Psychiatric Systems Medicine: Closer at Hand than Anticipated but not with the Expected Portrait

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Abstract

Almost all complex human diseases are context-dependent entities to which molecular components make a necessary, but only partial, contribution. This is particularly evident in psychiatric conditions such as schizophrenia and major depressive disorders. Here, classical analytical approaches based on reductionism lead to profound misconceptions of the actual nature of the problem. Consequently, a systems perspective may be the optimal method for approaching complex psychiatric diseases. However, attempting to productively apply systems principles to complex medical conditions is much more difficult than hitherto anticipated. Living systems are integrative and non-linear by nature and embody higher level functional principles that are not reducible to the molecular level. Furthermore, whereas systems biology functions on the basis of large data sets arising from highly targeted investigations upon homogeneous experimental material, systems medicine must proceed on the basis of existing, highly heterogeneous data. The challenge is therefore to assimilate a large, and often conflicting corpus of data to build and inform a systems-level model of the physiological alterations underlying the disorders while reaching beyond somatism (bottom-up approaches), which is provably largely insufficient to functionally explain multicellular living systems to a degree enabling informed therapeutic intervention. This paper factually documents how a modelling approach based on a combination of heuristics (top-down) and algorithmic (bottom-up) modelling strategies, together with the active participation of clinician networks can provide an effective roadmap to productively address psychiatric disorders at large, and schizophrenia in particular.

Introduction

Modern medicine often treats diseases from a reductionist point of view, technically called "evidence-based medicine", analytically characterised by population-based assessments using stochastic principles [1]. While, as a guiding principle, reductionism is remarkably useful, it becomes inefficient when the act of dividing a problem into its apparent parts leads to profound misconceptions of the actual nature of the problem [2–4]. Indeed, in clinical medicine, reductionism is helpful when one or several components overwhelmingly influence the system's behaviour. Diseases such as urinary tract infection, acute appendicitis, or influenza are driven primarily by a single pathology amenable to a specific intervention. However, in complex, chronic diseases, such as psychiatric/neurological disorders, a single factor is rarely implicated as solely responsible. Rather, multiple factors are participating, some of which are often unidentified, and the disease evolves through complex interactions [5].

For more than a century, it has been uncertain whether or not schizophrenia and bipolar disorder, the major diagnostic categories of psychosis, are distinct disease entities with specific genetic causes and neuro-anatomic substrates. The results of studies directed toward aetiologies and the interpretation of the complex relationships between genes and behaviour have shown very limited reproducibility. Schizophrenia (SZ) today is understood as a "disconnection syndrome" (too much and too few) where, as a result of neurodevelopmental deficiencies, structural and functional connectivity is insufficient.

Evidence from in vivo and post-mortem tissue studies indicates that SZ is characterised by selective impairments of the synaptic machinery

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within cortical circuits, particularly in the dorsolateral prefrontal cortex (DLPFC) and primary auditory cortex (AI) [6].

Mood disorders on the other hand are characterised by specific glial pathologies. Post-mortem findings consistently show reductions in glial cell density or cell numbers in prefrontal regions (subgenual anterior cingulate cortex, the orbitofrontal cortex, and the DLPFC) in association with reduced prefrontal grey matter. Specific astrocyte and oligodendrocyte alterations, such as marked reductions in amygdala oligodendrocytes densities in major depressive disorder (MDD), and microglial alterations in bipolar disorder (BD), including manic episodes, have also been consistently reported [7].

Synaptic plasticity, the regulation of neuronal excitability, neurovascular coupling and the homeostasis of networks dynamics (noise-induced propagation, signal pruning, synchronisation, etc. [8,9]) involve the active participation of astrocyte populations [10,11]. Slow-signalling glia modulates fast synaptic transmission and neuronal firing to impact behavioural outputs, including neurological and psychiatric conditions [12]. Indeed, the adult brain rapidly and reversibly adapts its synaptic architecture to functional needs [13] and astrocytes are involved in these dynamic processes [14] as well as in the aetiology of SZ [12,15], depression [16] and mood disorders [17], among other dysfunctions [18].

Hence, from an investigative standpoint, multifactorial diseases such as SZ and MDD cannot be reduced to either predominantly synaptic or predominantly glial defects since, in both cases, the interplays between non-neuronal and neuronal components are likely to be dynamically impacted and to retroact on each other [19,20] both in time and in space (cerebral anatomy) across several scalar levels (from metabolic to structural aspects) [21–23]. Thus, as a general rule, reductionism becomes deleterious in systems where interactions between components dominate the components themselves in shaping the system-wide behaviour. Consequently, a systems perspective which, unlike reductionism, focuses on these inter-relationships may be the optimal method for approaching complex diseases [2,24].

The Need to Change Analytical Paradigm

Systems biology addresses the need to shift from a component-based reductionist view of biology to a system-wide perspective. Systems biology explores the dynamic interactions between components of a living system, as well as their interactions with the environment, to elucidate how they determine its phenotype. Systems biology can be characterised as interdisciplinary, iterative, computationally intensive and information greedy [25].

Similarly, systems medicine aims to reconstruct organs and organisms using knowledge of their molecular components to determine clinical behaviours and interventions [26].

However, there are no inherent limits to the levels at which "a system" may be defined as an entity. In fact, there is no such thing as "a system" because structures that are parts of one system (a transport vesicle in a cell) may form systems in their own right at a different level of integration (in the contexts of receptor trafficking and targeted surface expression). Thus, systems biology interprets biological phenomena as dynamic processes, the mechanisms and consequences of which depend on the behaviour of the living entity studied. This ranges from submicroseconds for molecular-level interactions to days, months, and even years for the development of a disease in humans.

2 broad approaches to systems biology currently exist: the frequently followed mathematical procedures [27] and the more rarely encountered heuristic approaches [28–30], both of which are largely regarded as mutually incompatible [31,32].

Heuristics can be characterised as a problem solving approach evaluating each step in a process, searching for satisfactory solutions rather than for optimal solutions, using all available qualitative information. Thus, heuristic modelling starts from accumulated knowledge to produce a model capable of describing the biological events and the mechanisms that generated the observed experimental data and predict their modifications associated with a different outcome (top-down approach).

In contrast, mathematical modelling starts from quantitative data to produce models capable of reiterating these data and predict the outcome of a different experimental paradigm. Typically, the models thus produced express cell behaviour by means of quantitative concentration changes in the molecular networks, such as differential transcripts and gene product levels. These formal models, often based on ordinary differential equations, are abstracted from spatial distributions of molecules and cells and assume a bottom-up causation from molecular dynamics to cellular behaviour.

By focusing mainly on chemical and physical processes with the expectation that living systems can be fully explained from this perspective, this engineer's vision also includes the widespread analogy that presents functions within an organism as resulting from "modular organisation" [33,34].

This is in keeping with the dominant view of diseases as biomedical in nature, with molecular biology as the basic scientific foundation. This view assumes that diseases can be fully accounted for by deviation from the norm of measurable somatic variables, leaving no room for psychologically and environmentally modulated dimensions. This framework not only requires that diseases be dealt with entities independent of other modulated dimensions, it also demands that affective aberrations be explained on the basis of disordered somatic (biochemical and neurophysiological) processes.

However, in the late 1970s, it was pointed out that "rational treatment", directed only at somatic abnormalities, does not necessarily restore a patient's health, even in the face of documented alleviation of the abnormality, be it in the context of metabolic or of psychiatric disorders [35].

Since the boundaries between "well" and "sick" are far from clear [36], effective investigative and therapeutic approaches must also take into account our appreciation of what we perceived as "health states", the contexts to which they are applied, and the systems devised by society to deal with the disruptive effects of illness. It was further demonstrated that, since systems theory holds that all levels of organisation are linked to each other through hierarchical relationships, changes affecting one level also affect all the others [35,37].

The stability of a living system lies in its homeostatic capacity to re-establish itself. In a living system, the outcome does not crucially depend on strictly predefined operations of the parts. Rather, the structure of the whole determines the operation of the parts. Indeed, almost all human diseases are complex context-dependent entities to which genes make a necessary, but only partial, contribution. This is particularly evident in psychiatric disorders.

Thus, it was argued that by treating a set of related events collectively as systems manifesting functions and properties at different levels within the whole, it should become possible to approach health problems from a much more realistic and fruitful standpoint [35].
It was therefore advocated that such holistic frameworks, amenable to scientific inquiry and conceptualisation, collectively termed "biopsychological medicine", should be adopted in our approaches to the study and treatment of pathological states [35].

The Difficulties Associated with Implementation of Holistic Frameworks

Although this proposed approach met wide ranging support in the scientific and medical communities [31,32] it has found very scant actual implementation over the past 3 decades [38]. Amongst the most probable impediments may be the difficulties of applying the biopsychosocial model in medical care and of competing with the traditional biomedical concept of health, which has proved fruitful and dominant in medicine over the past 3 centuries.
However, there is another much more serious difficulty which only appears when attempting to build a "realistic" picture (systems model) of what could be functionally happening to develop a psychiatric condition.
The biopsychosocial model implies a "multidimensional conceptual reference framework". However, the spectrum of dimensions that could be conceptually addressed in a systems approach to psychiatric disorders is close to infinity. Since the definition of dimensionality is dependent upon the observer, reducing the spectrum through multivariate statistical treatment would amount to nothing more than blind reductionism. Indeed "biologically meaningful" does not necessarily equate with "most frequently held".
Furthermore, living systems are integrative and non-linear by nature. Irrespective of the level addressed, one is constantly faced with demultiplications associated to discontinuities. (One gene = multiple transcripts, the dominant forms of which cannot be predicted because dependent upon local contexts and amenable to sudden changes. One protein = multiple co-existing functional forms+multiple co-existing functional complexes, the effects and life-spans of which are also local context-dependent and amenable to sudden changes, etc., etc.). And that is merely considering the somatic aspects which, themselves, address levels ranging from the pico-metre to several thousand metres (total perfused cerebral vascular length of approximately 600–700 km in the human adult [39]).
Moreover, it is now very clear that somatism, which already is multidimensional, is largely insufficient to functionally explain multicellular living systems to a degree enabling "informed therapeutic intervention". There are functional behaviours that emerge from indirectly linked organisational hierarchies. These can be easily observed but not analytically approached through somatism. The pacemaker rhythm in the heart constitutes a prime example of this. The site of the pacemaker rhythm cannot be located at the sub-cellular and molecular levels. Yet, there is no difficulty in locating it anatomically at the level of certain cells within the whole organ [31]. Thus, if a particular biological function or entity does not exist at one level, this does not mean that it does not exist at all. Functional principles on a higher level obviously include phenomena which are not reducible to the molecular level.
Hence, attempting to productively apply systems biology principles to complex medical conditions is fraught with many more difficulties than hitherto anticipated. But there is a further level of complexity that suddenly appears when dealing with human pathologies.
Whereas systems biology functions on the basis of large data sets arising from highly targeted investigations (e.g., time-series, see [40]) upon homogeneous experimental material, a holistic approach to medicine (systems medicine), that could benefit patients and society, must exploit more limited data sets, arising from multiple open-ended investigations upon highly heterogeneous patient populations in conjunction with vast amounts of poorly correlated published results. Hence, systems medicine must proceed on the basis of existing, highly heterogeneous data and not on the basis of homogeneous datasets arising from specifically targeted investigations.
How to then productively approach the problem of implementing a systems approach to psychiatric/neurological disorders?

An Analytical Approach that could Foster the Advent of Systems Medicine

There is an analytical alternative that already exists, the utilisation of which has been shown capable of considerably accelerating the advent of effective systems medicine. This alternative model-building approach, known as CADI (computer-assisted deductive integration), associates algorithmics and heuristics. The tools and processes implemented have been described in several publications [24,29,30] and have repeatedly proven their efficacy in the discovery of (i) hitherto unsuspected mechanisms, pathways and interactions directly associated with phenotypic transitions in vivo (be they pathological or developmental), (ii) the corresponding biomarkers and, (iii) in the case of pathologies, novel therapeutic approaches in domains ranging from oncology to neurodegenerative and infectious diseases [41,42,80] and patents [81–84]. This approach was selected by the EU's DG Research as one of 3 examples of "state-of-the-art" in systems biology that benefit to medicine [85].
The logic behind this model-building approach (**Fig. 1**) does not assume functional linearity and the components of a model do not incorporate solely what is known. Indeed, since this approach relies upon strict and systematic implementation of negative selection of hypotheses, models arising from this procedure contain elements that have never been described but cannot be refuted by current knowledge and/or available biological data. Here, heuristic modelling plays the role of an architect (defines the nature, the structure, the functionalities and the contextual constraints of the system under study) while mathematical modelling, to be implemented at a later stage, plays the role of an engineer (reveals the dynamics and robustness of the structures while defining the set of parameters sufficient to give rise to similar or very different phenotypes).
Although the models arising from this analytical approach cannot, by any means, be regarded as biologically true in the absolute, they do represent a "least biased" and detailed view of the mechanisms potentially associated with a given physiological state and/or governed by the biological components under consideration, together with precise indications of the means whereby these could be manipulated. The new data arising from

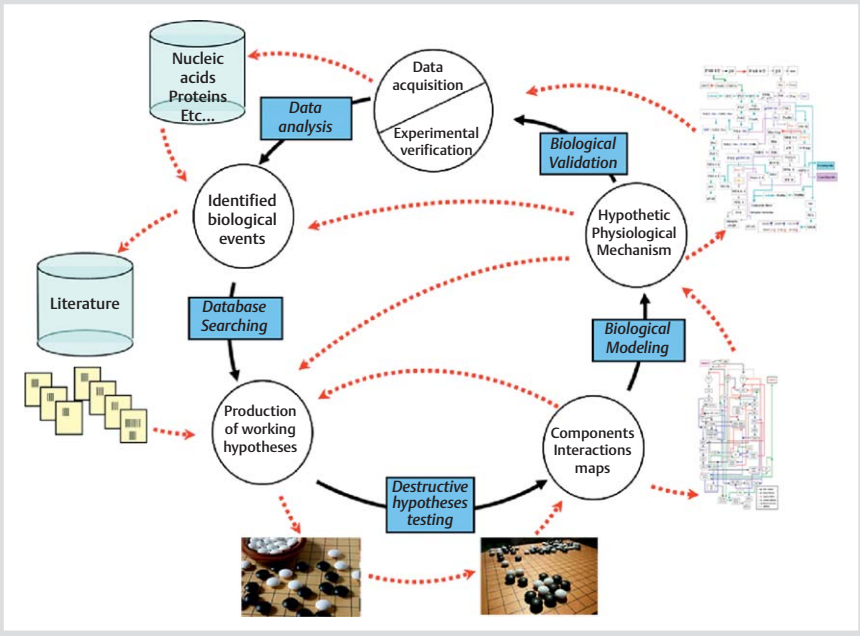

Fig. 1 The CADI modelling strategy. Working hypotheses, directly generated from datasets and the literature, that have resisted all destruction attempts (go boards) are merged to produce interaction maps. These are in turn merged to produce hypothetical physiological mechanisms. During each phase, "undetected" biological events are revealed while novel working hypotheses are being generated (dotted red arrows). These are, in turn, subjected to the iterative negative (destructive) selection procedure. Hence, this model-building process involves multiple levels of internal cross check procedures designed to eliminate any hypothesis that is not directly as well as indirectly supported by multiple data intersects. The results of experiments designed to directly challenge/validate the model thus obtained can then be, in turn, injected into this iterative analytical process.

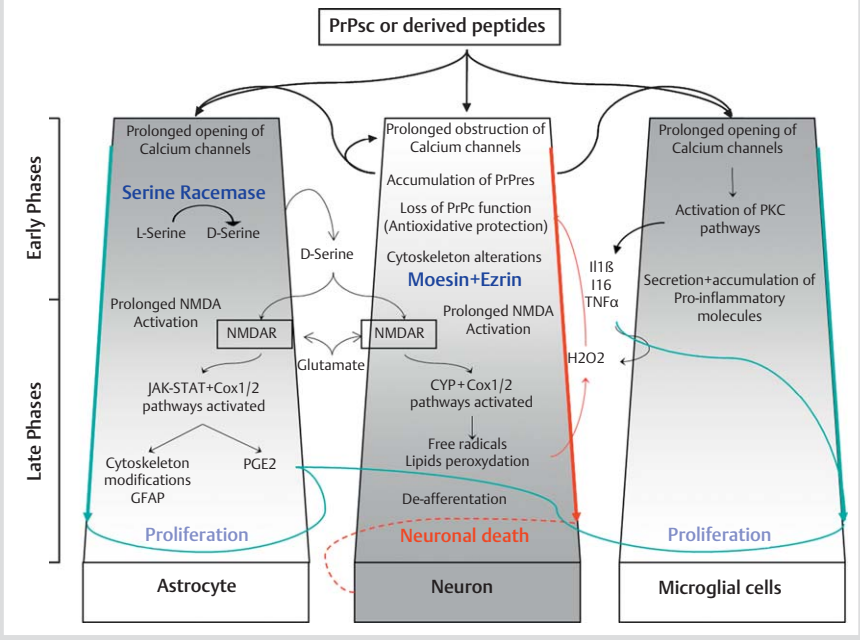

Fig. 2 The first version of the model, constructed from the literature only, described a situation where PrP-res infected neurons occupied the central place, eliciting glial and astroglial responses. The model predicted that a significant decrease in the levels of ezrin and/or moesin expression should be observed in the neurons of infected animals during the early, symptomless phase of disease development, concurrently with an increase in the activity and/or expression levels of glial serine racemase.

subsequent experimental verifications can then be re-injected into the model, rapidly leading to a clear and factual understanding of the biological processes under investigation.
A concrete example will illustrate the fact.

Creutzfeldt-Jakob disease as an example in applied systems medicine

In Creutzfeldt-Jakob disease (CJD), the prion-mediated pathogenic mechanisms leading to widespread neuronal death associated with a long latency period and a short, invariably fatal clinical phase remain largely unknown. The known cytological elements required for CJD pathogenesis are neuronal expression of PrPc and the presence of glial and microglial populations. Although the major pathogenic agent is known (misfolded PrP protein: PrP-res) and animal models that faithfully reproduce the clinical characteristics of the human disease are available, the possible neurodegenerative mechanisms remain elusive [43–45]. To address these issues, an investigative procedure based on iterative theoretical modelling, using the CADI modelling process, directly linked to in vivo testing upon rodent models of prion diseases, was devised.
The initial model (● **Fig. 2**), entirely constructed from the literature, suggested that, as the disease progresses, an alteration of neuronal ezrin-moesin-radixin (ERM) cytoskeletal system should be observed concurrently with a modification of astroglial serine racemase expression. Experimental evaluation, using quantitative PCR, showed a significant fall in ERM protein expression in an in vitro prion infectible neuronal model. In vivo, significant increases in ERM protein expression at the global CNS level were observed in mice infected with scrapie and BSE prion strains. Qualitative in vivo increases of ERM protein expression in GFAP and vimentine positive (activated) hippocampal astro-

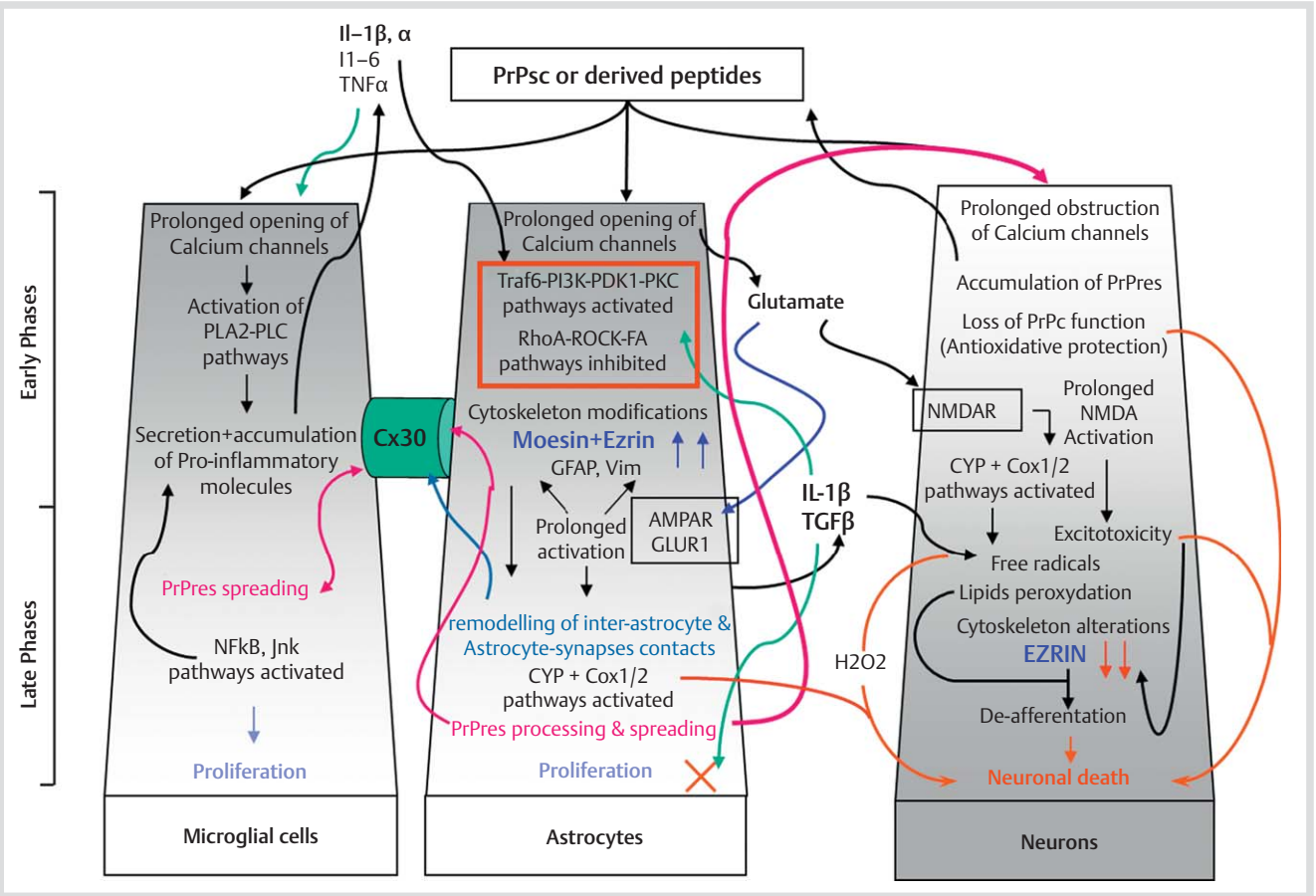

Fig. 3 The revised model, generated following integration of the results of targeted experimental challenges, depicts a situation where astrocytes play the central role in the presence of PrP-res. The model predicted that, in response to the presence of PrP-res and fragments thereof in their direct environment, together with mild levels of neuronal stress signalling, astrocytes will initiate toxic responses (activation) driven by autocrine and paracrine signalling (box and ▷ **Fig. 4**), culminating with a major change in syncytial connections (Cx30) accompanied by the inception of gliosis/astroglyosis. This should result in (i) a major change in the permeability of the local astrocytitic syncytium and the loss of its synaptic regulatory role, (ii) the local loss of glial neuro-supportive functions, and (iii) the local death of healthy neuronal and glial cells through bystander effects. The ensuing escalating level of neuronal stress-signalling, together with the spreading of PrP-res, mainly mediated by astroglial cells, causes the formation of ever spreading 3-dimensional, high permeability and activated astrocyte-sheets responsible for ever increasing neuronal losses. This slow process covers most of the asymptomatic phase of the disease. Once internal neuronal redundancy falls below the lower functional limits, symptoms become apparent (clinical phase) and the disease appears to progress rapidly.

cytes together with decreased ERM protein expression in live hippocampal neurons were observed.

These in vivo observations lead to a revised model (▷ **Fig. 3**) indicting that the pathogenic neurodegenerative mechanism was probably driven by astroglial responses to stress signalling from PrP-res-infected neurons (auto-infection waves, ▷ **Fig. 4**) and that, as a result, the unexpected restructuring of astrocytes cytoskeleton should be locally associated with a switch in astroglial connexins (Cx) intracellular trafficking and targeting (predominantly in the hippocampus). The model further suggested that this switch in Cx patterns would be associated with the formation of a localised, activated 3-dimensional astroglial sheet with diffusive properties radically different from those of control astroglial syncytium. Direct in vivo investigations (not shown) corroborated these suggestions and also revealed that the extent of both junctional modifications, in terms of Cx contents and syncytium permeability changes, were much larger than anticipated. Cx30 over-representation co-localised with heavy PrP-res deposits in all brain area, resulting in the formation of extensive 3-dimensional astsrocyte sheets with massively increased diffusive properties.

Cx gap junction hemi-channels permit the rapid exchange of ions and of small molecules (Ca^{2+}, IP3, glutamate, ATP, ADP) between the cytoplasm and the extracellular space and have been implicated in the regulation of calcium wave propagation and in the pathogenesis of neurological disorders [46]. Glial pathways of junctional communication appear determined by Cx composition and conductance regulation of junctional channels [47, 48]. Exacerbated hemi-channel opening, which contributes to the loss of chemical gradients across the plasma membrane, is reported to occur in metabolically inhibited cells, including cortical astrocytes [46]. Hence, changes in Cx hemichannel gating and diffusive properties ultimately disrupt ionic homoeostasis, leading to a plethora of injurious consequences [49], all the more so since inflammatory stimuli can facilitate the opening of glial hemi-channels [46]. Furthermore, there exists a direct functional link between astrocytic glutamate and extrasynaptic NMDA receptors that contributes to the overall dynamics of neuronal synchrony. Activity synchronisation of anatomically distributed groups of neurons represents a fundamental event in the processing of information in the CNS. This phenomenon results from dynamic interactions between neuronal circuits

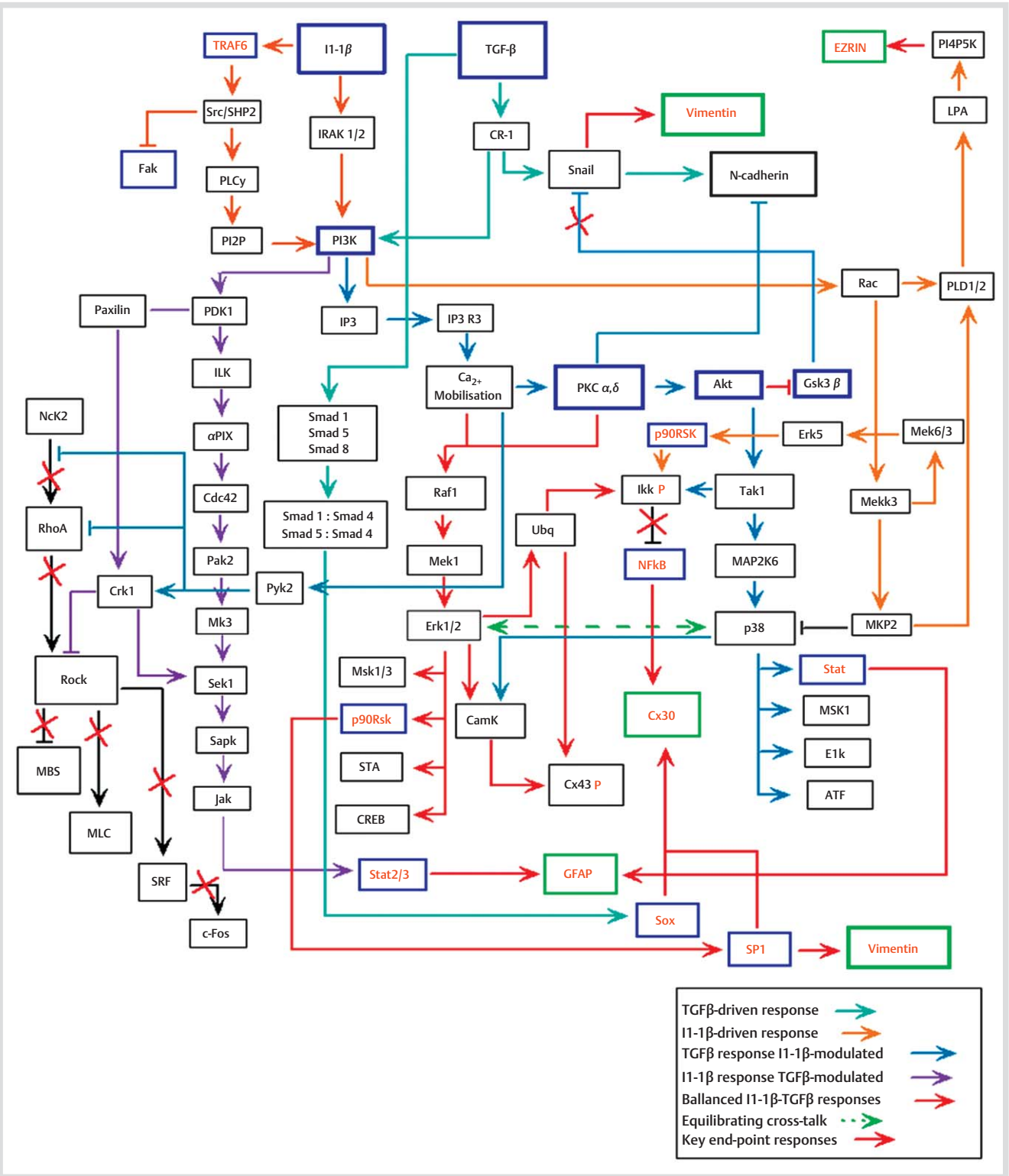

Fig. 4 The signalling cascades implemented following autocrine and paracrine signalling in astrocytes. Here, TGF-α(autocrine) and Il1β (mainly paracrine) signalling implement a complex cascade of responses culminating in increased expression of ezrin (cytoskeleton remodelling), vimentin and GFAP (indicators of astrocytes maturation and activation) together with a major switch in connexin (Cx30) distribution. The heavy boxes correspond to events experimentally verified in vivo.

and astrocytes that are directly involved in the generation of neuronal synchrony in the hippocampus. By acting preferentially on extra-synaptic NMDA receptors, astrocytic glutamate evokes synchronous, slow inward currents (SICs) and Ca^{2+} elevations in domains composed of 2–12 CA1 pyramidal neurons. Thus, astroglial gap junctions, and in particular selective permeability differences between the various Cx isoforms, play a significant role in the synchronisation and integration of neuronal activities [50,51] and in the generation and spread of seizure activity [52,53]. This takes a particular importance here since

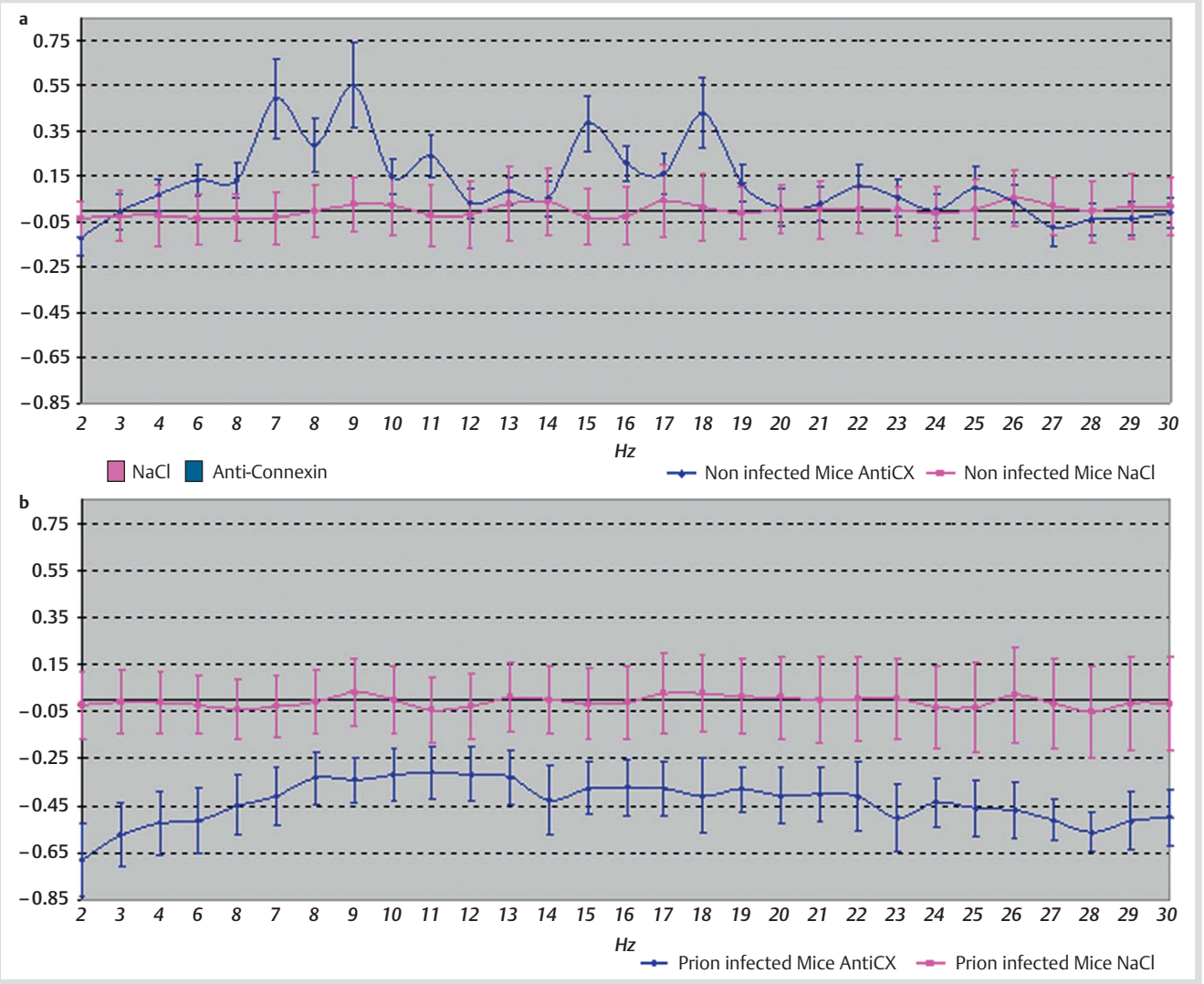

Fig. 5 Normalised quantitative EEG patterns recorded in vivo from the hippocampus of healthy **a)** and prion infected **b)** mice following vehicle (pink trace) and anti-connexin peritoneal injection. The abscissa corresponds to the frequency points recorded (2–30 Hz) and the ordinate to increases/decreases in relative EEG powers recorded. CNS glia express at least 6 connexins and astrocytes form 2 distinct classes of gap junctions with each other: those composed of Cx26 and those composed of Cx43 and Cx30. In addition, astrocytes establish 2 classes of heterotypic intercellular channels with oligodendrocytes, Cx26-Cx32 and Cx30/Cx43-Cx47 channels that may also be heteromeric [47, 75, 76]. **a)** In healthy CNS, Cx26 is dominant in the hippocampus and all cortical areas while Cx30 is mainly expressed in the thalamus. Inhibition of the connexin channels in healthy CNS results in very significant quantitative EEG powers increases in the θ and α ranges (4–8 Hz and 8–12 Hz, respectively) and in parts of the β1 range (15–18 Hz), all of which are associated with long-distance synchronisations [77–79]. Hence, in a healthy CNS, the role of connexins is to dampen long range synchronisations. **b)** In prion infected mice (late symptomless phase), the hippocampus and all cortical areas present very significant increases in Cx30 together with a practical disappearance of Cx26 and 43. Here connexins blockade results in large decreases in quantitative EEG powers at all frequencies recorded, indicating that, in this context, one of the roles of Cx30 could be the preservation of long-distance synchronisations, albeit at the cost of astrocytes functional alterations.

Cx30, reported to gate at significantly lower voltage than Cx26, its closest homologue, also has high permeability for ATP and glutamate release, particularly in presence of low extracellular Ca^{2+} or membrane stress [48].

In vivo evaluation of the functional consequences of the observed Cx30 over-representation in infected animals revealed a striking reversal in the role of gap junctions upon synchronisation of neuronal oscillatory responses (**Fig. 5**). Short distance synchronisation tends to occur at higher frequencies (γ-band; 30–80 Hz) than long-distance synchronisation, which often manifests itself in the β1 (12–18 Hz), the θ (4–8 Hz) and α (8–12 Hz) frequency ranges [54]. Here, selective permeability differences between the various Cx isoforms play a very significant role in the stabilisation of extracellular ion homeostasis, uptake of neurotransmitters, synaptogenesis and synaptic plasticity, forming the basis for the synchronisation and integration of neuronal activities [50].

In control animals, where gap junction contents in Cx30 are low, Cx activity represses long distance synchronisation, particularly in the θ and β1 frequency ranges [54]. However, in PrP-res infected animals, where gap junction contents in Cx30 are high, Cx activity clearly sustains long distance synchronisation at all frequencies analysed, particularly in the θ and β2 (22–28 Hz) ranges (**Fig. 5**). The hyper-synchronising role of Cx30-containing gap junctions thus clearly explained, for the first time, the origins of the typical electroencephlogram (EEG) evolution,

from non-convulsive status epilepticus to generalised periodic discharges, that characterises the early clinical phase in CJD [55]. Furthermore, besides explaining the origins of the long symptomless incubation phase and the rapidly progressing clinical phase characteristic to prion diseases [44] and the processes leading to neurodegenerescence and vacuolation (healthy neurons and glial cells killed through bystander effects), these results also shed light, for the first time, upon the mechanisms leading to neuropathies outside regions of detectable PrP-res deposits [56]. In CJD, massively increased Cx30-mediated coupling between activated astrocytes leads to the constitution of extensive 3-dimensional, high permeability astrocyte sheets that cannot be expected to maintain their low permeability-dependent neuro-protective functions [46,47,50]. More importantly however, besides defining the role this Cx isoform could play in neurological diseases characterised by neuronal losses in association with hyper-synchronised EEG patterns, these observations highlight the roles of astrocytes and Cx gap junctions in other CNS pathologies associated with gliosis and astrocyte activation, such as Alzheimer's disease [5], as well as dysfunctional synchronisation processes, such as epilepsy [51,53]. This lends broad therapeutic relevance to the pharmacological modulation of Cx hemi-channels functions in neurological diseases.

A Roadmap to Psychiatric Systems Medicine

The work described above was completed in late 2007. It led to a patent application filed in 2008 and granted in 2010 as a therapeutics class patent, jointly owned by the 2 groups (BMSystems and CEA Prionics Group) who carried out this ground-breaking work.

Since then, many innovations and have been brought to the above modelling approach and it now stands to provide a reliable roadmap that productively addresses psychiatric disorders at large, and SZ [24] in particular.

Impaired spatial working memory and disturbed experience of time are consistent findings in SZ patients and have been related to impairment in fronto-striatal connectivity [57–60]. These impairments may be related to social disability and explain some cognitive deficits that characterise the clinical presentation of SZ [61]. However, patients presenting either SZ or BD with psychotic features share overlapping neuropsychological impairments. Both are impaired on the spatial span tasks which require the maintenance and retrieval of stored information. In contrast, only SZ patients show a significant deficit in working memory (search errors), which requires both maintenance and manipulation of information. The pattern of slow cognitive processing in SZ patients only, resembles that reported in patients with basal ganglia disorders. Hence, there is a possible common disturbance in fronto-parietal circuitry in the 2 disorders together with a specific disturbance of fronto-striatal circuitry in SZ that does not appear present in BD [62–65].

The available evidence suggests that functional interactions between the hippocampus and prefrontal cortex in cognition (the consolidation of information and working memory) are more complex than previously anticipated, with bi-directional regulation of synaptic strength as a function of the specific demands of tasks. The hippocampal-medial prefrontal cortex pathway apparently integrates discrete sources of hippocampal information via cooperativity between short- and long-term plasticity [66–70]. But, although critically dependent upon hippocampal and entorhinal cortex integrity, cognitive processes involve intense, long range signalling traffic between many cerebral structures.

Human scalp EEGs have demonstrated that global coherence among distant areas increases during cognitive tasks, suggesting that oscillating neural activities work to generate global neuronal assemblies for cognitive functions. During declarative memory operations, oscillatory activity occurs in the γ (60–90 Hz) and θ (4.5–8.5 Hz) ranges of frequencies [71]. θ oscillations with large amplitudes, which emerge during mental tasks around the frontal midline region, associate with regional activities that depend on task conditions. Multi-electrode intra-cranial EEG (iEEG) recordings have provided unequivocal evidence that at many cortical locations, θ power rises sharply when working memory becomes required, is maintained throughout the memory task, and decreases when working memory is no longer required [72]. Thus, θ-modulation can be regarded as a mechanism of attention arousing, which prolongs responses to a selected stimulus while simultaneously protecting its processing against interference [73,74].

As demonstrated by the work on CJD, the origins, regulations and modulations of such complex mechanisms can be efficiently addressed using the approach described above. Indeed, the very first programme actually implementing systems medicine in the context of psychiatric disorders (mood and anxiety disorders) is about to begin. Besides top European scientific specialists, this programme will also implicate the active and very significant participation of a network of psychiatry clinicians.

Conclusion

However, while systems medicine might be much closer at hand than anticipated, it is likely to present an unexpected guise.

The exploration of higher levels of physiological functions through exploitation of experimental data using systems approaches necessarily implies an iterative interplay between experimentation and modelling. While this may be reasonably considered in the context of in vitro systems, it can hardly be contemplated when addressing CNS tissues from heterogeneous human origins. Not only is the necessary experimental material relatively scarce, it can seldom be obtained at the clinical stages and with the phenotypic characteristics required. Furthermore, while fraught with a multiplicity of confounding factors, such as alcohol and drug abuses or undefined effects of environmental characteristics, the majority of post-mortem study subjects will have been medicated at some stage of their illness, making it particularly difficult to coherently approach the pathophysiological mechanisms, thereby imposing the recourse to clinically relevant trait animal models.

However, given the human uniqueness of any one of these disorders, it is highly unlikely for a single animal model to satisfy all the necessary clinical requirements and it is probably an error to expect any animal model to do so. Indeed, animal models of a given psychiatric disorder could legitimately be viewed as caricatures of this disorder. Hence, how could data obtained from such animal models possibly improve our medical and clinical understanding of typically human psychiatric disorders?

Through the active participation of clinicians networks – indeed, the model-building process will generate mechanistic inferences derived from trait animal model data. While possibly coherent, each mechanism thus depicted will primarily address

a system that structurally and functionally differs very significantly from that encountered in humans. It therefore becomes absolutely necessary to confront them, or at the very least their functional attributes, to those operating in humans. To this effect, the inputs of clinical experts become indispensable to bring a model constructed from trait animal model data into coherence with the medical neurobiology of the corresponding mental disorder. Furthermore, the mechanisms to be thus scrutinised will span several levels of representation, from molecular events to structural and anatomic networks, and must be conceptually transformed to objective behavioural concepts. This, in turn, implies that the clinical experts must intervene each time a potentially pertinent mechanism has been identified with a reasonable level of confidence (coherent with the input data and irrefutable by current published observations). It is therefore indispensable that some of the clinical experts intervening in the process be fully familiar, if not proficient, with systems biology and its intrinsic modes of operation and limitations. Thus, clinical data will indeed be extensively utilised, but not in the manner anticipated. This is precisely why networks of clinicians will be required.

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Conflict of Interest: The author formally declares that all materials included herein are factual, have not previously been published elsewhere and are entirely free of any financial interest that might influence the scientific value of this article.

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