INBIOMEDvision
Promoting and Monitoring Biomedical Informatics in Europe

Bio-, Medical- and Neuro-informatics Supporting Neurosciences

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Introduction

Neurosciences and its applications are greatly developing worldwide and Europe is one of the important contributors to the advancement of this discipline. Because of the variety of topics that it has to address, and the need for developing new theoretical, mathematical, and computational tools, it is characterised by a very broad inter-disciplinarity and requires the cooperation of actors in several fields of knowledge. In this context, INBIOMEDvision which is an initiative promoting collaborative Biomedical Informatics in Europe, had a key aspiration to support the development of an interdisciplinary domain between Neuroscience and Informatics via organising a workshop that brings together expert researchers and healthcare professionals, in order to foster communication and sharing of knowledge between them.

The Bio-, Medical- and Neuro-Informatics supporting Neurosciences Workshop took place at the Barcelona Biomedical Research Park (PRBB) on 6 July 2012, under the auspices of INBIOMEDvision. It was organised by Prof Ferran Sanz who co-ordinates INBIOMEDvision, and chaired by Prof Gustavo Deco, Director of the Centre of Brain and Cognition at Pompeu Fabra University (Spain). It brought together more than 40 participants representing 20 different institutions from ten different countries, and comprised of six technical presentations divided into two themes; The Virtual Brain (VB) Platform and Clinical and Technical Challenges, followed by an open round table discussion.

The talks in the first session, presented by Dr Viktor Jirsa (Institute of Neurosciences of Systems, Aix-Marseille University, France) and Dr Randy McIntosh (Department of Psychology, University of Toronto, Canada), focussed on the Virtual Brain Initiative (http://thevirtualbrain.org/team/index.html). This is a $20M ambitious project running over 10 years with a consortium of 15 distinguished neuro-scientists, which is attempting to build a realistic informatics network model of the human brain based on real neuroimaging data of brain structure and function. Jirsa and McIntosh covered some of the challenges and successes that the Virtual Brain has had in its first few years of inception, development and implementation, and discussed the future goals of this exciting project. The presentations in the second session, presented by Dr Carles Soriano-Mas (Psychiatry Service, Bellvitge Biomedical Research Institute-IDIBELL, Carlos III Health Institute, Spain) and Prof Felix Tretter (Klinikum München-Ost, Germany) focussed on the challenges which are implicit to modelling a malfunctioning or damaged brain at a network level, and how one day this may aid in the treatment of psychiatric and neurological disorders, such as schizophrenia, obsessive-compulsive disorders and epilepsy.

Discussions in the round table focussed mainly on the Virtual Brain and particular challenges associated with realistically modelling the full complexity and plasticity of
the brain, which is much studied in the literature. The Q&A also covered the issue of accurate clinical and scientific identification and definition of states and emotions, at what point will the virtual brain research and developments translate into a useful pre-operative tool for the practicing neurosurgeon, and finally the degree of usefulness of the Virtual Brain towards novel drug design at the molecular level. The abbreviations used in this document are summarised in the Appendix.
This section will explain the motivation behind the Virtual Brain project, how informatics can provide insight into normal brain function, and how brain function may change as a result of damage.

Towards a Virtual Brain

Randy McIntosh

Most historic models assume brain functions are assigned and located within particular regions of the brain e.g. auditory/visual/somatosensory/motor coordination control regions – an idea based almost entirely upon mapping of lesions resulting primarily from strokes or bullets. However, this only indicates which regions are likely to be critical for a particular function, not how these functions originate. In 1861, Broca localised and mapped language problems as a result of brain damage, again showing that different parts of the brain do different things. Similar results have been observed for individuals suffering from spatial neglect, but we still do not really understand how and why these abnormalities arise, just that there is a correlation between specific lesion locations and specific deficits. With developments in brain imaging witnessed over the last 15-20 years it was hoped that we may be able to better localise and understand interactions, and thus perhaps understand better how functions emerge. But is high quality imaging alone sufficient to help us understand how the brain works?

Cabeza & Nyberg (2000) reviewed approximately 300 papers on functional imaging that had been published up to that point in time, and mapped the different loci that had been identified as being related to different cognitive functions. They found that some functions, such as spatial attention, are fairly tightly located, whereas others, such as working memory, tend to involve many different parts of the brain. While semantic retrieval is generally located to the left prefrontal cortex, episode retrieval requires a lot of different parts of the brain. Therefore it would appear that if we attempt to use just neuroimaging to map functions we could end up with a rather messy map. It is not actually the location that is important here but the distribution of regions involved, thus indicating that brain function really comes about through network operations, and distributions of different operations that are combined through their coherent interactions. This is an old idea, and until recently it has been impossible to quantify observations and thus test the hypothesis. However, we are now reaching the point at which we have the appropriate technology to start to address these questions.

Currently there is much interest, and many papers, focussing on networks in the brain and mapping of connections. Functional Magnetic Resonance Imaging (fMRI), Electroencephalography (EEG) and Magnetoencephalography (MEG) can provide
mapping of the brain in pseudo-real time. Measures of structure, in terms of grey matter, white matter and mapped connections are also available, and there are many databases that allow for integration of this information. In the case of the VB, the XNAT database is used which allows integration of genetics, imaging, and demographic information. However collation alone is not sufficient; we have to attempt to interpret the data, and this is where the VB comes in. Datasets are huge, typically larger than three Gigabytes per individual, but often approaching a Terabyte in some cases. So how we process all this information in a sensible manner that let us understand how an individual’s brain is working is a crucial matter which is under investigation. A single study will no longer be sufficient to answer this type of question. Integrative platforms are necessary to merge and interpret data across disciplines from researchers with different domains of expertise if we are to explain and understand a problem as complicated as how the brain works. The VB platform can help us arrive to some insights from all this information.

To this end, the Brain Network Recovery Group, a collaboration of 17 international scientists, each with a different specialisation ranging from computational modelling through to cognitive and clinical neuroscience, has been established. Headed by Randy McIntosh, the goal of the group is to use the notion of dynamic network function to understand both normal and pathological neural functions. In the context of the VB they do this by applying some fairly simple assumptions. The first assumption is that if we have a fairly good map of the brain’s structure, this tells us at least something about what this architecture enables i.e. the computational capacity of the system. For the connection matrices, the first approximation used in the VB was that of the macaque brain, obtained from the CoCoMac project (www.CoCoMac.org; Kötter, 2004), a wiring diagram of the cortex, developed from anatomical tracer studies, which was then transformed to the human brain space. They then introduce realistic activity dynamics for each neural population in the map to simulate large-scale neural system operations. The model can generate local field potentials and produce realistic activity measures such as EEG, and fMRI data, which can then be mapped back onto empirical measurements to see if the patterns are similar. Videos showing output of such models are currently available at www.thevirtualbrain.org. Data obtained using different models can be downloaded from the website and compared with a researcher’s own empirical data. This is an ongoing project and future improvements and refinements when more datasets become available will continue to be incorporated.

What have we learnt so far from the Virtual Brain?

1) An understanding of the relationship between structure and function, and what resting state really means. Does it reflect brain integrity, self-referential behaviour, or a combination of the two?

2) Importance of noise in the brain i.e. semi-stochastic activity that permits the brain to explore itself.
3) What happens with lesions from a network perspective, i.e. how the brain responds to damage and disease.

Damoiseaux et al. (2006) found consistent resting-state networks across a group of healthy subjects, including the visual cortices and the default-mode areas amongst others, and thus the question is if this really reflects the anatomy. Correlation analyses by Greicius et al. (2009) suggest that in part structure does predict function. Similarly, Honey et al. (2009) found a reasonable correlation between structure and function ($r = 0.44 - 0.48$) but not *vice versa.*

Noise turned out to be a critical feature for enabling dynamics. It allows the system to play around its anatomical structure and spontaneously form and dissolve functional networks, thus exploring what is possible (Ghosh et al., 2008). Honey et al. (2007) found that over longer time scales, i.e. of the order of seconds to minutes, functional connectivity tends to reflect structural connectivity quite reliably, but over shorter time scales the mapping is less stable, with small networks forming spontaneously, which then dissolve and return to the broader structural framework. Noise is critical for this exploration of the dynamic repertoire (Deco et al., 2009).

McIntosh et al. (2008) investigated the role of noise empirically in a face memory task at a range of ages, from children to adults. They found that children have less noise than adults, but as the brain matures it gets noisier and this noise correlates with better brain performance of the face memory task. The noisier the brain is, the more accurate the individual can perform the task. In healthy ageing there are additional changes in brain noise, but this is not homogeneous across the brain. fMRI data show that there is less variability in certain areas which correlate with the stability of reaction time, so the less variability there is in these areas, the less stability there is, and the more noise (variability) there is, stability tends to increase. Therefore some noise is necessary for the development of healthy brain function.

If connector hubs (parts of the brain that provide transmission between distant parts) in the brain are lesioned, there is a fairly broad effect on the capacity of the system to process information, whereas if we lesion provincial hubs, only specific functions are affected. Alstott et al. (2009) investigated the effect of lesions on more distant parts of the VB, and found that lesions can result into both increases and decreases in information processing capacity.

To summarise, the VB platform produces dynamics similar to the human brain both in terms of fMRI and EEG, and it can reflect ageing, damage, and disease e.g. demyelination. Currently the project is incorporating rewiring rules in an attempt to help the VB recover, through the establishment of alternative pathways following simulated damage. The VB can be as a template for a single person by incorporating personal data to parametrise the model e.g. Diffusion Tensor Imaging (DTI), fMRI, EEG etc., which can be simulated, thus giving rise to dynamics of an individualised
brain. In the future the hope is to be able to inform pre-surgical planning e.g. how the removal of diseased tissue affects epilepsy; to investigate why deep-brain stimulation works to some extent in diseases such as Altimeter’s and Parkinson’s; and finally to allow incorporation of genetic and epigenetic data into the platform.

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This section will focus on the scientific ideas that led to the development and implementation of the Virtual Brain, and how the challenges that were faced during development provide insight into the routing problem.

Towards the Virtual Brain: Implementation and Frontiers

Viktor Jirsa

When we consider the wave-particle duality of light, light is either viewed as a photon that takes a particular route (particle properties), or a wave that is distributed (not localised) and has interference patterns (state properties); we do not tend to consider both perspectives simultaneously. We observe an analogous dualism in brain research and brain function that emerges from integrative activity. Routes of information passage through the network of the brain are important, but when we consider the emergence of function then we are considering synchronisation between brain areas i.e. a state concept. Therefore in studying the brain we need to consider both perspectives: the brain network and routes of information passage, as well as brain function/state.

Neuroscience has often concentrated on specific sub-networks which are studied in great detail e.g. retina-LGN-V1-V2, although, in vivo, such systems are always a subcomponent of a larger-scale network, and while sometimes the use of a sub-network approach is valid, often it is not. The VB adopts the full connectivity network (to close the functional circuits in the brain), and focuses on network interactions and the emergent phenomena that arise. This is what distinguishes the VB project from other neuroscience research projects.

Nunez (1974) produced the brainwave equation in assuming homogeneous connectivity in the brain network, i.e. that every area is equally well connected to every other area and that connection probability decays over distance, thus ignoring topology. Since the 1990s various groups have elaborated more detailed models while maintaining homogeneous connectivity in the hope that it will provide an approximation of full brain dynamics, as reviewed in Coombes (2010). In reality, the brain is highly folded so we have to approximate its geometry to simplify computational simulations. This is achieved by first mapping the cortex to an unfolded but closed surface and then to spheres, since this makes it more straightforward to computationally simulate the full brain system dynamics for the hundreds of thousands of nodes involved (Jirsa et al., 2002). We can then solve all interactions in a forward manner, and map them back onto the folded cortex. When we assume homogeneous connectivity, the symmetry of the connectivity will determine the symmetry of the solution i.e. the dynamics, and thus the constraint of symmetry limits the dynamic repertoire. However the brain is not even close to being
homogeneously symmetric. Thus DTI data are necessary in order to reconstruct the heterogeneous connectivity and establish the correct topology in order to obtain correct brain dynamics.

In general every area in the brain will have a different connectivity, and we have different ways of measuring connectivity e.g. in-degree, out-degree, clustering coefficient, betweenness centrality etc. This provides some insight into the overall topology, but does not help in terms of emergent dynamics. If we consider the simplest of all systems that has broken symmetry (Jirsa & Kelso, 2000; Jirsa, 2004), connectivity is of a spatial nature, but also has time delays of the order of 30-120ms when we take the full brain connectivity matrix into account. If we maintain topology but change the time delay we observe stationary behaviour followed by oscillatory behaviour and then a return to a stationary pattern. The parameter space is segmented into areas of qualitatively different behaviour. These areas are separated by so-called critical hyper-surfaces, where we have bifurcations, and at these points even a tiny change in the time delay can potentially kill all activity depending on its location in the parameter space. In a 3D parameter space, above the hyper-surface the brain is no longer resting – it is either performing a task, or having an epileptic fit – while anywhere below the hyper-surface it is at rest. Here we are considering states, but the routing of information can affect the emergence of the states. Thus “space-time structure” of the coupling of the matrices is important and this is what we are attempting to investigate with the VB project.

While anatomical connectivity is generally a good predictor of functional connectivity, the inverse is not true. We can illustrate this using a toy example with three interconnected areas, and a time-delay between just one pair. For a given time-delay and set of activity strengths, these areas may display oscillatory behaviour and intermittent synchronisations. We can then calculate the degree of coherence between the pair with the time-delay, and observe how this affects activity in the third area (Rho et al., 2011). The proximity to the critical line between stable and unstable appears to play a crucial role; without noise the system is stable, indicating the important role of noise. In the presence of noise and in proximity to the critical line, the coherent activity between areas 1 and 2 (between which is the delay) affects the emergent behaviour in area 3 as a function of the time-delay and the degree of synchronisation in the first two areas. In other words, a given brain area operates in the spatiotemporal context of what the remainder of the network is doing. We can generalise this to anatomical connectivity, e.g. the coherence between inferior parietal cortex and posterior cingulate cortex is highly correlated to the Blood-Oxygen-Level-Dependent (BOLD) activity in other areas of the brain such as subgenual cingulated cortex, even though there are no direct anatomical connections between these areas, indicating an emergent network activity (Rho et al., 2011).

The VB platform release is in October 2012 at the Society for Neuroscience meeting in New Orleans. It is written in Python and open source, accessed through a web-
based interface incorporating Web Graphics Library (WebGL) for 3D visualisation. It can be run locally or on remote high-performance clusters (currently only available in Marseille, but mirror sites are planned in Toronto and Barcelona). It is an integrative neuroinformatics platform with a modelling rather than an analysis focus. The first step is to read in the DTI data and reconstruct the connectivity matrix, incorporating lesions and performing further editing if required. The data can then be rendered in 3D or plotted directly, and it is possible to interact directly with the connectivity matrix and save different versions as required. The VB generates a 3D representation of the folded cortical matrix and allows the running of region-based or surface-based network analyses. The former involves coupling of individual regions and ignoring in between spaces, while the latter, which is much more computationally demanding, involves having network nodes all across the cortical surface; e.g. for the two brain hemispheres and the thalamus we may have as many as 140,000 simulated points. We can then determine what we want to simulate e.g. EEG, MEG, BOLD signal etc. and we can change conduction time-delays, connectivity, local-coupling etc. and run the simulation.

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The focus of this section is the resting state of the brain, and in particular to describe a detailed biophysical model that has been developed within the context of the Virtual Brain, focusing on the application of the model rather than the definition of the model itself, and providing examples of how the model may be manipulated for use in clinically-oriented applications through two specific examples:

1) Explanation of the link between structure and functional connectivity in schizophrenia.
2) Pharmacological manipulation of acetylcholine (Ach) levels in the resting state model in an attempt to emulate sleep/anaesthesia-like dynamics.

Criticality and Ongoing Brain Activity at Rest: Clinical Relevance

Gustavo Deco

In order to investigate the resting state from a basic neuroscience perspective, we first have to model a black box representing part of the brain. Classically this has been done through a reverse-engineering approach i.e. providing different excitatory stimuli as input and observing the output. Through studying the relationship between these input-output pairs, we can learn something about how the brain functions, and most of the things we currently know about how the brain works were discovered in this manner.

We assume that the resting state of the black box is trivial in the physical sense i.e. a state of low level energy or uncorrelated noise. So, if we imagine the black box is water, at rest it is still. If we excite the water with our fingers, we generate an output in the form of waves. However, if we consider water in the real world, there will be some perturbations even at the resting state (e.g. due to wind). Nevertheless we will still observe reasonably reliable output in spite of these perturbations. However, if the resting state involved spontaneous waves, then we would not be able to apply this black box thinking, or at least it would be more difficult, since we would have to calculate the exact starting state parameters. The good news is that we can still learn a lot about the underlying structure and dynamics of the system just by observing the spontaneous spatiotemporal states that emerge during the resting state.

In a seminal paper from 2005, Fox et al. showed that the resting state of the brain is not trivial uncorrelated noise, as had been the prevailing view up until that point, but is in fact composed of well-structured patterns, such as the BOLT signal and default mode network, which vary depending upon the region of the brain, with some areas being strongly positively correlated with one another while other areas as inversely correlated. Those areas that are correlated under the resting state form a specific
network, of which there are between five and eight in humans, depending on the methodology used to assess them. Similar types of networks have also been observed under task conditions e.g. attentional networks, sensory-motor networks etc.

Independent Component Analysis across different subjects has helped define a variety of resting state networks e.g. motor, spatial (Mantini et al., 2007), and research using anaesthetised monkeys (Vincent et al., 2007) showed the existence of sporadic transitory resting state networks identical to the networks that are continuously activated when the monkey is performing a particular task e.g. sensory-motor networks. Thus it is no longer accepted that there is just low-level noise during resting state, but that actually there is structured noise i.e. specific spatiotemporal patterns as a result of the structure and connectivity that is intrinsic to the brain, a small world type of architecture with clusters and relatively sparse connectivity. Thus we might be tempted to intuit that function is determined by structure, but many types of models have shown that this is not the case. Structure influences dynamics, and determines dynamics, but it is never equal to dynamics. Thus we need to explicitly include structure and dynamics in our model, and study their interplay in order to observe what types of emergent dynamics arise.

For this we apply the VB philosophy i.e. DTI and Diffusion Spectrum Magnetic Resonance Imaging (DSI) information available for humans, together with parcellation templates (coarse or fine), are fused with a neuroanatomic connectivity matrix to provide a brain network model in the VB. Edges can be weighted by the number of fibres using information from DTI, though we do not know the effective strengths of these connections, only their relative strengths (i.e. the general scaling of these strengths is an unknown parameter). Using imaging methodology we can attempt to determine the global emerging dynamics, and observe under what conditions the simulated dynamics best fit the observed dynamics. This process will be illustrated here using fMRI-based signals from human subjects.

As we go from independent nodes to highly connected dependent nodes, we pass from trivial dynamics (in line with the historic assumption of asynchronous uncorrelated noise as representative of the brain resting state), through a critical bifurcation point at which the resting state is no longer stable, to a point where multiple independent stable states emerge that may co-exist, and radically changing the global dynamics. There are two constraints that determine global dynamics; the first is the underlying neuroanatomical structure, which is defined and thus constrained in any particular model based on the best mapping we have available, and the second is the dynamical working point which determines the general coupling. Thus the question we still wish to address is at which working point do we gain the best explanation of the observed reality, as measured by fMRI for instance, which is expected to be somewhere close to the bifurcation point.

To this end, we input the DTI/DSI-based anatomical matrix into the VB, each node having a relatively detailed model of asynchronous neuronal activity, of 80%
excitatory neurons and 20% inhibitory neurons. We describe the activity of each neuron with a simple integrate-and-fire spiking model, and try to describe as best as possible the associated synaptic activity using appropriate differential equations, to allow modelling of pharmacological manipulations. Using the VB, we observe that the best fit is close to the bifurcation point as expected (Deco & Jirsa, 2012). This implies that the resting state is a spontaneous state, though not the trivial spontaneous state where there would be no correlation at all, but, because it is close to the bifurcation point, the noise is making excursions across the dynamical repertoire of the network, and investigating the other side of the bifurcation where all the possible functions of the brain are available. Thus, very gentle stimulation of the spontaneous state can result in execution of the task required. The great advantage here is that when we observe the resting state, the noise will be reflecting the structure of the whole brain.

**Origin of functional network alterations in schizophrenia**

One of the hypotheses that has been put forward to explain some of the diagnostic symptoms of schizophrenia is the disconnection syndrome, which is also relevant for other diseases. In other words, neuroconnectivity in schizophrenic patients is believed to be a little sparser than it should be. Perhaps the brain has less tracts resulting in less physical connectivity, or perhaps it is pharmacologically weaker as a result of impaired synaptic mechanisms. This results in the inability of the brain to properly integrate neural processes segregated across distributed regions. Here we want to investigate if we can test this hypothesis within the framework of the Virtual Brain?

Experimental studies using graph theory have found significant functional network alterations in people with schizophrenia (Lynall *et al.*, 2011). Using fMRI under resting state conditions, they found that the parameters affecting the topology of the functional connectivity matrix (degrees of clustering, small worldness, variance, robustness etc.) showed significant differences between healthy individuals and schizophrenic patients. This leads us to question if these effects on the functional matrix are due to underlying differences in the structural matrix. Evidence from DTI analysis of schizophrenic patients suggests that there is indeed a certain degree of structural disconnection (Skudlarksi *et al.*, 2010: Zalesky *et al.*, 2011), though the link is not direct.

Using the VB framework we can attempt to investigate disconnection by observing what happens if we perturb the topological connectivity in the same direction as observed in schizophrenia; do we observe the same outcome? If we take a healthy network we can either weaken links (pharmacologically *in silico*), or prune links and measure the overall effect on the network. What we find is that the values returned by the simulations for clustering, hierarchy, and functional connectivity etc. always move towards the values observed in schizophrenic patients as disconnection is increased. Simulation data based upon weakening of coupling by five percent provide quite similar measures to those found in patients. Thus there is a strong relationship between the underlying network structure and the disconnection...
syndrome, i.e. disconnection syndrome alone can cause the functional alterations we observe in schizophrenia.

A final example is that of explicit manipulation of the underlying pharmacology of acetylcholine in modelling the resting state. This is a model of sleep induction and anaesthesia. The slow sleep waves (0.4-1.8Hz) were plotted as the model passes from wakefulness (high Ach) to sleep (low Ach), alongside the envelope of the power spectrum over that range. In deep sleep it was found that we mainly have synchronised slow sleep waves. This was interesting because studies in rats have observed sporadic slow sleep waves, so they wanted to investigate if these were structured as in the resting state, and it turns out that they are. Investigating the BOLD signal during waking and sleeping has shown that during sleep the resting state structure is lost, i.e. the connections become uncorrelated and disordered due to the slow oscillation starting to synchronise other structures. Thus the take home message is that during the resting state we are actually exploring the dynamical repertoire rather than being at a state of perfect rest.

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The focus of this section is how to tackle schizophrenia (and other neuropsychiatric disorders) by joining clinical psychiatry, experimental neurobiology and computational science / systems biology in order to construct exploratory formal models of mental disorders.

Systems Neuropsychiatry – Schizophrenia

Felix Tretter

Psychiatry is a soft science, so it can give rise to some problems in connecting physicists, mathematicians, neurologists and clinical psychiatrists to tackle topical issues in an integrative manner. However it is very important from the perspective of public health that we manage to do so, considering that conditions such as depression and bipolar disease will continue to have significant economic impacts in forthcoming years. In psychiatry we question what the brain is doing when producing the depressive/addictive/schizophrenic symptoms that we observe. So far we have some qualitative models that help with the exploration of these conditions, but no formal quantitative models that can really help explain what is going on. This is where a multi-level systems-modelling approach may be useful; the goal being to integrate macro-anatomic modelling and molecular modelling approaches in order to get a better overall understanding of these conditions.

From a theoretical point of view, we must remember George Box's insight of “All models are wrong, some are useful”. The current problem is that Neurobiology is generating so much data that we can not really interpret it - there are many correlates for various mental disorders, but no full causal explanations of the clinical phenomena. We also need to consider a philosophy of mind, about which there is much current debate, and an emerging field of neurophilosophy. Tretter proposes that we need to consider Systems Science as a distinct research field.

In order for the psychiatrist to better understand schizophrenia at a systemic level, we need a better understanding of psychopathology and psychology. When considering schizophrenia, the psychiatrist always has in mind the molecular mechanisms, even while talking with the patient. Tretter is interested in the Bermuda triangle formed of psychiatry, neurobiology, and systems biology/computational science, and to this end is part of a collaborative network of European researchers who meet annually to share findings and ideas in this field. Their first interest was in the formalisation of Arvid Carlsson’s classical model of the global circuitry of the brain. Subsequently they have had meetings focussing on working memory, addiction, schizophrenia, and bio-oscillations. Investigation always cycles between empirical data and theory, and between qualitative and quantitative research. We start with experiments that provide a data matrix, from which we develop a verbal
qualitative model and hence a more detailed graphical model, and subsequently quantitative computer-based models from which we run simulations which help us understand, literally and intuitively, complex inter-related dynamics; i.e. dynamics of inter-connected parts of the system, and this is systems methodology.

Nearly any subject can be seen as a system, i.e. a structured entity of related parts. However as the number of parts, and thus the number of relations increase, running analyses becomes very complex very quickly. With the brain having billions of neurons and trillions of synapses, it is clear that it is not a straightforward system to analyse, and thus computer simulations are essential in the analysis of multi-component dynamics. Psychiatry has always focussed on specific areas of the brain believed to be associated with the condition under investigation, but recently researchers have started referring to networks underpinning conditions. This though does not give us any greater understanding of the pathogenetic mechanism itself. Tretter believes the development of a universal graphical modelling language will help in the visualisation of complex networks, flows of energy, molecules and actions. Concepts such as that of the energy landscape can help in this respect – where the shape of the landscape can qualitatively represent the dynamics of cognitive, positive or negative, symptoms (Loh et al., 2007).

In terms of the present state of modelling in schizophrenia, we cannot fully describe a disease with any model, but we can attempt to describe and model certain symptoms e.g. hallucinations, delusions, ambivalence. New definitions of schizophrenia in DSM-V may affect issues somewhat, but we do have rating scales that indicate the severity of defined symptoms that will help us define targets that we might wish to explain using novel models. Currently research in psychiatry is very much influenced by the molecular systems biology movement, but so far there is no systems biology of the neuron or the brain. Molecular Systems Biology attempts to integrate experimental and computational approaches to study cells, tissues, and organisms. Studies are of a quantitative nature in data collection and mathematical modelling, and focus on interactions between individual elements.

Schizophrenia is defined by three major groups of symptoms: hallucinations and delusions (positive symptoms), withdrawal and anhedonia (negative symptoms), and attention and working memory deficits (cognitive symptoms). We also have to consider the temporal course of these symptoms, which range from acute to repetitive episodes of schizophrenic psychotic states, and can include some procedural states. Several different types of disease time course are observed, and the severity of symptoms is very variable between individuals. Studies range from behavioural to molecular with neurology filling-in between. From a top-down perspective, we observe behavioural problems in the clinic and attempt to explain them through global brain circuitry, but local networks in the brain are known to be important too. Then we reach the highly studied level of the synapses, and basally we have genetic and proteomic approaches helping to identify the cellular molecules involved in schizophrenia.
Thus the ultimate goal is to construct models that link electrophysiology and biochemistry, in order to reflect both electrical and chemical signalling in an appropriate manner. This is a challenge for a systems biology view of the synapse. We also have to be able to characterise the different psychological functions which we can measure in the clinic in order to describe the clinical syndrome as precisely as possible, in order to allow us to determine quantitative correlations with ordered brain structures, or brain function. At the moment no one is focussing on this extension of psychopathology. The focus is primarily on imaging. Ideally one would have a network describing how any mental state is related to other mental states at a phenomenological level, since many different areas of the brain are implicated in any distinct behaviour, process or symptom.

Cabral et al. (2012) showed that schizophrenia is not associated with a single locus/focus of the brain but is a network disorder. There have also been attempts to link genetics to affected structures in the brain in schizophrenia, such as the case of DISC1 polymorphisms affecting brain activity (Callicott et al., 2005), but the missing link is the mechanism by which such effects are reached. In 1959, Carlsson developed his famous circuit for dopamine activity, which suggested that dopamine hyperactivity in the brain stem might provoke overflow in the cortex due to a disinhibited thalamus, and Tretter and colleagues attempted to model this using distinct oscillatory phenomena. This is an example of qualitative modelling of empirical results, which is a challenging process but essential in this field. From the micro-anatomical perspective, we know of different gamma oscillations patterns observed in schizophrenia (Spencer et al., 2008), and we have detailed morphological knowledge of many cortical structures.

Therefore we have many biophysical models, but few deal with dopamine receptors, and there is still a large gap towards disease understanding. If we have too much or too little dopamine we have bad working memory function. D1 receptors dominate over D2 receptors in the prefrontal cortex, but the ratio is altered in schizophrenia resulting in weaker activity and concomitant reduction in task performance. Dynamics of the intrasynaptic dopamine concentration have also been simulated and the resulting effect on pre-synaptic and post-synaptic dynamics. However so far there are no good integrative models of drug interaction at the synapse.

Tretter and colleagues have developed the theoretical framework of the neurochemical mobile, which utilises the physics of coupled pendula, resulting in non-linear behaviour, thus representing the dynamic balance that exists between 5HT, dopamine, GABA and glutamate which is altered in schizophrenia, with GABA and glutamate being elevated, resulting in dysfunctional behaviour. This hypothesis thus qualitatively incorporates a variety of apparently conflicting hypotheses in the literature, and is helpful as a heuristic to aid understanding of the complexity of neurochemical transmission and associated disorders.

In summary, the brain is an electrochemical oscillator for which a huge amount of
data is now available. A systems view of the brain in schizophrenia would appear to be appropriate. Integration of different levels of investigation is beginning to bear fruit and the effort should be sustained.

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Further Reading

This section focuses on the use of navigated magnetic stimulation and functional DTI tractography for preoperative functional diagnostics in brain tumour surgery.

Functional Tractography for Neurosurgical Patients

Gerardo Conesa

Neurosurgeons can play an important role in validating and testing models of brain function. Imagine we have a patient who has a large insular tumour and is experiencing epilepsy. We need to inform the patient whether he needs to have surgery or not and what the likely outcomes and associated risks are, with a certain degree of certainty/uncertainty. From a clinical point of view, fMRI provides some useful information, e.g. in the case of motor function and activity around the Rolandic fissure. However in the case of language abilities, it is not so easy to predict outcome following surgery. Nevertheless it will be possible to validate some of the model predictions with waking patients, or using an electrode grid and stereo-EEG. When we stimulate the cortex electrically, we assume we are generating virtual lesions in the patient e.g. given a particular language task and stimulation at a particular cortical or sub-cortical locus, could the patient still perform the particular task. This works well invasively but of course we would rather not explore this route, and this is where magnetic stimulation proves useful.

Various coils are available that can provide a range of effect from focal to widespread current, thus providing different image resolutions. Generally it is the most focal type of coils that are useful for this work, and the stimulation that can be achieved is fairly similar to that which can be achieved in theatre, with some restrictions. The best-validated type of map we have so far is the motor map, which is very precise (by virtue of stimulating millions of neurons in a square centimetre). Using an electromyograph to track muscle response, the smallest response that can be observed is so small that often the patient does not even feel the motor response, and in particular hot-spot regions where it is possible to stimulate extension and flexion, finger by finger. When we come to validate these findings in the theatre, there will be some shift in position due to loss of fluid when the skull is opened, and also due to the fact that usually the patient is lying down as opposed to being seated. Picht et al. (2009) were the first to use transcranial magnetic stimulation (TMS) in this manner and found that, for the primary motor cortex at least, it is very effective for functional mapping to an accuracy of less than a centimetre.

However when it comes to removing the tumour, we also worry about subcortical structure; and this is where DTI tractography helps. While we miss cross-linking fibres, we can view the various regions involved in particular motor controls;
however, sensory localisation is much more difficult. Following tumour removal, the patient may often fully recover motor skills to pre-surgery levels, assuming he was not a concert pianist for example. Particularly in the case of slow growing tumours, where the network will have been reorganising, it may be that particular motor roles are already being controlled elsewhere. However the areas predicted to be important by fMRI and those observed intra-operative (i.e. post operating) do not always overlap. Monitoring during resection with the patient awake in the theatre allows confirmation of whether the predicted outcome is actually that that has been observed.

Using TMS for speech mapping while the patient is performing a language task is less precise, in part due to induced muscular movement, which is uncomfortable for the patient. A further problem is that TMS can only affect axons that are parallel to its axis, while it is refractory towards perpendicular axons. Of course axon stimulation can be in any direction, so we need to take measurements from a variety of different angles in order to get the full picture. Nevertheless some nice correlations have been achieved for tasks such as naming or verb generation. In bilingual patients who could switch between Spanish and Catalan they achieved 82.1% sensitivity and 95.6% specificity in correlations between direct cortical stimulation and TMS, in the case of motor-language functions.

They have also mapped the areas responsible for the control of the cricothyroid muscle, which is involved in vocalisations, and found it to be related to Broca’s region, unsurprisingly, but also found some connection to Wernicke’s area.

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This section examines the relationship of structure and functional connectivity in distinguishing between individuals who are at risk of suffering from Obsessive-Compulsive Disorders, and establishing the degree to which they may suffer from this condition.

Mapping Functional Connectivity and Structural Covariance of the Striatum: Applications to Obsessive-Compulsive Disorder

Carles Soriano-Mas

Obsessive-Compulsive Disorder (OCD) is characterised by intrusive thoughts (obsessions) that generate anxiety. As a result, patients engage in compulsive repetition of overt or covert behaviours (rituals) in an attempt to alleviate their anxiety. It is typically accompanied by feelings of doubt and incompleteness regarding the compulsive behaviour. A classic example is that of a sufferer whom having shaken hands with a stranger, believes their hand to be dirty, and consequently engages in protracted hand washing in an attempt to clean the hand.

Evidence from a number of fields, including neuropsychology, neurosurgery and neuroimaging, began to accumulate towards the end of last century suggesting that frontostriatal systems may be implicated in OCD. For example, while sufferers do not suffer from memory problems, they do have organisational problems when performing memory tasks. OCD can also arise following insult, particularly with regards to the frontal lobe, and while it is typically managed with drugs and/or behavioural therapy, some sufferers are candidates for psychosurgery. In the latter case, the most effective treatments (lesion or stimulation) are those aimed at the vicinity of the ventral striatum. Furthermore, in PET scans, OCD patients show hyperactivity of the frontal lobe and striatum relative to healthy controls. Hence investigating the involvement of the striatum has inspired most of the research into OCD over the last 10-15 years.

Structural MRI analysis has helped to better characterise structural alterations in the form of volume increases and decreases of specific structures in the brain. In a meta-analysis of region of interest MRI studies, Rotge et al. (2009) found that OCD is characterised by a reduced volume of structures such as the anterior cingulate and orbitofrontal cortex, and an increase in volume of subcortical structures such as the thalamus. Furthermore they found that the severity of symptoms correlated significantly with effect sizes for the thalamus. Whole brain methods such as voxel-based morphometry also show volumetric decreases in the medial frontal gyrus, medial orbitofrontal cortex, and insular and posterior-cingulate cortices, accompanied by volume increases in striatum, thalamus, midbrain and anterior cerebellum (Pujol et al., 2004; Soriano-Mas et al., 2007). Therefore while the frontal
lobe and the striatum do not represent the whole story, they clearly play an important role.

Functional MRI has shown that OCD patients have alterations in the frontal cortex (e.g. in reversal-learning tasks of association between stimulus and reward); OCD patients are slower to become aware of changes in the association, and decreased activation of the orbitofrontal cortex and the striatum, amongst other regions, is noticeable when performing the task. The parietal cortex has also been implicated in further studies, and this relationship is found in relatives of OCD patients, leading to the suggestion that these alterations may represent an imaging endophenotype of the disorder (Chamberlain et al., 2008). OCD patients also perform poorly in the Tower of London task, which is associated with decreased activation in dorsal regions of the prefrontal cortex, and increased activation in ventral and cingulate regions when performing the task. Furthermore, if symptoms are provoked (e.g. through display of provoking images while the subject is being scanned), increased activity of the thalamus, orbito-, dorsolateral- and medial-prefrontal cortices, as well as posterior brain regions are observed. There also appears to be a difference in terms of which regions are activated between symptom subtypes of the disorder.

The circuits involved in the normal functioning of frontostriatal loops were mapped as early as 1986 (Alexander et al., 1986). Each circuit underpins different classes of function, such as motor, cognitive, and emotional/motivational functions, but they are believed to work in parallel, involving different parts of the same structure. In OCD the functioning of such circuits is altered. Specifically, the thalamus, which acts as a final output relay of the circuit to regulate cortical excitability, is dis-inhibited, resulting in increased overall activity. This ties in well with the observations from early PET studies.

Until recently functional connectivity between the different parts of the cortico-striatal circuits had not been considered – it had merely been shown that some parts of the circuits do not appear to be acting correctly in OCD patients. The first evidence of connectivity disruption came from DTI studies where they observed anisotropy alterations in the white matter tracts of the prefrontal and parietal cortex, as well as in the cingulate gyrus of OCD patients (Szeszko et al., 2005; Menzies et al., 2008). In this context, together with their colleagues, Harrison (Melbourne Neuropsychiatric Center) and Soriano-Mas decided to investigate functional connectivity within the fronto-striatal circuits in OCD patients. Prior functional MRI experiments were performed by observing whole brain activity while presenting the patient with on and off stimuli, to see which regions were activated in response to specific stimuli. Conversely, in studying functional connectivity, the first step was to study the brain at rest and extract time curves for particular regions and observe which regions of the brain correlate with one another. Relevant fluctuations are mainly located in the low frequency bands (<0.25Hz, and mostly <0.08Hz).
Di Martino et al. (2008) showed that if time-series are extracted from different locations in the striatum, the correlations predicted by the Alexander model are observed; i.e. dorsal regions are more connected with the dorsolateral prefrontal cortex, and ventral regions with ventral regions of the prefrontal cortex. Harrison et al. (2009) have shown that OCD patients have altered functional connectivity patterns involving different regions of the striatum. They extracted the appropriate time series of four striatal seed regions involving the dorsal and ventral subdivisions of the caudate and putamen nuclei, and then performed a general linear model assessment. While they observed a degree of overlap between patients and controls, for the dorsal caudate (DC) region there appeared decreased connectivity with several dorsolateral prefrontal cortex regions in OCD patients, whereas for the ventral caudate (VC) they observed increased connectivity with medial orbitofrontal regions. This was the first study to really show there is a functional connectivity deficit involving the fronto-striatal circuits in OCD patients in comparison with healthy controls. They also observed a correlation between increased connectivity between the VC and the orbitofrontal cortex and the severity of the disorder; the more connectivity a patient has, the more severe are the symptoms with which they present.

This initial study was performed with 22 patients, but the study has now been replicated with 74 patients, and it is clear that the DC is less connected to the dorsolateral prefrontal cortex and that the VC has increased connectivity with orbitofrontal and medial frontal regions in OCD patients. They have also replicated correlations between levels of connectivity and symptom severity. Furthermore they have investigated the specificity of these correlations in relation to symptom subtypes such as patients with prominent washing, checking, symmetry, hoarding, or sexual/religious symptoms. They found that the connectivity of the VC shows some degree of regional specificity according to the main symptom dimension of the patient. However, it must be remembered that these are group averages, and thus it may not be straightforward to classify an individual patient based solely on connectivity observations, though this is something the investigators are currently working towards.

Structural covariance, that is the correlation of volumes between distant regions of the brain, is known to be related to connectivity, as has been shown in the relationship between the size of certain regions of the thalamus and the visual cortex. As a result, Soriano-Mas and colleagues expect to find correlations in the functional subsystems they are investigating. They have initiated their analysis by first investigating functional connectivity in healthy controls to see if they can replicate the functional circuits at the structural covariance level, and have observed partially overlapping results. The DC is mainly correlated with dorsal regions such as cingulate and medial prefrontal regions, and the insula. However the VC shows a distinct pattern, with structural covariance observed with the orbitofrontal cortex region, more ventral regions of the cingulate gyrus (where most limbic inputs arrive), the amygdyla, and posterior brain regions. They have also found that dorsal putamen is
correlated with the ventrolateral thalamic nucleus (i.e. the motor nucleus), amongst other putamen correlations (Soriano-Mas et al., 2012). In addition it was shown that structural covariance is not a static phenomenon, but that it interacts with both age and gender e.g. the correlation between DC and sensory-motor regions was not present in younger subjects (who are under 32 years of age), but is observed in older subjects, while the reverse is true of the correlation between VC and medial-thalamus. One possible explanation for these findings would be in relation to the hypothesis that when we are younger our behaviour is more goal-directed than when we are older.

Such findings are not completely new as Zielinski and colleagues (2010) reported similar patterns of covariance in other resting state networks, and also found that such patterns interact with ageing. Currently Soriano-Mas and colleagues are performing the same studies in OCD patients, and have found some alterations in structural covariance e.g. DC has decreased structural covariance with inferior temporal regions, while VC structural covariance is decreased with dorsolateral and insular regions, and increased with mid-cingulate regions. Finally, they have found structural covariance increases between the subgenual cingulate cortex and the ventral putamen in OCD patients.

In conclusion, it is clear that functionally connected regions are also correlated in volume, and that structural covariance may be a useful tool in characterising brain disorders from a connectivity perspective. In the future functional and structural connectivity may be able to help in distinguishing between individuals who are at risk of suffering from Obsessive-Compulsive Disorder, and help determine the degree to which they may suffer from this condition.

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Round Table Discussion

Chair: Gustavo Deco (GD)

Participants: Carles Soriano-Mas (CSM), Felix Tretter (FT), Gerardo Conesa (GC), Randy McIntosh (RM), Viktor Jirsa (VJ)

**Question 1.** How much variability is there in tractography? There are many thresholds and acquisition parameters that can be adjusted, resulting in different connectomics. Has work been done on finding the optimal set of tractography parameters?

**VJ:** We had to address exactly this issue with the Virtual Brain, in particular McIntosh’s group who has experience seeding it with the CoCoMac.

**RM:** Part of the reason for doing the Human Connectome Project was to try to address this question, e.g. how robust are parameters such as diffusion spectra. The second component that also increases variability is the post-processing of data. Some groups use streamline methods for tractography while others are using probabilistic or deterministic methods. I believe that stability in parameters will come as diffusion imaging evolves further, and that it is not so important in the large tracts, but more of a problem with shorter less dense fibres, where we will even observe changes within an individual if we vary the pulse sequence.

For comparisons between patients it is obviously best to stick to the same parameters where possible. Part of the Connectome project’s mandate is to establish how much variability is due to measurement error, and how much is a true reflection of variability in the biology between humans. We are currently investigating cross-individual variability when using the same acquisition sequence, working on a small project with 50 subjects for which we have DTI, fMRI, and EEG data, across a range of 18-50 years of age. We are looking at their tractography measures and how differences in structural architecture affect emerging dynamics in the VB simulation. We hope to have an answer to this question by Spring 2013. We have the same issue with fMRI; with the same protocol and patient, but a different scanner, we observe a different pattern of activations, possibly just a field strength issue, or maybe the pulse sequence too. Both fMRI and DTI are now converging on a stock sequence that is feasible for most subjects, and this will result in a reduction in measurement error that will allow the focus to move towards post-processing issues.
Question 2. Will there be problems related to the low spatial resolution, and the fact that the signal is always symmetrical?

RM: Again this is something the Connectome Project is working on; modifying scanners to address this issue, but unfortunately the scanners will be very expensive and thus not accessible for many groups. However some of these problems may not be solved, so a certain level of ambiguity will need to be accepted. We are currently using the method developed by Zaleski for tractography which appears to be a bit more robust regarding the crossing fibre issue i.e. going from A to B tends to give the same result as when going from B to A. More details are available from the Connectome website (http://www.humanconnectomeproject.org). Post-processing improvements may be able to help with this.

Question 3. When we build the Connectome we can choose the number of fibres passing through, but is this a good measure for the density of a connection?

RM: This will depend on the resolution and the matrix acquisition size. In terms of relative measures it is probably a good proxy. We have investigated something called the capacity measure (how many fibre bundles go between two particular areas as a proxy for density of connection) in the Zaleski algorithm, and it isn't too bad. A pure anatomist would cringe at this being used to measure conduction strength, but it is the best thing we have at the moment for measuring diffusion.

GC: There are very few studies done with real cadavers e.g. performing DTI to test the algorithms. In theory it is possible if you have good diffusion results to validate the predictions of the model.

VJ: The group in Leipzig is doing exactly this with cadavers and different types of scans including tractography. So far no results have been published, but they are already working on this.

RM: The cadaver has to be processed so that you do not change the water properties too much; you can use a fully perfused cadaver. However, you are still looking at white matter properties rather than true connectivity. Blunt dissections can of course be done afterwards.

GC: Blunt dissections are important but very complicated.
**Question 4.** Does the VB only include cortex, or the brain stem as well?

**RM:** Thalamus and basal ganglia are included, but not the brain stem as of yet.

**VJ:** This is a common question i.e. to what degree will more detailed models be able to be inputted once the VB is released, for example visual cortex, columnar structure etc. which are currently just blobs with no detailed spatial resolution. In principle it will be possible, but the question is to what extent. Firstly, at some point the limits of computational capacity will be reached, and secondly it is the scientist who will need to fix the assumptions/parameters. So while more detail may be useful, too much detail may be pointless/irrelevant.

**CSM:** There are some very important things to model in the brain, such as emotions, which are very important in psychiatry. Thus if my question was psychiatric in perspective, I may not need a very complex model, but I will need something that allows me to make my own model e.g. in the case of emotion, a way to highlight the most important features e.g. some sort of feedback loop.

**VJ:** To describe the technical state-of-the-art in a little more detail, what you can model is intrinsic activity and resting state with different levels of sophistication, and you can intervene on different levels, manipulating local or global coupling and inserting stimuli wherever you want. These stimuli can then be adjusted, or loaded in sequence to stimulate the system, and local potential can then be measured. By making the stimulus-activity dependence you can establish a feedback loop. So far this has not been implemented, but technically it is not very far away.

**FT:** In terms of emotions, I feel the history of the conceptualisation of what emotions are is important. From self-stimulation studies e.g. dopamine stimulation in rats of the nucleus accumbens, we observed that dopamine is elevated in the nucleus accumbens by certain behaviours, such as alcohol or cocaine consumption, and therefore we assumed that elevated dopamine is equal to pleasure. However, now we say that dopamine has an error-signal function according to the experiments from Schultz; it fires in response to reward or a conditional stimulus, and is suppressed if reward is withheld, so really it has no emotional function. An important task for psychiatry is to decide if we can have a functional definition of what an emotion is. Pain cannot really be “operationalised” in technical terms as an experimental circuit.

**CMS:** Pain is a good example of an emotion that is pretty well characterised in fact, and methods are currently being developed to classify pain, and the intensity of pain. Different regions are activated with pain from those associated with social rejection, a related emotion; also the degree of activation of different regions depends upon the degree of pain. While there is a degree of overlap between activation as a result of pain and that of social rejection, it is possible to distinguish between the two. So
while the definition of an emotion has always been difficult, we are not so far away from being able to conceptualise emotions based on imaging methods.

**FT:** If we do not have a fine definition of an emotion, we can not find a sure correlate at the neuronal level. Cognitive science is not psychology; it is artificial intelligence. It is not so interested in how to define the difference between anxiety, aggression, desire, pleasure, happiness etc. These are only epiphenomena if we do not understand the functional structure of the process of emotion. If we do not have a precise definition of the concepts in which we are interested, we just end up with correlates of change e.g. dopamine has gone from being a pleasure substance to an addiction substance to an error substance.

**CMS:** I agree with most of what you say and feel that this is more of a philosophical issue, but maybe we can turn things on their head and rather than using concepts to try and define areas of the brain, we can use what we observe in the brain to get definitions of concepts. Then perhaps we can look for a common language between the two fields.

**GD:** It has been suggested that perhaps we should use neuronal correlates to define psychiatric conditions rather than the lists of descriptive symptoms that are currently used to diagnose and define a disease.

**CMS:** For example in cases of hyperactivity or hyperconnectivity between the ventral striatum and the orbitofrontal cortex that have been observed not only in OCD but also in addiction and other disorders, it may be that they can be treated using the same treatment. There have been several recent papers advocating change in the diagnosis procedure in psychiatry, through for example, using endophenotypes to cluster the disorders rather than the symptoms because there is a lot of heterogeneity in current diagnoses.

**FT:** The problem in psychiatry is the loss of psychopathology. There is no culture of describing how the patient is in the interaction-exploratory situation. The problem is the training of young doctors to use grading scales e.g. Hamilton's depression and anxiety scales. However there was a high correlation between these two items, and thus no way to discern between the two. From the subjective perspective of the psychiatrist on the other hand, it is straightforward to distinguish between the two. Thus these objective rating scales are actually resulting in the loss of an important level of description. As a field psychiatry believes that if it can metricise psychological terms in terms of neurobiology we become hard scientists. However, this involves a move away from subjectivity which is still critically important in psychiatry. Thus I do not agree with constructing biological concepts such as endophenotypes at the expense of eliminating psychopathological terms. As early as 1910, schizophrenia was described as an association disorder, analogous to the way we are now describing it in terms of disconnection, so we do have an intuitive qualitative
GD: So how do we reconcile this view with the belief that the VB could be used for psychiatry if you don’t believe in the underlying neuronal correlates of diseases?

FT: I believe in correlates. When computer-tomography was first developed it was very difficult to distinguish between psychiatric disorders and neurological disorders, but now with imaging methods it is very easy to distinguish between micro-lesions and circulation issues and true psychiatric disorders. However stating that a particular neurostructure is underlying a particular psychiatric syndrome is something I have problems with, and see this only as a correlate. The predictive value of such structural analyses of the type Prof Deco is doing should be very useful, but there are associated ethical issues e.g. if we observe some sort of lesion in a young person that predicts that they will develop schizophrenia, what should we do?

**Question 5.** Under what conditions would Dr Conesa be willing to use the Virtual Brain to help him operate? What would he like to see? What would help him gain trust in it/its predictive simulations?

GC: Usually when a patient presents at my clinic, we send him/her for imaging first. Sometimes we will see something very obvious during imaging, for example a herniated lumbar disc, but when we observe the patient, we see that this is not having any discernible effect, and thus we have to change our model. We do not operate on the back of photographs, but on the basis of clinical situations, and the model has to fit these situations, as it needs to for psychiatry. Thus we would require personalisation of the VB model for our patients. It would be good to test some of our cases with the personalised DTI or tractography modelled in the VB, and very probably there would be some predictive power as most of the things are very logical. The platform should have all possible inputs; one thing that is lacking is the comparison of the prior situation (i.e. the VB model) with the reality observed in the clinic, in order to see how well the former fits the latter, and what can be improved. Continuous feedback of this nature will provide a general model in which to fit all the different parts, and a personalised model that will help longitudinally to understand plasticity.

VJ: This is one thing we are doing with John Regis, a neurosurgeon in Marseille, in the context of epilepsy. We are doing pre- and post-surgical DTI scans as is standard. We are attempting to virtualise 3 patients to the best degree we can, using a variety of imaging including CT, stereotactic-EEG and DTI-EEG, MEG and fMRI before intervention, and EEG and fMRI afterwards.

GC: Stereotactic EEG provides a fantastic pre-surgical model to test e.g. sometimes you have a hypothesis and you have taken out your epileptic focus and the patient
has not recovered, and thus you have to repeat the process. In these cases you will have the opportunity to refine the hypothesis and retest.

**GD:** In your experience, in order to develop such a case what would be your recommendation for a clinical scenario?

**GC:** I think epilepsy is the best case because you have the validation process afterwards. The studies discussed in my talk, illustrate what were formerly thought of as essential language centres (ex-gold standard). However I know of two cases where we have taken out one of these essential areas. One was a bilingual patient who said he wanted to be able to speak Catalan, but did not care about Spanish, and immediately following tumour removal he did not speak Spanish, but after six weeks he had fully recovered his Spanish speaking ability and therefore it was not an essential site after all; plasticity was able to reroute and reshape the brain. This would be a nice model to test, and to see if we could predict what was going to happen.

**GD:** Yes we need to develop a test case and proof-of-concept, and we are in the process of choosing the best option.

**GC:** I think memorisation is a very good option as well because it is easy to see what is being stimulated and observe real connections in real time.

**FT:** I think it is very interesting and fruitful to use computer models and simulations in the context of case studies. Extreme cases are useful to compare syndromes such as addiction, obsession, and schizophrenia. Also, focusing on one structure such as the striatum and building a model of this and then looking at experimental and empirical data and adapting the model further in a continuous cycle of observation and testing to improve iteratively should prove valuable. Then we could use the VB for case studies.

**RM:** This is one of the aspirations of the VB.

**VJ:** It is for this reason that the DTI needs to be sufficiently reliable and trustworthy.

**Question 6:** Can the Virtual Brain at the moment predict this sort of plasticity?

**VJ:** Plasticity is a big issue because it is reorganisation of connectivity on a slow time scale, so we need a mechanism which we do not have. However, we can change the connectivity by hand and study under what conditions of connectivity changes we observe cases of this sort. However, an additional issue here is that there may not only have been a connectivity change but also a change in coding or
representation. So in the future perhaps it will be able to predict plasticity but at the moment it is more of a network processor.

**GD:** But we can explain the origin of the plasticity by refining the model and fitting the observations, and we will have an idea of what happened clinically in a particular patient at least, and know which parts were plastically relevant.

**GC:** It is difficult because many times when you do two fMRIs and you say it is plasticity, but sometimes it is not, as it is just a hyperactivation. So how much of this effort is really getting the correct target, and how much is maybe losing inhibitory actions, which is actually bad activity for this function, is a further confounding effect.

**VJ:** You do not know if it is plasticity or a global reorganisation. But this we can check in the VB by making certain assumptions.

**GC:** This is something we can manipulate with the TMS. We can observe how the fMRI has been acting longitudinally and then inhibit or excite a certain area on the surface non-invasively and observe the results. This is something else that will be useful to add.

**GD:** This is my particular hope for the Virtual Brain, that one can perhaps with the Virtual Brain predict which path of plasticity is the most convenient for compensating a particular function. In the case of stroke, people often attempt to compensate using the whole brain, which is not convenient. Perhaps if we can predict with the VB which is the most convenient path with which to compensate, then we can then use TMS and promote that the patient uses this particular path.

**VJ:** You can go even further. McIntosh has mentioned that deep-brain stimulation works for many diseases; one hypothesis being that it stimulates, or initiates, or enhances the process of plasticity thus helping or catalysing the reorganisation. This would be an additional manipulation that could be performed.

**GD:** When you have to remove some part of the brain, sometimes there is paradoxical damage - it would be convenient maybe to damage another region unrelated to the tumour, to re-establish the “symmetry”, and thus compensate for the paradoxical damage. Perhaps models in the VB could help to predict this.

**Question 7:** Would it be possible to implement in the VB things such as function, better than plasticity i.e. changes in volume of structures due to decrease of use of these structures (co-activation). Functional connectivity also changes during life and if we practise things. Will it be possible to incorporate
this into the VB as another variable to explain normal behaviour?

**VJ:** If you know how to formulate this mechanism through a model-system, then the answer is yes. The architecture is as general as possible so that layers can be easily added e.g. a stimulus has the same nature as a local coupling i.e. a set of parameters that defines it spatially. Thus another layer with a spatial distribution can be added that will change your parameters in a neural population on a very slow time-scale. That will be equivalent to plasticity, where the changing of parameters is somewhat dependent on local connectivity or contextual activities. But the science needs to be done first to envision what is happening. There are not many plasticity-based models, and most are based on spike-time. This type of intervention incorporating activity-dependent changes of the field-structure on cortical surface is currently being attempted; a frequency-dependent effect that will change the parameters of the model.

**Question 8.** How do you see the VB for drug-design, or drug interactions, at the molecular level?

**GD:** If you have good models of the underlying pathways at the molecular level and the output of those models is at the level of the microscopic part of the Virtual Brain's levels e.g. conductivities of glutamine or GABA receptors, and the appropriate latency, then the link is there because there is access to those parameters in one of the models of the VB, and the connection is straightforward. The main problem is that the degree of development of mathematics at the molecular level is not that good. If this can be surpassed then it is possible.

**FT:** We have the technical problem of global brain-scanning of receptors which have different distributions in different brain regions. For example there are subtypes of benzodiazapine receptors that have a specific regional distribution. Then we have synapses which are adaptive processors with adaptation and up/down- regulation of receptors etc so it is a very confusing picture. It would be possible to make models of why anti-psychotics have certain side-effects for example, but we focus on understanding synapic dynamics of dopamine transmission, and it is really very hard to have 30-100 differential equations, and have the kinetics of any process in the context of other processes. In experimental biochemistry we generally just try to isolate everything in an attempt to identify the kinetics of a particular substance in which we are interested. With billions of receptors in the brain it will be very difficult to establish all the questions associated with chemical connectivity in order to deal with these pre/post- synaptics if we wish to understand diseases such as schizophrenia. It requires modelling of modules in different regions, e.g. the striatum and the prefrontal cortex and their respective interactions which differ depending on location i.e. multi-level modelling to link the global VB with these micro- and molecular-systemic processes will be necessary.
## Appendix - Abbreviations Used

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<th>Abbreviation</th>
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<tr>
<td>5-HT</td>
<td>5-HydroxyTryptamine (serotonin)</td>
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<tr>
<td>Ach</td>
<td>Acetylcholine</td>
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<tr>
<td>BOLD</td>
<td>Blood-Oxygen-Level-Dependent</td>
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