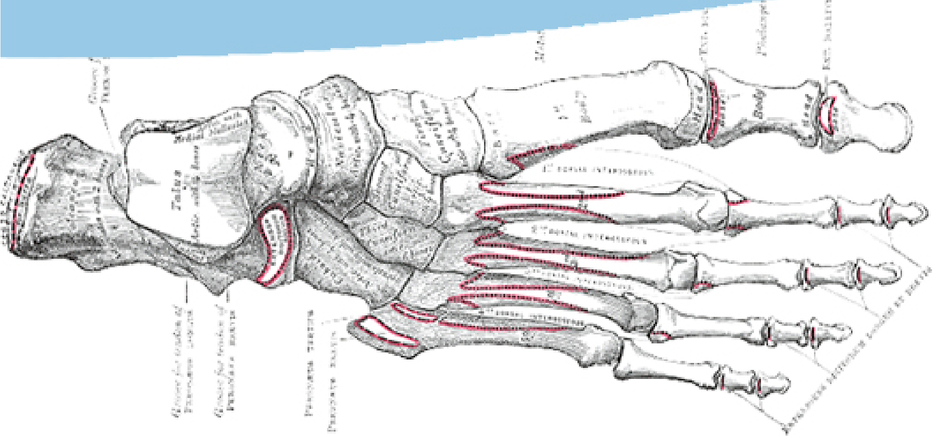

4. Revisión 2

General perspective of current knowledge and ways we may increase it in neuroscience

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Abstract: Brain function is a somewhat complex issue. However, based on the theory of the network system that includes concepts such as Modularity, Scaling, Connectome, Emergence and Specialization, we can draw some points in common that allow an approximation to the underlying mechanisms of cerebral connectivity. In the field of neuroimaging, there is a large number of techniques that allow the brain to observe the anatomical and functional approaches in different ways and allow us to make correlations that guide us in order to unravel the mechanisms of brain function. The most commonly used techniques in neuroscience are magnetic resonance, electroencephalogram, and magnetic stimulation. And it is by combining those theoretical concepts with the data obtained from the different techniques that allow neuroscientists to expand their knowledge in neuroscience. The aim of this work is to combine and facilitate the understanding of some complex concepts regarding the functioning of the brain and to serve as an introduction to research work in the field of neurology.

Network Theory

The field of Network Theory is one of the most complex as of today. It studies several phenomena , recently including neuroscience, but comprising fields as diverse as social sciences, economy, biology or meteorology.

A network consists of simple or complex components and connections. The first thing to look at is whether it is possible to deduce the properties of a given system by looking at its components or such a task is not possible. According to Sporns, a complex system is one in which elements enter into dynamic interactions from where new phenomena arise on a global scale that shows properties that cannot be deduced from the properties shown by its isolated elements.

This theory of complex network systems began with an intersection of four different fields: mathematics, computer science, statistical physics, and social sciences. It seeks to provide a framework for examining complex systems that show non-trivial component-to-component connection.

The simplest application would be to use statistics to describe any connection in a system. It is possible from there to seek the underlying organizational principles of the system to identify which properties best fit the system for its intended purpose. This is known as applying graph theory.

When making more complex analysis, the graphical properties of random systems can be used to predict their characteristics and even their functions, and conversely, to construct an optimal system for a certain purpose. Further developing this idea would imply extending the graphic models to create more intricate models in which information about individual component characteristics, functional algorithms, and other variables is added to simple connection maps. The result of this would be a complex system.

Although there are many points of contact between the network theory and the human brain, describing them goes beyond the scope of this work. Only those that are present in most of the literature found will be mentioned:

Modularity
It is the property by which a system can be decomposed into subcomponents or "modules", which can perform unique functions and can adapt or evolve according to external requirements. Taking the social sciences as an example, it would be possible to decompose the entire ”Facebook” network into small networks of friends (in which case the network of every two readers of this article would be different and could constitute different modules). **Scaling**
It implies a similarity between the organizational structure of a phenomenon along the multiple scales of a system.

Conectome and Conectivity
The connectome is the complete map of the connectivity of a system, in which is possible to have different types of connections. For starters, it is feasible to have different relationships or connections between two elements of a system. This relationship will give a different function to the set (the elements with their connection). The types of relations possible are: a simple connection in which A is connected to B (structural connectivity), a more complex connection in which A and B are activated (or inhibited) at the same time but it is unknown if A influences B, B influences A or both are influenced by C (functional connectivity) or a connection in which A directly influences B as a causal relation (effective connectivity).

Emergence
Defined as the way in which a complex phenomenon arises from a collection of relatively simple interactions between the components of a given system. A simpler way to put it would be to say that it is the concept in which the properties of the system are more than the sum of the parts at a particular level or between levels. The classic example is a glass of water. If a single molecule of H2O is observed, it cannot be determined whether that particular molecule is in a liquid, solid or gaseous state. It is necessary to look at the entire system (in the given example, liquid water in a glass) and observe its properties in order to determine the physical state of the water. So the complex system "water" has a property (its physical state) that cannot be predicted only knowing its individual parts.

To conclude this section, we will unite all these new concepts with neuroscience and apply these characteristics of a complex system to the human brain. It is a complex system because its properties are unpredictable only by studying neurons, glia and blood vessels (this being a case of simplification of its components). It has components (neurons) and connections between them (axons and dendrites).

In the brain, we can see the example of spatial modularity by looking at the different anatomical components in which it can be divided, and one could see temporal modularity by dividing the memory module into short-term memory and long-term memory. With this example we are already exploring the characteristics of Scaling when viewing the modularity in two different scales: function and time.

When considering the connectivity and the examples mentioned, it is possible to subdivide the cerebral connectome into these three types of connectivity:

1. Anatomical connectivity: structural. In this case, it means that there are tracts of fibers of white matter between two regions.
2. Functional connectivity: temporal correlation. Meaning that when area A is active, area B is also active, not forgetting that A and B can be close to each other (local functional connectivity) or completely separated (remote functional connectivity).
3. Effective connectivity: causal correlation. It implies that area A is responsible for the activation of area B.

Establishing these types of connections and being able to say with certainty that area A does something, in particular, is much more complex than it may seem and goes beyond what medical students learn in neurophysiology in their first years of studies. There is extensive knowledge about the general area in which most sub-areas play a role, but getting deeper information is much more difficult as variables and complexity increase exponentially the deeper one goes.

To date, through the use of the neuroimaging techniques reflected in the next segment, many studies have been conducted allowing not only to characterize and classify the individual components of connectivity but has also combined structural and functional information to better understand how and to what extent structure reflects the function at different scales. The main conclusion is that the presence of a structural relationship between different areas correlates with a greater probability of functional relationship and the functional relationship reflects but does not necessarily imply the existence of a structural relationship (Basset 2011).

Another important conclusion when facing these studies concerns Specialization, which refers to the fact that different modules have different tasks and results in a specific outcome of this task so that the system is more efficient. Some authors call this functional differentiation. One might think that to study the function of area A one would only need to study the nearby connections (local connectivity) since they are close and the information process would be faster. However, studies show that the level of specialization of a particular area is only partially influenced by the type of local connectivity. Functional expression requires other brain areas to be complete, including remote and seemingly unrelated connections as far as current knowledge goes. Therefore, the main idea currently resides in that any brain function is an Aggregate Function since it requires a certain pattern in time and space of regions connected to other regions. Therefore, it would be advisable to get rid of these prejudices (arising from didactic tools that seek to make the knowledge more affordable for students) that come from the neuroanatomical and neurophysiological training before trying to understand the connectome.

There is also a lot of information regarding neural network architecture. In applying graph theory model to real-life systems, studies have shown that the architecture of the human brain network has a property that is common to many natural systems (the Small-World Network). This means that the network consists of a large number of neural circuits with a degree of interconnection that is inversely proportional to their distance and with an intrinsic level of order intermediate between totally regular and completely random. In other words, the brain is organized in the spectrum of a completely independent and fully interconnected system (Benedictis 2011).

Instead of having 10 neurons doing the same action and obtaining an average result of the same process, the brain would function rather with two neurons receiving a stimulus and filtering information on what is relevant and what not, two neurons crossing that information with memory and previous experience, two neurons processing the information and receiving the contribution of memory, two neurons preparing the response to the stimulus and two effectively giving the answer (we could apply here the concept of modularity replacing the word neuron by module). This architecture is optimal in terms of energy expenditure, integration, and information processing.

This theme of optimal architecture is present throughout the neural network. The human brain has many redundant circuits when processing information. This, however, does not imply a repetitive use of information, but quite the opposite. The use of the same structures for the processing of different types of information so that energy and time are saved in the different processes.

It can be concluded, after this section, that the brain is a complex system in different ways. It is not possible to say only by looking at a set of neurons if these are important in speech or motor function. The function of the different parts of the brain is somewhat intricate and difficult to elucidate.

Neuroimaging techniques:

Many neuroimaging techniques are available to neuroscientists and are their main tool in their attempt to understand the human brain, observing from sets of neurons to hemispheres, on a time scale that ranges from milliseconds to decades.

Due to the fact that the field of neuroimaging is an immense field of study, this review will briefly introduce those techniques most used and relevant.

Magnetic Resonance Imaging (MRI)

In the following paper, we will analyze the diverse procedures that can employ regarding different purposes. Each one has its pros and cons:

Structural MRI (Magnetic Resonance Imaging): The division between structural and functional image is difficult to establish since structure and function are usually complexly related in the brain. When taking a biological stance, the functional images may be the method providing dynamic physiological information, while the structural image gives stable anatomical information. The T1 and T2 sequences are the more important sequences regarding structure, and they are present in most resonance protocols. They are useful for both, clinical and research applications. Their key properties are the ability to enable us to see the structural anatomy of the brain, their general features, and the different structures in high resolution, which allow us to define lobes and gyrus and to differentiate white from gray matter.

Functional magnetic resonance imaging (fMRI) It provides physiological information. The field of fMRI is increasing every day. Blood-Oxygen-Level-Dependent (BOLD) imaging is usually employed in research, and it is a measurement of the hemodynamic response (HDR) signal. This signal is employed as a contrast by assuming that, if in a determined period of time (seconds), the area A is more active that the area B, there is a vasodilation in A and vasoconstriction in B. Simplifying, vasodilation means high HDR, and vasoconstriction low HDR. Thus, HDR in B is minor than in A and we may encounter a contrast between active and inactive areas.

It is a non-invasive procedure with a high spatial and temporal resolution (millimeters and seconds), as well as with a high fidelity to the signal, which means that the observed signal is very close to the original signal. However, it is still an indirect measurement of the nerve cell activity, and although the signal is strong and consistent, it needs more acknowledgments to be done before the interpretation of data. The main problem in the interpretation of data is that the fMRI signal emerges from the complex interactions among nerve cell activity, metabolism blood flow and blood volume. In addition, this occurs in a voxel, which can contain hundreds or thousands of nerve cells. In short, active and inactive areas contrast, but they may be interpreted carefully, otherwise we may obtain hurried conclusions on the relation between the different brain areas.

Diffusion Tensor Imaging: DTI It is a procedure that focuses on white matter, especially in the direction of the white matter tracts. It uses the fractional anisotropy (FA), a measurement of the diffusion of the water molecules, to predict the direction of the white matter tracts in a determined voxel. From a simplified point of view, if we consider an axon (or any other structure with a narrow cylindrical shape) from left to right, we can say that water molecules will diffuse quickly on the horizontal axis and almost nothing on the vertical axis (since the cell wall or the cylinder wall would stop them). This would not happen if the water molecules were in the middle of a sphere since there they would be free to go to any direction. The cylinder would have a high FA (near 1) because the diffusion occurs almost entirely just in one axis (horizontal). The second example, the sphere, would have a low FA (almost 0) because the diffusion would not be restricted to any direction. Thus, applying the physical and mathematical calculation to this property of the water molecules inside the human brain, we can measure the FA of the same voxel in different directions and, simplify, check the direction of the tract, which would be the direction in which we get closer to 1.

The DTI allows neuroscientists to assess structures that before were invisible in non-invasive imaging. This may help the brain mapping by providing bidimensional and tridimensional tractography images. Nevertheless, the DTI has still some technical challenges, such as sensitivity to a subject's movement among others. Previous research on DTI shows that its main limitation is its low resolution, since there are hundreds of axons in a voxel, and the DTI establish a measurement of the direction of the fibers in three dimensions. This is not a problem when axons travel straight and parallel, but when two axons cross, the measurement is not reliable and we lose information. The spinal cord fibers are also difficult to analyze since there is a big interference due to the movement and the air associated with lungs.

The magnetic resonance imaging provides also very important clinic results, especially in patients suffering from stroke, in whom we can observe the injury, and in patients suffering from multiple sclerosis, since the decrease of myelin, made mainly by water, results in a different diffusion pattern: there is not such a strong preferential orientation for diffusion, because the molecules move more freely through the axons. It is a procedure with great potential. However, we should keep in mind that the obtained data are the result of a processing which may have many errors, and thus we have to be aware of its limitations.

Electroencephalogram (EEG)

It is the record of the electrical activity throughout the pericranium. Its main advantage is a high temporal resolution of milliseconds (magnetic resonance imaging reaches just seconds). This, together with the lower cost, make the electroencephalogram an excellent technique to complement magnetic resonance imaging studies.

However, the interpreting of the data obtained is more difficult and the technique is also more difficult to employ than brain imaging. In addition to neuroanatomy and neurophysiology, it requires a lot of additional knowledge regarding different waves (alpha, beta, delta. . .) and their potential power. Likewise, we may take into account that the cerebral cortex is the only structure that can be evaluated with this technique since we are testing an external record around the cranium.

Due to the technical complexity, its employment in research has decreased. However, it has a great potential to measure the brain activity interaction in real time and in more complex research such as the research about the association of the electroencephalogram with the transcranial magnetic stimulation.

Transcranial magnetic stimulation (TMS)

This technique uses a fast-changing magnetic field (magnetic pulse) as a stimulus, which is applied in the pericranium by inducing an electrical charge through the cerebral cortex. It is similar to the EEG regarding their disadvantages. It is only able to excite the cortical areas (2cm deep is not enough for subcortical structures) and other more lateral-inferior applications of the temporal lobe or even the inferior frontal gyrus cause much pain to the stimulation – due to the superficial muscles. This makes difficult to employ TMS in the Broca area for speaking and language experiments, for instance. Furthermore, it has a low spatial resolution (cm).

As it is a brain stimulation tool and modulates the frequency of repetitive stimuli – instead of giving one single pulse, by using a repetitive TMS – it is possible to excite or inhibit specific areas of the brain, which allows the neuroscientist to examine and test functional theories that may arise from the neuroimage. However, it is important to bear in mind again that the neural activation from TMS is not specific. The activated volume of the brain tissue contains excitatory, inhibitory and neuromodulatory compartments, which are potentially stimulated. Separating these compartments to get more space resolution and strengthen the focal stimulation may be the future of this technique.

An interesting application of all these techniques is the possibility of combining them. A structural magnetic resonance could be obtained and then be used in a neuronavigation system in order to activate the targeted areas of the brain more precisely while the answer is recorded with an EEG hat. Thus, depending on the purpose, it is possible to select the most appropriate methods in order to get the best possible data.

Use of neuroimage to establish the network model

In order to answer the question in the title of this article – "how to understand human brain" - it is necessary to combine all the information given so far.

The human brain can be subdivided into subsystems or modules. When conceiving anatomical modules as the different cerebral lobes, brain stem (with its subdivisions) and cerebellum the structural resonance can be used in order to see their anatomic limits. T1 images also allow differentiating between white and gray matter.

Taking the modularity to the following level the brain can be divided into functional areas such as the motor cortex, the somatosensory area, the auditory cortex… These functional areas can be and, in fact, are currently studied by using fMRI, EEG and/or TMS. For instance, fMRI can be used by selecting a group of healthy subjects and giving them an auditory stimulus in order to identify the brain areas which are being activated and extract from it the same fMRI image without the stimulus. Therefore, it would be possible to identify the area which has answered the auditory stimulus and could be part of the primary auditory cortex (PAC). After that, it would be possible to take this group of healthy subjects and asked them to do a simple motor act such as drumming with a finger and using EEG (by extracting the noise of the basal activity as well). Thus, a specific pattern related to the muscles in the finger used in this activity will be identified and, later on, it would be possible to use focal TMS in the region identified with EEG and record the electrical activity of the same muscles in the index finger used in the motor act. If the region is properly identified, motor evoked potentials (MEPs) would be recorded in those specific muscles, which would confirm that this cortical area is related to the control of those muscles.

Back to the three types of connectivity, DTI is the preferred technique to analyze white matter fiber tracts and establish anatomic connectivity. On providing information about the direction of the fiber, DTI can properly and precisely establish anatomic connectivity between the different regions in the millimeter scale.

In order to obtain functional connectivity and the temporary correlation between two areas, fMRI and/or EEG can be used. Its difference lies in the spatial and temporal scale of interest. Firstly, it would be possible to access the phenomena happening in the milliseconds which follow that stimulus by considering the same auditory stimulation experiment and then see the cortical areas activated by using EEG. However, if the interest only lies in the spatial scale, the fMRI will detect the subcortical region which the EGG cannot. No matter which one is employed, it would be possible to detect the activation of more than one area and establish a functional connection between both. All in all, they are involved in processing the presented stimulus.

Establishing effective connectivity is more difficult. To that end, experiments combining TMS and EGG could be used. In both experiments, the cerebral cortex is activated and its electric waves are registered at the same time: the brain response is registered in real time after a pulse TMS. A response pattern may be detected and

then obtain reproducible data. A possible purpose would be to excite an area of the frontal cortex and obtain a consistent activation or an inhibition in other areas so that a relation of effective connectivity can be established.
There are other properties like Emergency or Small-World Topology, which can be tested with other combinations (RestingStatefMRI, which evaluates the BOLD signal with no task for the subject), although it exceeds the purpose of this work. Most parts of the neuroimage techniques that can be used to construct a simple diagram of the brain wiring as a network model with the nodes and connections described so far.

Conclusion

The human brain is complex at different levels. There are a lot of techniques on research trying to gather as much information as possible in order to understand it, although they have some limits. As a first step to understanding it, disposing of some ideas would be useful. While it is true that these ideas are helpful in a first approximation to the human brain functioning, they contradict the complex reality of this network system.

After this, the most difficult task for a researcher in this area is to find the correct question on which to base their experiment. From this point, it is possible to design a model generating results which allow expanding the objective knowledge which we have about the brain and, thus, be able to reveal one of the biggest mysteries: understanding the human brain.

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