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

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.
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 both in time and in space (cerebral anatomy) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across several scalar levels (from metabolic to structural aspects) across 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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 do not incorporate solely what is known. Indeed, since 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.

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
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 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.
Proliferation of neurons and astrocytes was probably driven by astroglial responses to stress signalling, indicating that the pathogenic neurodegenerative mechanism dominantly 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 astrogial 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 astrocyte sheets with massively increased diffusive properties.

Cx gap junction hemi-channels permit the rapid exchange of ions and of small molecules (Ca²⁺, 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 homeostasis, 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.
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 \cite{50,51} and in the generation and spread of seizure activity \cite{52,53}. This takes a particular importance here since

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**Fig. 4** The signalling cascades implemented following autocrine and paracrine signalling in astrocytes. Here, TGF-α (autocrine) and IL-1β (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.
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 θ (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 electroencephalogram (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 neuronal impairments outside regions of detectable PrP-resistant 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 hemic-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 neuropysiological 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 θ (60–90Hz) and θ (4.5–8.5Hz) 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 also implicate the active and very significant participation of a network of psychiatry clinicians.
a system that structurally and functionally differs very significa-
antly 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 scruti-
nised will span several levels of representation, from molecular
events to structural and anatomic networks, and must be con-
ceptually 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 biol-
y 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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