Our awardee, Mr Thomas Bolton, developed a computational tool which, in a more elaborate manner compared to existing approaches, models the interaction between large-scale functional brain networks, notably in the resting-state; for instance, how the visual system will influence the auditory system, etc.

Interview

1) In a few words, what is an fMRI scan and a resting-state fMRI?

A functional MRI (fMRI) scan, at the start, involves what we call an *MRI scanner*: a sort of gigantic magnet producing very strong magnetic fields, in which the subject we wish to analyze the brain activity from is positioned.

Functional MRI, as its name indicates, thus enables to monitor the activity (the function) of the brain: as a reminder, the ensemble of our cognitive and sensorial abilities, be it your capacity to speak, to move, or to stand my soporific monologue, depend on an exchange of electrical information between *neurons*, the most widely studied cellular type of the brain.

If we project ourselves at the scale of a neuronal sub-network (roughly a mm^3), the electrical signal that would be recorded would be almost instantaneous, as seen on the illustration. The fMRI signal, however, is much slower: it takes several seconds to fully develop.

The reason is that it depends on a metabolic response, and not on the brain electrical activity *per se*: when a region from the brain activates, we observe an oxygen influx through molecules called the hemoglobins; and as sometimes, luck does things well, the magnetic properties of oxygenated and deoxygenated hemoglobin are distinct, which is captured by the measured signal.

You probably wonder what the purpose of focusing on such an indirect and imprecise signal is? Beyond a clear masochist tendency from the majority of researchers, the explication is that through the fMRI signal, we can measure responses throughout the whole brain, purely non-invasively.

To now get to the second half of your question, following the myriad of concepts that I have just introduced, you certainly long for a small break; a little time span in which you would be free to let your mind wander, without thinking about anything in particular. That is exactly resting-state fMRI: we record cerebral activity without the subject engaging in a particular cognitively-oriented task.

2) Why is resting-state fMRI a promising tool, and what are its challenges?

Resting-state fMRI is first promising due to its reduced acquisition time span: indeed, only around ten minutes of recording enable to obtain analyzable data, compared to much longer if a particular paradigm is implicated.

This simplicity in design and short duration also enable to much more easily record the cerebral activity from clinical populations, for instance if those have a tendency to panic or do not grasp instructions.

Now, to the disappointment of many, we are not magicians... and thus, somehow logically, an analysis relying

on less data implies that this should be compensated for elsewhere. It is for this reason that in my opinion, the main challenges concern adequate resting-state fMRI data handling and processing, so that its subtleties can be revealed without falling in the trap of over-interpretation.

3) In what way is the data analyst knowledge indispensable, and complementary to the work of clinicians, in that context?

If I may be allowed a caricature: the clinician is a bit like the doctor in medical TV series: he/she observes the acquired images and concludes, given his/her clinical knowledge, that the cerebral activity profile is normal or not.

However, to get to those colorful images, one must previously obtain them through preprocessing, the determination of what should exactly be computed and shown (activation profile; statistical inter-dependence; others), and from when the results are sufficiently significant to be soundly interpreted. It is in those steps that the data analyst enters into play, and undergoes daily headaches since the involved data are as huge (hundreds of thousands of activation profiles) as they are noisy (oftentimes, not more than 1% of the signal fluctuations

4) Can you explain what your model studies through deconvolution? That is to say, the correlation between "large-scale functional brain networks", and their specificities?

This is a difficult question, which even some neuroscience PhD students would, I believe, have troubles properly answering! Let me still give it a shot...

Deconvolution is a step belonging to the preprocessing of my data: in a sense, one can view it as a way to *go back*, converting fMRI signals (representative of metabolic coupling, as previously explained) into electrical activity, thus bypassing the initial sluggishness constraints of the response. It is thanks to this tool, which was incidentally developed by a former laureate of the Vasco Sanz award, that I could work with a particularly precise cartography of large-scale neuronal networks, of which you have a few examples in the illustration.

Functional correlation, as we call it, is the statistical dependence between two variables. The two networks that are highlighted here, for instance, are strongly correlated, because when one turns largely active, the other one does as well. Further, in the present case, those are two networks implicated in visual processing, and we thus expect this property.

My main idea was to look to extend this information: indeed, a strong correlation does not tell which network influences the other; there is no *causality* relationship. To explain things simply, the models that I developed enable, after many calculations, to... draw an arrow instead of a line!

5) In what do data-driven approaches enable a new opening in the analysis of fMRI signals, as compared to the methods starting with an* a priori *hypothesis?

Let us take a concrete example to illustrate this point: subjects are placed in an MRI scanner, and during a first recording half, watch a movie. It contains many sensorial and social cues, which will activate distinct brain areas. With a *traditional* approach, we could define particular features of the movie, such as when we observe *fun* as opposed to *science* scenes. Using appropriate models, we could then define which regions of the brain suit this *a priori* model. Some of my colleagues have been developing such tools, for what is in itself already a fascinating question.

Now, let us consider the second half of recording: subjects are at rest, and we all have our own way to be so: some daydream, others remember past events, project the end of their evening... In that case, one cannot use an *a priori* hypothesis as before, since the neuronal dynamics differs in each of us, given the variety of possible introspective processes! Instead, we thus need to rely on *reverse engineering* tools, where a model will be extracted from the data themselves, following which we will focus on it to formulate conclusions (such as, for instance, when some individuals performed daydreaming). This analytical domain is also a fairly vast instance.

6) Explain how you started from simulated data to build your computational model, and the extent to which its accuracy verified itself on experimental data.

The goal of my model is to understand how a neuronal network will influence the others. Thus, this is exactly what I simulated: I created *fake data* in which we find this type of interactions, and verified that my model would retrieve those relationships in precise manner.

Consider the following example: I simulated the activation profile from three networks, injecting the causality relationships that you observe on the graphical display: network 2, when active, will augment the activation level of the two others. With classical tools (such as the correlational measures discussed above), one cannot find the directionality of the process, and on top of it, the results are partly erroneous! With my method, on the contrary, we stand quite close from the ground truth.

On experimental data (the neuronal networks that you already saw, and their activity profiles), I then observed that those interactions were also present; and this was despite many analytical steps aiming at solely conserving the strongest and most significant interactions. I will not detail them here, mainly because although we stay quite close from the Geneva Hospital, I do not wish to send half of the auditorium to the hospital due to strong headache.

7) For what types of pathology will this information serve us?

The above pieces of information are relevant in understanding any pathology in which communication between several neuronal networks plays a role. Actually, in particular, an influencing model of high-level brain function has been posited a few years ago: the triple network model.

In this framework, we find back the networks implicated in introspective processing (memory, rumination, etc.), and the ones playing a role in *extraspective* (externally oriented) abilities, in a balance regulated by the salience networks, which receive and integrate external stimuli and modulate the balance accordingly.

In that model, we retrieve causal links between those networks, that is, information exchange that can be captured by my models. And it turns out that several large-scale pathologies are believed to take root in impaired such interactions. Thus, schizophrenia involves a disequilibrium between introspective and extraspective processing (hallucinations, problems to focus); depression goes together with excessive rumination; and autism is partly related to an impaired attribution of salience to some stimuli (e.g., not more interest towards people than objects).

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