we cannot separate language from thought, speaking from thinking, therefore the "auditory" areas should be considered as essential not only for hearing but to give a meaning to the experience. Thinking consists on a series of actions: identifying, gathering, picking, naming and categorizing the objects of nature in order to store concepts in our minds. But to *Logos* also belongs the communication and sharing of the outcome of the process of thinking. That is the logic of thinking. *Logos* must be translated as thought and say. *Intellectus ex sua natura est locuturus*⁸ (the nature of thought is speech).

The temporal pole roles

Until the excellent review of Olson et al.⁹ the functions of the anterior-most portion of the temporal lobes was an

enigma. Now it is considered to play an important role in both social and emotional processes, including face recognition and theory of mind.

The right anterior temporal lobe appears to be associated with emotion and socially relevant memory. The right temporal pole is the storehouse¹⁰, or site of recollection¹¹ of personal, episodic memories. The resection of the right temporal pole leads to a difficulty in recalling personal memories relevant to the test faces, diminishing the ability to recognize, or recall any information about famous or personally familiar faces^{12,13}.

In contrast, the left anterior temporal lobe is more closely associated with semantic memory. Left resection surgery leaves the ability to generate information about people intact, but causes proper naming abilities¹³ and face - name associative learning¹⁴ to plummet.

These findings raise the possibility that the right temporal functions to link high-level sensory representations with emotional responses and social memory. The left temporal pole functions to link high-level sensory representations, such as a face, with semantic information.

Again, our hypothesis is that the increased activity of the left temporal pole, which links the representations of meaning that are distributed over the cortex¹⁵, and which is involved in the recognition of persons⁹ gives an answer to who belongs that face? The higher activity may mean that in our delusional patients could be interpreted as the fact that a picture of a non-familiar face is recognized as a person already know and a name is given to a non-familiar face, i.e., a (supposed) persecutor.

The decreased right temporal lobe activity in delusional patients has a totally different interpretation. A reduced activity affects deteriorates of personal, episodic memories, hampers recalling personal memories relevant to the perceived faces. Answers the question with whom? The hypoactivity in delusional faces may be at the base of the fact that familiar faces are deprived of emotions and memories of past experiences, leading to social withdrawn, autism and mistrust.

We fully accept the nature highly speculative of our explanations, but we believe that the task of future research should go in this direction and that it will be a task for a generation. On the other hand, what could be the brain activities involved in the complexity of the process of thinking and sharing meanings.

OVERCOMING DUALISM

Dualism has been challenged by neuroscience. Again we refer to our paper on body experience an identity¹⁶ where we have analysed several proposals. Of course it is easy to

behead soul, psyche, mind and consider them as emanations or fabrications of the brain. This is the radical posture of Crick, which has been thus expressed:

*Science has shown to you that "you", your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will are, in fact, no more than the behaviour of a vast assembly of nerve cells and their associated molecules. As Lewis Carroll's Alice might have phrase it: "You are nothing but a pack of neurons; and the mechanism is what matters: the rest is nothing else than a game of words."*¹⁷

Radical, chiasmic Janusian monism

Our proposal has two arms: chiasmic and Janusian:

1. Chiasm or chiasmic or ring structure is a literary device used in turns of phrase or narratives especially in the political and religious jargon. Chiasmus is a *crosswise arrangement* of concepts or words that are repeated in reverse order, crossing each other as the two branches of the Greek letter X. An example is enough to see what we mean: *Mankind must put an end to war, or war will put an end to mankind* (John F. Kennedy).

The chiasm is used by Merleau-Ponty to designate the "unitary dualism in itself", which means that it is the structure of the thought that compels to consider the phenomenon of the human body, the body itself, from two perspectives and not two realities.

*The chiasm is a thought schema that allows us to conceive the relations of a duality in terms of reciprocity, intertwining, complementarity, superimposing, reversibility, mutual reference [...] All the contrary of the dichotomy, dualist schemas, that conceive the relations in terms of exclusion, exteriority, mechanical and lineal causality, hierarchy and priority. The chiasm schema is what allows us to consider duality as a unit in process, in evolution.*¹⁸

Janism refers to the Roman god Janus. According to the myth, Janus helped Saturn, who was expelled from the heaven by Jupiter. He, with very much hospitality, took care of him for quite some time, in gratitude, Saturn gave him the power to see past as well as future clearly and simultaneously in order to act wisely under any circumstance. Therefore Janus is represented with two faces looking in opposite directions. One does not see the other and also cannot see the world that the other is seeing. One face looks to the past, another to the future, one to the interior (*Janus Clusivus*), another to the exterior (*Janus Paltusius*), one to the beginning and one to the end, which is beginning and end, entrance and exit door. Indeed Janus was the god of the entrance doors, of the beginnings and the endings. The first month of the year was dedicated to him and has its name:

Ianuaris from where January derives. Janus, alone, protects the universe (*me penes est unum vasti custodia mundi*)¹⁹ (transl.; My power alone is the custody of the vast of the world), keeps the harmony, especially in the critical transition moments. Definitively, Janus is the god of the transitions, of the critical moments of the steps that cannot arise without its divine, powerful and wise protection.

The need to know, to learn to live and survive, has led to the view that there are two aspects of the real world to be explained by the limitations of human knowledge, which ultimately leads to a methodological dualism, for which with regardless of how reality is, the only way to approach it from two different perspectives that uses two distinct and irreconcilable methods, the physical and mental. In one reality we have to move, measure our steps, on the other we have to relate to other human beings, live together and compete. Unicellular beings need only information on the characteristics and physical changes in the environment in which they are to survive, feed and reproduce. Just as higher animals, including those of our species, that knowledge needs to move or settle, avoid danger, feeding or breeding. If I were not to perceive the heat of the candle as in the drawing with which Descartes illustrated his dualism, I would burn me, or I would fall down a staircase if unable to measure distances. But developed animals are beings with a high degree of socialization and knowledge here we are in a different situation. Recognize friend from foe, identify with one or other, cooperate for the purpose of the group, integrated into a hierarchy, look for opportunities to reproduce and raise offspring requires knowing more than just a physical dimensions, *a res extensa*.

Neuroscience has defended a similar position, particularly in regard to the double aspect theory whereby the brain constructs the two ways of knowing, rational and empirical, and therefore the two realities, the physical and mental.²⁰

Therefore, we came to the conclusion that a radical monism it is possible, compatible with one more essential aspect, which is the adaptive value of a double cognitive, empirical and personal value. It is a *Janicular, chiasmic monism*. The challenge for the future is to investigate how these two forms of approach, or construction of reality, are integrated with each other, in a spontaneous and unproblematic way, because we did not spend life with a GPS in one hand and a greeting in the other.

CONNECTIVITY AND NETWORKING

The alternative to phrenology is to look for the interaction between centres, to how they communicate with each other and their integration in networks at different levels of complexity. This is an old story once and again eluded. Avoided for too long, both in psychopathology as in neurobiology.

Connectivity and networking in schizophrenia

If we go back to Kraepelin and Bleuler we immediately see that the notion of loss of links, of splitting comes once and again when describing the disease:

*Dementia praecox is characterized by the destruction of the internal links of personality and loss of the inner unity of the activities of intellect, emotion and volition in themselves and between each other.*²¹

The definition of schizophrenia Bleuler²² is, in this aspect, identical:

In any case there is a more or less distinct division of mental functions: once the disease manifests itself, is personality loses its unity; suddenly one those mental complex represents the person: the mutual interference of the different complexes and strivings is insufficient or missing outright; mental complexes come together no longer as in the healthy to a conglomerate of strivings with consistent results, but a complex dominates the personality temporarily, while its other imaginative or striving group are "divided" (original German: "abgespalten") and wholly or partially invalid.

Let's put it in another way, what is important is the disharmony between psychological functions, no so much a specific alteration of any of them. There, is no paralysis but a "ataxia of feelings" also called "intrapyschic ataxia" (Stransky^{23,24}) is therefore useless locate that are affected nerve centres in the disease. No wonder they are the following comments: endogenous psychoses are the Delphic oracle of psychiatry^{25,26}, schizophrenia is the graveyard of neuropathology²⁷ and molecular genetics²⁸.

*Stransky has ..., said that in our patients is not so much a devastation of mood, as an "ataxia of feelings," the loss of the relationship of psychological processes with each other. I am inclined to assume that this confusion is in the emotional life caused mainly by weakening the higher, lasting feelings, whose job it is one the hand to dampen sudden changes of emotions, on the other to give even enduring tension and warmth in order to ensure the consistency of our emotional relationships with the outside world.*²¹

The clinical core of schizophrenia

The clinical core of Schizophrenia has disappeared from in the ICD-10 and DSM-III and IV, which are statistical tools based on operational definitions and qualifiers, which say nothing about what diseases are themselves²⁹. The descriptions in both manuals correspond to a subgroup of patients, suffering from delusional paranoid hallucinatory schizophrenia.

The specific symptoms of schizophrenia are impaired thought processes, associative losing connection, there is then a *Spaltung*, a rupture of the association of ideas.

*Among the hundreds of associative threads that guide our thinking, this disease appears to interrupt, fairly capriciously, sometimes a single thread, sometimes a whole set and sometimes fragments of them.*²²

Bleuler's ideas about schizophrenia were influenced by the word association task psychological test developed by Jung and Riklin at Burghölzli because he believed that some sort of disorder of association underlay the symptoms of dementia praecox. This led to his concept of *loosening of associations*.

Since Kraepelin and Bleuler and up to ICD-8 there is an invariable concept of schizophrenia which is defined by the presence of:

Fundamental clinical core manifestations, considered as a trait, which is present in a spectrum (schizoid and schizophrenia latent), which affects all domains of consciousness (subjective experience, expression, cognition, emotions, behavior and willingness), whose specific characteristics can be grasped from comprehensive gestaltic level and not understandable from consideration of isolated features, which has been called in different ways (*Zerstörung*, autism, *Spaltung*). Research on the fundamental characteristic of schizophrenia has produced a long series on observations and interpretations such as: *Zerstörung* (devastation, Kraepelin²¹), intrapsychic ataxia²²; 'disjunction' (dementia sejunctiva, Wernicke³⁰ and Gross³¹), *Spaltung* (splitting, dissociation, Bleuler), *dynamische Entleerung* (dynamic emptying, Janzarik³²), alteration of the experience of self (Wyrsh³³, López Ibor³⁴), self-disorder or ipseity disturbance (Sass and Parnas³⁵) and so on.

1. Positive psychotic features (state)

We call attention to the facts that the disease affects all domains of mental life, that its characteristics can only be captured in its wholeness, as it is not altered specific functions, because what is wrong is the connections between them. Now we can understand the statements by Hofer³⁶, and Tellenbach³⁷ on the nature of manifestations of endogenous psychosis as phenomena and not as mere symptoms or isolate dysfunctions mentioned above.

2. This core of schizophrenia has disappeared from the ICD-10 and DSM-III and IV²⁹, which are based on operational definitions, which are statistical tools and qualifiers, which say nothing about what diseases are themselves. Both systems mainly considered a subgroup of patients, those with delusional paranoid hallucinatory schizophrenia

Connectome and connectomics

In 2005, almost simultaneously Olaf Sporns and Patric Hagmann provided two new and equivalent terms:

connectome and connectomics, names that have given rise to a new perspective of neuroscience that opens new possibilities.

The objective is to achieve connectomics full matrix brain interneuronal connections. The connectome encompasses everything from a detailed map of neurons and synapses in part or in all of the central nervous system of an organism to the macroscopic description of the structural and functional connectivity of all cortical areas and subcortical structures.

Moreover, neuroanatomy has not been very receptive to the importance of brain circuits. The first description cortico-subcortical circuits and even a visceral brain is of Christfried Jakob in studies carried out between 1908 and 1911³⁸. These circuits are not mentioned again until in 1937 James Papez³⁹ circuit described the emotions circuits that bears his name (transformed by many in Papez-Jakob) and Paul McLean in 1949 the limbic system or the emotional brain.

The connectome is being studied through a combination of histological techniques (dissection and staining of white matter fibres, axonal degeneration studies) of neuroinformatics (database management), functional imaging (DTI, tractography). The connectome is a dynamic map, which varies with the sensory input, the overall state of the brain, learning, development, tasks to perform.

There are several levels of connectivity:

1. A macro-scale (resolution of millimeters) searched is on areas or nodules with different connectivity patterns, which aims to build a structural and functional map of the human brain by combining different neuroimaging techniques and resolutions, as is carrying out the project Human connectome of the National Institutes of Health, a consortium led by St. Louis University of Washington and University of Minnesota.
2. A meso-scale (hundreds of microns resolution) are studied populations of neurons in local circuits (e.g. cortical columns), or invasive techniques using high-resolution MRI.⁴⁰
3. A micro scale (neuron to neuron) using electron microscopy techniques, considering that 1010 is in each brain neurons connected through synapses 1014. The Open Connectome Project is an open science project on the Internet⁴¹, anyone who has access to a computer, regardless of training or knowledge.

It is very important to underline, that terminology connectomics is not a neuroscientific one. It belongs to the social sciences, and especially the economy. There concepts such as: network (the entity set a specified pattern of relations between them), the connectivity of a system, the extent to which agents (entities) interacting system, the cost of a network, the cost of building connections between nodes (vertices) of a network (regardless of the physical links

that may exist between them, defined as the total number of end divided by the maximum possible number of edges).

Van Horn et al.⁴² have reconsidered the hypothetical brain damage case of Phineas Gage famous previously had analysed Damasio et al.⁴³ concluding that the rod that penetrated the skull destroyed railroad worker about 4% of grey and 11% white matter, and they were able to identify lost connections whose effects would be felt at a distance,

Networking in science

Scientific disciplines are the "infrastructure of science". They are enlivened in scientific journals, textbooks and lab manuals, in academic curricula, in university departments and in professional societies. But, according to several contemporary authors⁴⁴⁻⁴⁹ scientific disciplines are best understood as ideological discourses of power as well as instruments of knowledge production from the perspective of economies of practice. They are born and develop not as the consequence of a rational process of decisions, but rather as the consequence of institutional mechanisms regulating the market relations between consumers and producers of knowledge. Furthermore, disciplines determine scientists' relations to other contexts, scientific and non-scientific and therefore, academic identities are primarily disciplinary identities⁵⁰.

Scientific disciplines advance knowledge but at the same time they are power instruments: *"Disciplines are dynamic structures for assembling, channelling and replicating the social and technical practices essential to the functioning of the political economy and the system of power relations that actualize it."*⁴⁶

According to Foucault⁴⁶ within a given discipline or field, both objects and concepts are co-produced in discourse, which itself is immersed in a historically conditioned process, where the configuration, coexistence, and grouping of statements takes place. These statements do not possess a meaning by reference to a previous set of objects, on the contrary, meaning is constituted within a "complex space of juxtapositions, associated domains, and bordering fields, connected not by an immanent logic or progressive historical unfolding but genealogically, that is, by series of historical contingencies related by constancy of use."

On the other hand, this construction of statements is directly associated to the structure of the notion of truth, which itself is related to the notion of power. Every society is based on what Foucault⁴⁷ calls a regime of truth, defined as: "a system of ordered procedures for the production, regulation, distribution, circulation and operation of statements. In other words, disciplines are structures for "systematizing, organizing, and embodying the social and institutional practices upon which both coherent discourse and the legitimate exercise of power depend."⁴⁶

If, in a certain way, no one creates disciplines, and scientific disciplines are culture bond realities, an economy of practice approach should help to clarify the problem of discipline formation⁴⁹. One of the conclusions of this way of progressing is that the scientific field, a particular case of the more general cultural field, is a "locus of competitive struggle", in which the specific issue at stake is the monopoly of scientific authority, defined inseparably as technical capacity and social power.⁴⁹ For that reason, scientific field and economy of practice are glued together so that the political struggle to dominate resources becomes inseparable from the cognitive task of defining what constitutes authorised, legitimate science. For this reason scientists are engaged in legitimating their power to define domains of the (scientific) field in which they have interests (so they can gain recognition for their outcomes). Scientific disciplines are considered to be "political institutions that demarcate areas of academic territory, allocate privileges and responsibilities of expertise, and structure claims on resources." Meanwhile, disciplinary programs are described in this context as "strategies for organizing parts of the scientific field through developing channels of recruitment, establishing service roles, training, and building political alliances with neighbouring fields."⁴⁶

From this perspective out, there is no unity in science, and if so, the implications for the discussion in the present paper are gigantic, and should be considered in the networking strategies do develop and implement. In economic terms, by treating scientific practice as a political struggle for the control of capital (in the form of credibility, material resources, intellectual products, etc.) science is depicted as a disunited social enterprise, where patterns of scientific rationality and coherence are coalesced with external factors and irrational elements of socio-political interest.⁴⁶

Network medicine

Network medicine is a recent concept⁵¹⁻⁵³ which is changing the distinctive roots of modern medicine. As we have already mentioned, contemporary classification of human disease dates to the late 18th century, and is the consequence of the anatomo-clinical method that correlates observations initially at bedside and clinical and pathology findings. Throughout the last century, this approach became more objective, as the molecular underpinnings of many disorders were identified and definitive laboratory tests became an essential part of the overall diagnostic paradigm.

With the complete sequence of the human genome a reality, and with a growing body of transcriptomic, proteomic, and metabolomic data sets in health and disease, medicine can define human disease precisely, uniquely, and unequivocally, with optimal sensitivity and specificity⁵⁴.

Thus, the network concept reveals a number of surprising connections between diseases, forcing us to

rethink the way in which we classify and separate them. In the long run, networks may affect all aspects of medical research and practice.^{51,55}

Nowadays the needs of care, research and even teaching, cut crosswise disciplines and new specialties have been implemented (i.e., geriatrics). Networking is the emerging trend that shakes medicine as a science and as practice.

Disease is rarely a consequence of an abnormality in a single gene, but reflects the perturbations of the complex intracellular network. Given the functional interdependencies between the molecular components in a human cell, the emerging tools of network medicine offer a platform to explore systematically not only the molecular complexity of a particular disease, but also the molecular relationships between apparently distinct (patho)phenotypes⁵⁶. Advances in this direction are essential to identify new disease genes, to uncover the biological significance of disease-associated mutations identified by genome-wide association studies and full genome sequencing, and to identify drug targets and biomarkers for complex diseases.

Most cellular components exert their functions through interactions with other cellular components, the totality of these interactions representing the human interactome. The complexity of this network is overwhelming: circa 25000 protein-encoding genes, about a thousand metabolites, and an as yet undefined number of distinct proteins and functional RNA molecules, the distinct cellular components that serve as the nodes of the interactome exceed one hundred thousand. The number of functionally relevant interactions between the components of this network, representing the links of the interactome, is expected to be much larger and remains largely unknown⁵⁷.

This subcellular interconnectivity implies that the impact of a specific genetic abnormality is not restricted to the activity of the gene product that carries it, but can spread along the links of the network, and alter the activity of gene products that otherwise carry no defects. Therefore, the phenotypic impact of a defect⁵⁸ is not determined solely by the known function of the mutated gene, but also by the functions of components with which the gene and its products interact and of their interaction partners, i.e., by its network context.

A disease is rarely a consequence of an abnormality in a single effector gene product. Instead, the disease phenotype is a reflection of various pathobiological processes that interact in a complex network.

The human interactome consists on molecular networks (protein interaction networks), metabolic networks, regulatory networks (regulatory relationships between a transcription factor and a gene) or post-translational modifications (i.e., between a kinase and its substrates) and RNA networks (capturing the role of RNA-DNA interactions

such as small non-coding microRNAs and siRNAs in regulating gene expression).

There are also phenotypic networks (co-expression networks, in which genes with similar co-expression patterns are linked) and genetic.

Network medicine relies on a series of advances in network theory⁵⁹⁻⁶³, which have provided insights into the properties of biological networks more generally. Hub proteins must play a special biological role. Indeed, evidence from model organisms indicates that hub proteins tend to be encoded by essential genes⁶⁴, and that genes encoding hubs are older and evolve more slowly than genes encoding non-hub proteins.

The hypothesis is that once a few disease components are recognised, the other disease-related components will likely be in their network-based vicinity. That is, we expect that each disease can be linked to a well defined neighborhood of the interactome, often referred to as a *disease module*. There are three distinct but interrelated phenomena: A *topological module* (a locally dense neighborhood in a network, such that nodes have a higher tendency to link to nodes within the same local neighborhood than to nodes outside of it); a *functional module* (the aggregation of nodes of similar or related function in the same network neighborhood) and a *disease module* (a group of network components that together contribute to a cellular function whose disruption results in a particular disease phenotype).

Often the rate-limiting step in mapping a disease module is the small coverage of the available cellular interaction maps in the vicinity of the known disease components, requiring additional experimental efforts to identify relevant interactions. This approach was successfully applied to several diseases, including schizophrenia⁶⁴.

The highly interconnected nature of the interactome means that at the molecular level, it is difficult, if not counter-intuitive, to consider diseases as being invariably independent of one another. Indeed, different disease modules can overlap, so that perturbations caused by one disease can affect other disease modules. The systematic mapping of such network-based dependencies between the pathophenotypes and their disease modules has culminated in the concept of the *diseasome*⁶⁵, representing disease maps whose nodes are diseases and whose links represent various molecular relationships between the disease-associated cellular components. Uncovering such links between diseases not only helps us understand how different phenotypes, often addressed by different medical sub-disciplines, are linked at the molecular level, but can also help us comprehend why certain groups of diseases arise together. The comorbidity of conditions culled from the *diseasome* offers insights that may yield novel approaches to disease prevention, diagnosis, and treatment.

Contemporary approaches to the classification of human disease are based on observational correlations between pathological analysis and existing knowledge of clinical syndromes. Yet, modern molecular diagnostic tools have shown the shortcomings of this methodology, reflecting both a lack of sensitivity in identifying preclinical disease and a lack of specificity in defining disease unequivocally.

Current disease classification, in general, tends to neglect the interconnected nature of many diseases. This failure is partly a response to the focused nature of medical training, as well as the reductionist paradigm that has driven medical diagnosis in the modern era. In an effort to correct this shortcoming, we recently proposed a systems-based network framework for defining human disease⁵⁴. Network-based approaches to disease have the potential, therefore, to provide a new and useful framework for classifying disease, defining disease susceptibility, predicting disease outcome, and identifying tailored therapeutic strategies.

The notion is that most human diseases are not independent of each other, as they are associated with the breakdown of functional modules that are best described as sub-networks of complex of genetic, regulatory, metabolic, and protein - protein interactions in a cellular network which is at the core of the pathophysiology of human diseases. On top of this there are two more layers. The middle one is a disease network in which two diseases are connected if they have a common genetic or functional origin. Functional should be interpreted as relevant for adaptive purposes. Barabási quotes as an example that the genes involved in obesity are connected to at least seven other diseases (diabetes, asthma, and insulin resistance). The third level is the social network, which encompasses all human-to-human interactions (e.g., familial, friendship, sexual, and proximity-based contacts) that play a role in the spread of pathogens.

CONCLUSION

In a first part we have gone through a recurrent crisis of psychiatry around three main elements: classification, dualism and localizationism. Of course, there are other elements that could have been considered, but the three chosen seem to us quite nuclear and help to envisage strategies in psychopathology and neuroscience in general.

The limitations of clinical research can be overcome if the emphasis is put on psychopathology and in the adaptive value of symptoms and dysfunctions. Localizationism can be overcome. Progressing as we have done, suddenly we became aware that the crisis of psychiatry is not unique. The whole of modern medicine is running away with its deepest tradition. Diseases are not to be investigated *per anatomen* nor the *sedes et causae* looked for in organs. The issue is networking, the study of the human interactome and the

diseasome. Connectomics is the new discipline which encompasses neuroscience with social being in the process of give rise to a new language. Curiously enough the princeps descriptions of Kaepelin, Bleuler and many other of the great masters, insist, once and again, on the breakdown of links between the functions that shape personality.

Network medicine and network psychiatry open new avenues for research. They are a great opportunity and greater challenge. Let's hope that they will be the end of the Sisyfication of psychiatry, both as a scientific discipline and as medical specialty.

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