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Can a systems approach produce a better understanding of mood disorders?

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Keywords: affective disorder; bipolar disorder; computational biology; drug development; systems biology

Abbreviations: 5HTT = serotonin transporter; BD = bipolar disorder;, , BDNF = brain-derived neurotrophic factor, COMT = catechol-O-methyltransferase; GEM, genome-scale model of metabolism; MAO-A = monoamine oxidase A; UD = unipolar disorder

Abstract

Background: One in twenty-five people suffer from a mood disorder. Current treatments are sub-optimal with poor patient response and uncertain modes-of-action. There is thus a need to better understand underlying mechanisms that determine mood, and how these go wrong in affective disorders. Systems biology approaches have yielded important biological discoveries for other complex diseases such as cancer, and their potential in affective disorders will be reviewed.

Scope of Review: This review will provide a general background to affective disorders, plus an outline of experimental and computational systems biology. The current application of these approaches in understanding affective disorders will be considered, and future recommendations made.

Major Conclusions: Experimental systems biology has been applied to the study of affective disorders, especially at the genome and transcriptomic levels. However, data generation has been slowed by a lack of human tissue or suitable animal models. At present, computational systems biology has only be applied to understanding affective disorders on a few occasions. These studies provide sufficient novel biological insight to motivate further use of computational biology in this field.

General Significance: In common with many complex diseases much time and money has been spent on the generation of large-scale experimental datasets. The next step is to use the emerging computational approaches, predominantly developed in the field of oncology, to leverage the most biological insight from these datasets. This will lead to the critical breakthroughs required for more effective diagnosis, stratification and treatment of affective disorders.

1. General Introduction

The post-genomic era promised much with respect to a greater understanding of human biology, and the development of new, more effective medicines [1]. While this has been achieved to some degree, it can be argued that the genomics era actually produced as many questions as it solved, if not more. This is particularly true with regard to the human brain, which has one of the most complex transcriptomes in the human body [2-4].

There is a pressing need to develop effective treatments, or management strategies, for many complex diseases, including cancer, fatty liver disease and mental disorders [5]. This review will consider one aspect of mental disorders: mood, or affective, disorders. The spectrum of affective disorders afflicts an estimated 14 million sufferers in the USA alone, representing 4.4% of the adult population [6].

1.1. The potential of systems biology

At it's broadest definition, systems biology is, quite literally, the biology of complete systems [7]. The aim of systems biology is to predict the emergent biological phenotype from the interactions that occur within a system [8]. Emergent properties are those that cannot be easily divined by study of the individual components of the system. For example, all life can be seen as an emergent property of the interaction between the proteins, lipids and other chemicals that make up an organism. While it is obvious that the human phenotype emerges from these interactions, it is not possible to define what a person will look like by studying the phosphorylation of MAP kinase. It is only through the systems approach, where the study of these individual components are connected, that higher-scale properties emerge. Systems approaches are now standard practice to understand the complex interactions that occur within biological systems. In addition, they are increasingly used to the understand aberrant behaviour of these systems (i.e. disease states), helping identify novel therapeutic options [7, 8]. It could be argued that this approach is of particular importance for the examination of complex biological phenomenon such as

mood. This is an area where much knowledge has been gained at the molecular level, but it is still not fully understood how such interactions link together to produce a particular mood phenotype. This review will cover three questions:

(i) Can a systems biology approach determine how the phenotype 'mood' emerges from multiple biological interactions?

(ii) Can a systems biology approach determine how common errors to this system result in affective disorders?

(iii) Can a systems biology approach be used to develop effective treatments, pushing the affective phenotype back towards normal?

To fully understand the potential for systems biology to benefit the understanding of affective disorders, it is important to unpick the definition of systems biology further. This will clarify both what we can hope to achieve using a systems approach, and what tools are available to achieve this.

1.1.1. What is systems biology?

If systems biology can be defined as a means of studying the biology of an entire system then we must first define what we mean by system. At one end of the biological spectrum we ultimately wish to understand the biology of an entire organism. The recreation of an entire organism *in silico* can be achieved with simple, single-celled organisms such as bacteria. However, the reconstruction of an *in silico* human is currently beyond our technical and biological understanding. In these cases, we usually define a system as a lower level of organisation, such as an organ or cell, or even an individual sub-compartment of the cell. Robustly reconstructing these individual components, will allow their merging to create larger structures, eventually leading to the *in silico* human [8].

Once we have decided on which biological system to study, there are two major flavours of systems biology that can be explored: *Experimental systems biology* undertakes measurements of the system at the global-scale., while *computational systems biology* involves the integration of experimental data *in silico* in an attempt to improve biological understanding [8]. Consideration of these two sub-

disciplines leads to the realisation that they are highly dependent upon each other. For example, computational modelling is a logical way to attempt to interpret the large experimental datasets produced through omic approaches [9-11]. Conversely, computational models require experimental data to both inform their construction and to validate the final model. This leads to the conclusion that computational and experimental systems biology must be envisaged as an iterative cycle, rather than a linear pathway [12].

1.1.2. Tools to study experimental systems biology

Biological systems may be viewed as series of interconnected levels. The most obvious interconnection is the central dogma, the flow of information from DNA to RNA to Protein [13]. Experimental systems biology was initially concerned with the capture of the total information at each of these levels. For example, transcriptomic studies utilise microarray or RNASeq technology to examine all the transcripts within a system [14, 15]. Analogous measurements can be made at the level of the genome and proteome [16, 17]; in addition, study of the chemical complement of a system, the metabolome, is becoming increasing common [18]. As shown in Figure 1, these technologies provide a comprehensive snapshot of the vertical information flow from blueprint (i.e. DNA) to phenotype (i.e. chemical composition).

Consideration of this vertical information flow has yielded significant insights into a wide range of biological questions, plus an impressive legacy of experimental data [19]. However, to examine the vertical flow of information alone ignores the control that exists within each vertical level. For example, the importance of post-translational modifications in setting the biological activity of proteins is well established [20, 21]. The post-translational modification status of proteins will be captured in a standard proteome analysis, but its significance may be lost in the deluge of data: a case of not being able to see the trees for the wood. Targeted analyses must be used to focus on specific sub-populations of the proteome, such as the phosphoproteome, methylome or acetylome [21-23]. Likewise, analysis of the horizontal control within the genome (i.e. epigenome), transcriptome (i.e. small non-coding RNAome) and metabolome (i.e. fluxome)

can be undertaken. Considerable work is also now focussed on the interaction of human biology with our symbiotic bacteria, mostly through study of the microbiome.

Experimental systems biology is focussed on the capture of comprehensive information on biological systems. These high-density data are ideal for identifying novel biological features, as they provide increased analytical power. They provide the building blocks for computational models, hypothesis generation and targeted follow-up experiments. Figure 1 presents a cartoon of the omic levels of investigation, and highlights those that have been utilised to date in the study of the biology of affective disorders.

1.1.3. Tools to study computational systems biology

Computational models can, essentially, be categorised by two important factors: the size of network, and the level of parameterisation. The reconstruction of large molecular networks, often utilising omic level datasets, aims to integrate large amounts of data, either automatically or through manual curation. In contrast, 'bottom-up' approaches create highly detailed models of small biological networks, which may later be combined to create larger models, if desired [12].

The desired degree of parameterisation within a model is often a deciding factor for many decisions within computational systems biology, including the size of the generated network. To fully represent a biological system in the most accurate manner possible requires complete parameterisation for every species and reaction within the system. This would include the absolute concentration of every mRNA or protein (accurately), plus the kinetic parameters for all enzymatic reactions, the rate of transcription, translation *etc.* This level of detail is seldom available for all components of a biological system, meaning that fully quantitative models are usually limited to small-scale 'bottom-up' approaches [24-26]. One potential work-around for this problem can be seen in physiologically based pharmacokinetic models; these predict the movement of chemicals around the entire body in a quantitative manner. This apparent paradox is achieved through the use of a reductionist approach, whereby

reaction kinetics are simplified to a level that can be approximated. To this end, transport of a chemical across a membrane is often represented by a single mathematical term based upon experimental measurement *in vitro*. This term reflects not a single process, but the net effect of multiple uptake and efflux process, at least some of which have poorly described kinetic parameters [27]. This effectively reduces the size of the computational network by reducing the number of species that need to be parameterised, while still allowing the representation of a large biological network. One important difference between such models and quantitative mechanistic models is the use of experimental data to 'fit' model parameters. In a mechanistic model each step is accurately reproduced, and the larger scale behaviours of the network emerge from the interconnections of these steps. In contrast, in reductionist models the parameter values are fitted so that the model reproduces larger scale behaviours; in the case of physiologically based pharmacokinetic models this is usually the concentration-time curve for the drug in plasma. While the difference may seem trivial upon first perusal, it is in fact a fundamental difference in approach, leading to different advantages and disadvantages for each approach.

Large-scale models often comprise networks based upon hundreds or thousands of interactions, meaning it is highly unlikely that all kinetic parameters will be available. Such models will, by necessity, be qualitative in nature and aim to capture the complexity of the biological network without reproducing its behaviour in a quantitative manner. This means that while such models are not able to predict the exact concentration of a substance in the model, they can predict if that substance can be formed by the network. These large-scale models are ideal for examining the design principles of a network, leading to an understanding of why biological systems have certain network connections and how these my go wrong in disease [8]. Examples of such qualitative models include large-scale reconstruction of signalling networks [28], or the use of genome-scale metabolic networks (GSMNs) [29]. It should be noted that while these models are qualitative in design, experimental parameters can be added to *constrain* the system, producing more realistic simulations. Such an approach can be seen in the integration of omics level data and a GSMN, tuning it to a

particular cell-type or biological context [30, 31]. Essentially, any reaction in the network catalysed by a protein not present within a particular cell-type is switched off, helping the GSMN to represent the cellular phenotype [32].

A full description of computational biology approaches is beyond the scope of this review, but the interested reader is pointed towards the following reviews [7, 8, 12, 29].

Computational system biology uses a range of approaches to reconstruct the features of biology *in silico*. The aim of such reconstructions is twofold: first, to improve understanding of how complex phenotypes emerge from multiple biological interactions; second, to provide a virtual platform to generate hypotheses for further experimental investigation.

2. Can a systems biology approach determine how the phenotype 'mood' emerges from multiple biological interactions?

The exact molecular underpinning of an individual's mood phenotype is still unclear. What is clear is that mood is a highly complex phenotype that emerges from a number of signalling pathways. The monoamine hypothesis proposes a role of three major neurochemical signalling molecules in determining mood phenotype, with their deregulation contributing to the development of affective disorders: noradrenaline, serotonin and dopamine [33, 34]. This hypothesis may be further sub-divided into three hypotheses, each centred on an individual monoamine. The catecholamine hypothesis focuses on levels of noradrenaline, with increased levels resulting in a euphoric/manic mood phenotype, while decreased levels elicit depressive-like symptoms [35]. The permissive amine hypothesis focuses on the control of noradrenaline activity by serotonin. This has an indirect impact on mood phenotype, as deregulation of serotonin signalling impacts on the noradrenaline-mediated control of mood [33]. Finally, the dopamine hypothesis focuses on its known action in reward and behavioural reinforcement [36]. Beyond neurochemical signalling networks, other hormone systems have been implicated in the determination of mood. Production of growth hormone is regulated by a number of factors, including noradrenaline, dopamine, somatostatin. Levels of somatostatin have been reported to decrease

during depression and increase during mania [37, 38]. Deregulation of thyroid activity has also been observed in approximately ten percent of depressives, suggesting it has a role in determining mood phenotype [39, 40]. Finally, deregulation of the hypothalamic-pituitary-adrenal (HPA) axis leads to altered cortisol and noradrenaline release. This has been associated with the development of affective disorders, and will be more completely covered in section 3.2. It is important to note the interconnected nature of the signalling pathways listed above. Given this high degree on interconnectedness, it is difficult to tease out which effects are causative of affective disorder, and which are consequential or unrelated. As a systems approach aims to integrate the input of individual components to predict the emergent biological phenotype it is a logical tool to try to understand the aetiology of affective disorders, and predict potential therapeutic options.

When considering mood, it is perhaps pertinent to consider why mood is so flexible, and why it appears relatively easy for individuals appear to deviate from 'normal' mood phenotypes to adverse affective disorders. One possible explanation for this is that the neural networks that underpin our cognitive ability and mood are, by design, some of the most flexible biological networks in the human body [41, 42]. This is not surprising given the requirements of neural networks in comparison to many other systems within the body. In the liver, for example, the gene-, signalling- and metabolic networks are designed to provide a robust control of central metabolism. Their drive is to change only enough to allow a return to chemical homeostasis, whereupon the network returns to the original state [43]. In contrast, neural networks are designed to adapt to external stimuli, producing new connections that allow the organism to best survive in this new environment. The liver may be defined as a *robust* system, always aiming to return to a base state, while neural networks can be seen as *fragile* or *evolvable*, meaning they can alter to adapt to stimuli. A whole branch of computational systems biology is dedicated to understanding flexibility within biological networks [44]. While evolvability in neural networks is important to allow our long-term adaptation to new challenges, it does increase the possibility of evolution into extreme states. From a systems perspective, one would

presume that the more evolvable the system, the more likely it is to produce outliers in performance. Such extreme states may underlie the significant evidence linking creative individuals with affective disorders [45, 46]; this has been termed the 'edge of chase' hypothesis [47]. Outliers could be seen as either beneficial (i.e. creative) or adverse (i.e. affective disorders), with evidence existing to support an inverted-U shaped relationship between creativity and mental illness. Under this hypothesis, as the evolvability of a neural network increases, so does creativity. This continues to a point where the system becomes unstable, symptoms of mental illness predominate, and a decrease in creativity is observed. Evidence for such a relationship exists both in affective disorders and other mental disorder such as schizophrenia [48, 49]. Alongside empirical evidence, the striking number of highly creative individuals who have been diagnosed with, or who expressed symptoms of, bipolar disorder is noted: Tenesse Williams, Charles Dickens, Otto Klemperer, Vincent van Gogh, Steven Fry *etc.*.

The field of understanding mood is complex and rapidly evolving. A systems approach appears a logical means to understand the emergent phenotype from the highly interconnected neural network. However, systems approaches have been sparingly applied toward understanding the normal functioning of the brain in determining mood phenotype. This probably reflects the variable level of information available in this area, with some areas of biology well understood and others still largely conjecture. A major threat with systems approaches is the so-called 'garbage-in, garbage-out' paradigm. Garbage does not just refer to poor quality data, but can also mean high quality data that has a low coverage of the biological phenomenon under study. As such, systems approaches may currently be of limited use to study the normal function of mood. Only when we have a significantly enhanced mechanistic understanding of the individual components of neural functioning will systems approaches be robustly applicable.

3. Can a systems biology approach determine how common errors to this system result in affective disorders?

3.1. Mood disorders

Affective disorders are characterised by the shared feature of a pathological disturbance of mood ranging from extreme elation or mania to severe depression. In addition, the majority of affective disorders also comprise one or more other symptoms, such as disturbances in thinking and behaviour, which in extreme cases may present as psychotic delusions and hallucinations [50]. Affective disorders may present as a primary symptom, or as a secondary symptom, to another disease state [50]. A final distinction is made between unipolar and bipolar disorders, being those that present only one aspect of mood disturbance (i.e. mania *or* depression), compared to those that cycle between these states, respectively [50]. A full description of the classification of affective disorders is beyond the scope of this review, and the interested reader is directed to these reviews [50-53].

One potential confounder for delineating molecular mechanisms of affective disorders is incomplete patient diagnosis and stratification. Despite the publication of diagnostic guidelines [50], there are still a significant number of missed or incorrect diagnoses. Data from the USA suggest that upwards of three-quarters of all bipolar disorder patients are misdiagnosed upon first presentation. The most common incorrect diagnoses are unipolar depression (60% of cases) and anxiety disorder (26%) [54]. As mentioned previously, a potential limitation of a systems approach is the 'garbage-in, garbage-out' paradigm. In the case of missed/incorrect diagnoses for affective disorders, the effect is to limit the size of the pool available for analysis, potentially reducing the power to discern interactions. Diagnosis of an individual with an affective disorder when they suffer from another condition would introduce potential confounding; this form of incorrect diagnosis is comparatively rare compared to the reverse, meaning confounding to due positive misdiagnoses is limited. Even once an individual is correctly diagnosed with an affective disorder, the known heterogeneity in presentation (and potentially mechanistic underpinning) may cause issues. Analogous to the study of breast cancer, when tumour heterogeneity is a major concern [30], analysis of affective disorders without further stratification will almost certainly confound biological insight.

3.1.1. Human studies

In common with most complex diseases, the genetics behind mood disorders has been extensively studied. For at least the past eighty years, twin studies have been used to demonstrate the significant contribution of genetics in the aetiology of affective disorders [55]. These studies suggest a heritability for unipolar disorder of 33-42% and for bipolar disorder of 80-90% [55]. Identification of the genetic component for any disease or disorder can be assessed through either a hypothesis-driven candidate gene approach, or a data-driven omic-level approach. In general, the use of data-driven approaches has become prevalent in the past few years, with good quality candidate gene studies adding additional valuable insights in their own right, and being essential to validate the conclusions of data driven studies.

The use of Genome-Wide Association Studies (GWAS) has identified a number of chromosomal regions with significant linkage to different affective disorders: the regions most commonly linked are described in table 1 [56-58]. It is of note that there are only limited consistent findings across these studies, with meta-analyses required to predict the most significant hits and identify those loci likely to be linked to affective disorders [56]. A number of candidate genes that show linkage with affective disorders have been identified through hypothesis-led research. The majority of these genes are, perhaps unsurprisingly, associated with neurotransmitter systems. The evidence surrounding each candidate gene is often conflicting, with both positive and negative reports present in the literature, and a meta-analysis approach is required to identify candidate genes where variants are commonly associated with affective disorders: these are presented in table 1. It is of note that these genes do not reside within any of the regions commonly identified through linkage studies. Despite this, there are a number of studies that have looked at candidate genomic regions rather than genes, and these do show some overlap with the GWAS data. The meta-analysis of Badner and Gershon identified 22q as showing significant linkage to bipolar disorder [59], while other reports linkage between Xp11 and bipolar disorder [60, 61]. These reports are conflicted by other publications that report no associations, and hence must be treated with some caution.

Given the large amount of research that has been undertaken on the genetic basis of affective disorder, why are the data underlying gene associations often conflicting? Three possibilities exist for these cloudy interpretations: first, the interaction is not real and has emerged from underpowered/confounded studies. Second, that the association is only pertinent in a specific subset of the population and reflects the heterogeneous nature of affective disorders. Third, a real association exists, but it is indirectly linked to the candidate gene. Mood is almost certainly impacted by multiple genetic and environmental inputs, each contributing to the emergent biological phenotype. An affective disorder phenotype could emerge from many different combinations of these inputs, leading to a common phenotype but heterogeneous molecular underpinning. This highlights the importance of improved patient stratification, and larger studies with higher statistical power, allowing examination of these different molecular mechanisms.

It is becoming increasingly clear that a major challenge with understanding genetic data is placing it in the context of a biological system. Standard statistical approaches are usually based around the concept of over-representation. They rely on the premise that if something is present at a higher frequency than would be expected by chance, then it will have a biological impact. However, these approaches ignore the interconnected nature of biology, and how this may impact on the emergent phenotype. For example, increased expression of a single gene within a pathway does not mean that activity through that pathway will increase. If other proteins maintain a higher control coefficient in the pathway (i.e. rate-limiting steps), then it is their expression levels that will be critical [62]. However, even if all the genes within a pathway show increased levels of expression, higher activity through this pathway may not be achieved. If the level of a critical co-factor or precursor molecular produced elsewhere within the biological system is limiting, then the activity through the pathway under examination will still be limited. This is the concept of stoichiometric constraint, whereupon the activity of one part of the network is constrained by the chemical flow through a distant part of the network. It is becoming increasingly common practice to overlay genetic-level data on biological

networks, with the additional stoichiometric and thermodynamic (directionality of reactions) constraints allowing greater biological insights to be made [10, 12]. This approach has been mainly applied in the area of oncology, with a number of studies examining the biological networks associated with different aspects of cancer [31, 63, 64]. Not only can this approach be used to trim the list of potential candidate genes by looking at how feasible they are within the context of a biological network, it can also be used to examine disease heterogeneity. Heterogeneity is a significant issue in both affective disorders and cancer, and studies are now emerging in the area of oncology on how systems biology can be used to help stratify patients [30]. This should lead to improved understanding of the disease itself, improved stratification of patients, and ultimately improved selection of the most appropriate therapeutic regimens.

Systems biology approaches can also be used to examine indirect associations identified through genetic approaches. Such a relationship can be seen as analogous to genotyping studies where we initially look for linkage with a trait, and then focus on identifying the true association. For indirect associations, we presume that selection of the candidate gene is correct with respect to linkage, but proof of the association is not forthcoming. One possible explanation for this is that the protein encoded by the candidate gene interacts with a network containing a protein important in disease aetiology. A systems approach can be used to examine the interactome for the initially identified candidate gene, expanding the number of potential candidate genes significantly. A good example of this is brain-derived neurotrophic factor (BDNF), a neuropeptide that has been linked to brain plasticity [65]. Studies examining the linkage of BDNF with bipolar disorder have reported both positive [66, 67] and negative findings [68, 69], meaning its importance is open to question. Yeh, Kao and Kuo used a range of computational approaches to marry GWAS with the known BDNF activity network [70]. They concluded that no significant association was observed between BDNF and affective disorders in the majority of genomic studies, although a consistent relationship between plasma/serum BDNF and affective disorders was reported. They identified 363 proteins with significant evidence for interaction with BDNF using STRING, a database of known and predicted

protein-protein interactions [71]. This list included proteins such as AKT, IGF1 and NOS3, and a clear association between their biological networks and affective disorders emerged [70]. Hence, by using a systems approach to expand a query from a single protein to several hundred interacting proteins (the interactome), novel biological insights were gained.

If novel insights can be made by examining the interactome of a single candidate gene, could further insights be gained by overlaying interactome data from several candidate genes? In theory, such an approach would further constrain the available biological network, producing more meaningful predictions. Detera-Wadleigh and Akula have taken such an approach, building molecular interaction networks based upon six candidate genes [72]. When the interactomes for each of these candidate genes were examined, certain biological hubs were consistently represented, suggesting their deregulation as a common factor in affective disorders. For example, patients with ANK3 and CACNA1C allelic variants associated with increased risk of affective disorder also show enhanced activity within the MAPK and adrenergic signalling hubs [72, 73].

Given the overlapping phenotypes observed for many psychiatric disorders, a potential further approach would be to analyse interactomes for all psychiatric disorders together. Recently, the Psychiatric Genomics Consortium took the first steps toward such an approach. They analysed genotype data for cases and controls in schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders and attention-deficit/hyperactivity disorder [74]. A high genetic correlation between common SNPs for schizophrenia and bipolar disorder (0.68) was observed, while moderate associations were observed between major depressive disorder and schizophrenia (0.43), bipolar disorder (0.47) and attention-deficit/hyperactivity disorder (0.32). This systematic analysis should help identify common biological hubs that merit further examination of their role in mood and mood disorders, as well as potential generic druggable targets. At least some of this overlap is almost certainly due to incorrect diagnosis, with up to 15% of initial diagnoses incorrect, but some biologically important commonalities should be revealed [75]. In addition, by exclusion of common hubs, it should be possible to identify unique mechanisms

underlying each mental disorder, improve nosology, and suggest targeted therapies. This latter approach has the (large) caveat that hubs identified by exclusion may exist due to a lack of data coverage, rather than a true uniqueness. This could be addressed by either further clinical studies, or the use of systems approaches such as the interactome analysis of Yeh, Kao and Kuo described above [70]. These would further extend the biological coverage of the genomic analysis, improving the robustness of the 'disorder unique' or 'common between disorders' call for the identified biological hubs. As more candidate genes are analysed through such approaches, and the results pooled, it is hoped that key biological hubs commonly deregulated in affective disorders will emerge. This will not only lead to an improved understanding of the aetiology of affective disorders, but may also identify the most fruitful points within the network for therapeutic intervention.

Examination of genomic variability in disease has made a significant contribution to the understanding of a range of complex diseases. However, this only addresses the first vertical level of biological organisation (Figure 1). It is also important to examine transcript, protein and metabolome studies, as well as any studies concerned with horizontal regulation. Experimental systems biology has been used to capture data dense, omic level information on gene expression profiles in normal and affected individuals. For such studies, the source material is critical, and can have a significant impact on the quality of data produced. Human-derived biopsy tissue is the gold standard for such approaches, but in the area of psychiatric disorders, sample sourcing is complicated by the fact that human tissue is only available post-mortem, potentially affecting quality [76]. Despite these difficulties, studies have been undertaken on post-mortem tissue from bipolar patients with promising results [77, 78]. Iwanoto *et al.* reported the gene expression profiles of post-mortem brains from a number of mental disorders, including 11 patients with bipolar disorder [78]. The transcriptome profiles of the bipolar samples were quite distinct from both schizophrenia and major depressive patients, with only a minimal overlap in differentially regulated genes when compared to samples from 'healthy' individuals. Examination of the commonly differentially regulated genes identified that they

could be linked to processes associated with all conditions, representing common biological hubs. Foe example, the shared up-regulation of the membrane-bound water transport protein AQP4 could lead to altered water permeability across the blood-brain barrier; such water accumulation has been linked to the white matter hyperintensity observed during MRI of brains from patients with psychiatric disorders [78]. To identify biological processes unique to an individual disorder, it is necessary to examine the unique differentially regulated genes. Amongst those genes identified as down regulated only in bipolar post-mortem brains were several associated with membrane receptors or transporters: specifically, the glutamate receptors GRM1 and GRIK2, the nucleoside transporter SLC29A1, the calcium channel CACNA1A, and the insulin-like growth factor binding protein IGFBP6. These observations are consistent with the reported literature: GRM1 and GRIK2 have both been identified as candidate genes *via* SNP analysis for both schizophrenia and bipolar disorder [79, 80], while altered calcium dynamics has been suggested as both a cause of, and potential treatment for, affective disorder [81, 82]. Such studies therefore support the use of omic-level analysis in post-mortem brains, with two important caveats: first, the correct controls are in place to ensure high quality data is extracted; second, that sufficient samples are used to correctly power a robust systems analysis.

The analysis of omic level data for affective disorders, especially when constrained by biological networks, should provide novel biological insights into affective disorders. For this potential to be realised, however, it is important that sufficient, high quality experimental studies are undertaken to ensure meaningful insights can be gained. Experimental systems biology has progressed to different degrees across the omes. Significant progress has been made analysing genetic variation (genome), mRNA expression and splice variants (transcriptome). Analysis at the proteome, metabolome and horizontal regulatory levels is far patchier.

3.1.2. Animal models

Given the issues associated with obtaining post-mortem tissue, and the pitfalls of it's correct processing, alternative models have been explored. The first of these alternate approaches is the use of animal models, with a number of pharmacological or genetic models proposed. Table 2 contains an overview of the major models, with a more in depth review provided by Nestler and Hyman [83]. It should be noted that these models are not representations of complex affective disorders such as bipolar disorder, and generally reproduce only one of the modalities, either depressive- or mania-like symptoms. This means that they may shed light on the individual modalities, but are unlikely to be of significant use in terms of understanding the bistability between the two states that is observed in bipolar disorder patients. In addition, as noted by Nestler and Hyman, although these models reproduce the desired phenotype, there is often a lack of convincing evidence that this phenotype has been reached through the same aberrant biology observed in the human conditions [83].

Animal models have produced a wealth of mechanistic understanding across a range of human biology, including neurobiology. Such data may be further examined through computational systems biology approaches, but only with the understanding that you are exploring the biology of an animal model, and not the human condition. In complex diseases such as affective disorders, where the interconnected nature of the neural network is still not fully understood, this caveat is particularly important.

3.1.3. Reverse engineering mechanism from treatment

A second alternate approach to the use of post-mortem tissue from affective disorder patients is reverse engineering. While the underlying mechanisms that determine an individual's mood phenotype are not clearly understood, the pharmaceutical agents used to treat affective disorders are well established. The efficacy of these agents suggests that they must act on the biological systems that determine mood phenotype. Studies on their mode-of-action should, therefore, provide insight into the biological mechanisms of both normal and abnormal mood phenotypes. There have been many studies to examine the transcriptome

impact of affective disorder treatments, most commonly lithium and valproate [84-86]. In addition, an increasing number of studies are looking at other levels of global organisation, such as the epigenome [87, 88], proteome [89, 90], phosphoproteome [91], and the metabolome [92]. It should be noted that for these therapeutic agents, their exact mode of action is unclear, and the high doses required to achieve efficacy suggest a non-specific, multi-target effect. This further complicates the analysis of the information dense datasets produced by experimental systems biology, as non-specific effects must be identified and removed.

An exciting development is the analysis of data from diverse datasets, analogous to the combination of genome data from multiple psychiatric disorders (section 3.1.1). This approach looks for commonalities in biological networks activated by multiple mood stabilising drugs, presuming these represent core biological hubs associated with affective disorders. A number of studies have been undertaken to compare mood stabilising drugs, most commonly lithium and valproate [84, 86, 93]. While the data from this approach is still emerging, it does seem to highlight programmed cell death as a common feature, consistent with an alteration in neural plasticity [94].

Reverse analysis of drug action to determine disease mechanisms is a well-established approach, and has yielded success in other therapeutic areas. Given the difficulty in sourcing high quality human post-mortem tissue, and the caveats associated with current animal models, this reverse engineering approach has potential to add to our biological knowledge of affective disorders.

3.2. Cortisol and Affective disorders: An example of network interconnectivity

An example of where systems approaches may aid understanding of the drivers for, and potential treatments of, affective disorders can be seen in the case of cortisol. Cortisol undertakes a number of critical functions within the body, and interacts with a large number of biological sub-networks [95]. Along with melatonin, cortisol is a key regulator of the circadian clock, acting to connect the

central oscillator to the rest of the body. In addition, cortisol has a major role in the 'fight or flight' response to stress. Here, we examine the role of both circadian biology and stress in affective disorders and how systems biology can be used to integrate these large biological areas to provide novel insights into affective disorders.

Disruption of circadian rhythms has been associated with a range of disease aetiologies, including acute cardiovascular disease, metabolic syndrome, cancer and affective disorders [96, 97]. Kripke et al. reported that free-running circadian rhythms were faster in patients with bipolar disorder [98], while Steinan et al reported that approximately ten percent of patients with bipolar disorder also fulfilled the criteria for delayed sleep phase disorder [99]. The molecular understanding of the circadian clock, and how to manipulate it, is well advanced [100-102], and this knowledge may be used to understand some aspects of affective disorders. As detailed in table 2, genetic knock-out of CLOCK, a core gene in the circadian clock, is the basis for an animal model of mania [103]. In addition, manipulation of circadian rhythms has been suggested as a treatment for affective disorders [104, 105]. A case report of Leibenluft and Suppes reported how improvements in a patient's bipolar disorder could be achieved through active management of their sleep wake cycle. In addition, they noted that when sleep was disrupted through shift work the treatment regime for bipolar disorder became less effective and their condition deteriorated [106]. Kripke et al. observed that lithium treatment of individuals with rapid cycling circadian clocks led to a decrease in circadian period to within the normal range [98]. In summary, clear evidence linking affective disorders with disruption of the circadian clock exists, although the underpinning biology has not been fully elucidated.

Data also exists to support an association between chronic stress and affective disorders [107, 108]. Chronic exposure to stress, or even acute exposure under certain conditions, appears to be able to elicit a shift toward an affective disorder phenotype. These effects have been observed not only in individuals, but appear to cross generational boundaries via exposure of the developing foetus to maternal stressors [109]. The association between chronic stress and affective

disorders has been attributed to altered neuronal plasticity, with stress leading to reduced plasticity. As detailed in section 3.1.1, neuronal plasticity may be defined as the ability of the neural network to respond to novel stimuli. Reduced neuronal plasticity manifests itself in a phenotype of poor adaptation to stressors, common in affective disorders [50]. This is consistent with the observation that early (even pre-natal) exposure to stressors shows a particularly strong association with affective disorders. Such early exposure occurs during the period when neural network development is still underway and most easily disrupted [109, 110]. As previously noted, deregulation of BDNF, a key modulator of brain plasticity, has been associated with affective disorders [65-67]. BDNF is under transcriptional control of the glucocorticoid receptor, one of three nuclear receptors that have cortisol as an endogenous ligand [111].

There exists a comparatively good understanding of the molecular mechanisms underlying both the circadian clock and glucocorticoid signalling. Circadian rhythms have been extensively studied using systems approaches, both experimental and computational. Beyond the classical molecular dissection of the mammalian circadian clock, there have been a number of excellent transcriptomic and metabolomics studies in this area [112-115]. In addition, a number of computational models of the circadian clock have been developed, at varying levels of abstraction [116-118]. The glucocorticoid signalling network has also been extensively studied using both experimental [119-121] and computational [25, 122, 123] systems biology approaches. As both circadian rhythms and stress have an impact on the emergent mood phenotype, and have been subject to intense study at both the experimental and computational biology levels, it is tempting to speculate what might be achieved through the integration of these three fields. The integration of data from circadian rhythms, stress and affective disorders into a holistic model using computational systems biology seems ideal for such an approach, and could yield significant biological insight once completed.

4. Can a systems biology approach be used to develop effective treatments, pushing the affective phenotype back towards normal?

A major aim of systems biology is the development of novel therapeutic treatments. Traditional drug design has focussed on key regulatory hubs and/or druggable targets, which are, usually, identified through hypothesis-led research. A systems approach allows a more holistic viewpoint, considering how the total network interacts to produce the emergent biological phenotype. This raises the potential of identifying key choke-points in the network that may represent novel drug targets. In addition, a systems approach is ideally placed to identify novel network targeting drugs [8]. Traditional combination therapy has relied on using two drugs that target different aspects of a disease, with the hope of a synergistic interaction when used together. Successful combinations are often designed empirically by trying combinations of already approved drugs in the hope of achieving improved patient response. However, in a systems network targeting approach, the combination is designed first, and then the relevant drugs identified. In fact, one, or both, of the drugs used may not fit the classical definition of drug, and may have no efficacy when used alone. An example of this is the concept of synthetic lethality: The action of a cytotoxic agent can be reduced by biological re-routing, leading to drug resistance. Targeting these rescue pathways can significantly enhance drug efficacy [12, 124]. To design such a combination, it is imperative to examine the entire network, such that the relevant biological chokepoints can be identified for targeting.

The majority of research into network targeting has been undertaken in the oncology therapeutic area, leading to novel combinations that are currently being examined in clinical trials [31, 64, 124]. Affective disorders seem to be ideally suited to treatment through a network targeting approach, but while this has been discussed, it is not an area that is being fully explored. One reason for this is that, as previously stated, the underlying biology of mood is far less fully understood than in the oncology arena. Hence, it is more difficult to build robust predictive models from which network-targeting approaches can be designed. The rapid growth in experimental systems biology data in this area, leading to

testable mechanistic hypothesis, may help to address this important deficit in the next few years.

5. Conclusion

The application of systems biology has reaped significant rewards in the study of a number of complex diseases. It has helped to suggest novel biomarkers for patient stratification, shed light on disease mechanisms and help design novel treatment paradigms. This success has been based on a bedrock of solid mechanistic understanding and high quality, data rich resources. Within the sphere of understanding mood, and its deregulation in mental disorders, systems biology is yet to reach fruition. This almost certainly reflects the poorer understanding of the highly complex biology underlying mood and affective disorders. Increasing numbers of experimental systems biology studies are being undertaken, and coupled with highly refined targeted experiments are producing a legacy of high-quality datasets. A major challenge in the understanding of mood and affective disorders is to leverage this legacy data fully, utilising the advances in computational systems biology to gain a holistic view of how mood emerges from the complex neural network. Such studies will naturally lead to a better understanding of what goes wrong during the development of an affective disorder, and propose new targeted treatments.

6. References

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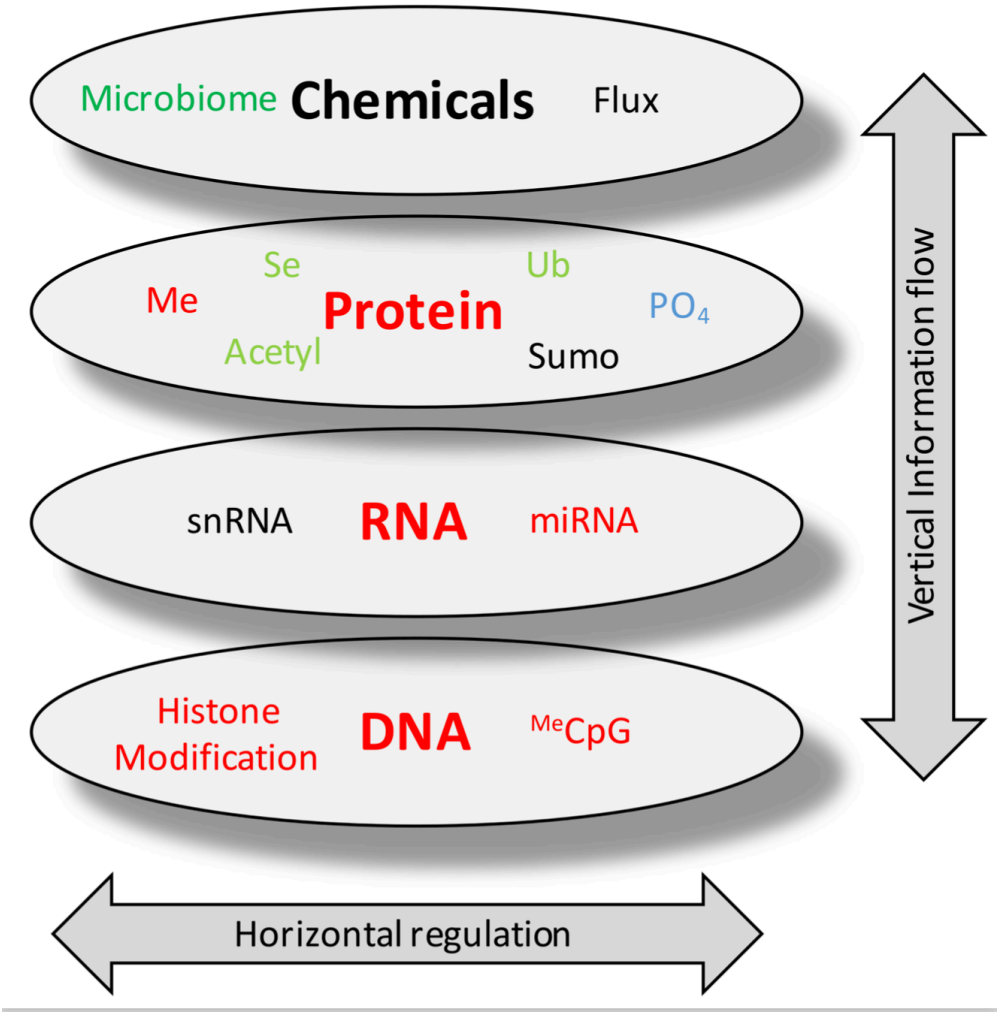

Figure 1: The omic levels of organisation and affective disorders.
Information flow within the cell can be envisaged as being a vertical continuum from DNA, through transcript and protein, to metabolites. Within each of these levels exits horizontal regulatory levels, controlling the vertical flow of information. For each 'ome', the extent of experimental systems biology devoted to the understanding of mood and affective disorders is indicated. Black text indicates no major studies reported to date; Green indicates some evidence for a role in affective disorders, but limited and/or sub-omic level analyses. More robust experimental systems biology approaches are required to further investigate; BLUE indicated that omic level studies have been undertaken, but only in animal models or in vitro. Extrapolation to human situation therefore complicates their interpretation; red indicated a good number of omic level studies have been undertaken, including in human studies, providing a solid legacy knowledgebase

Tables

Genomic Region	Disorder	Ref	Genes	Disorder	Ref
2p13-p16	BD	[125]	MAO-A (Xp11.3)	BD	[126]
4p16	BD	[127]	COMT (22q11)	BD	[128]
4q32	BD	[129]	5HTT (17q11)	BD	[130]
6q21-q25	BD, UD	[127]	BDNF (11p13)	BD	[66, 67]
8q24	BD	[131]			
13q32	BD	[129, 132]			
12q22-q24	BD, UD	[127]			
15q14	BD	[133]			
15q25-q26	UD	[134]			

Table 1: Genetic loci associated with affective disorders. BD = bipolar disorder, UD = unipolar disorder, 5HTT = serotonin transporter, BDNF = brain-derived neurotrophic factor, COMT = catechol-O-methyltransferase, MAO-A = monoamine oxidase A. It should be noted that disorder represents the disorder most commonly demonstrating linkage to a particular genomic region/gene, and does not suggest complete exclusion of the other disorders

Model	Comments	Ref
Genetic Models – Knock out		
Clock	Mania, reversible by lithium	[103]
WFS1	Poor adapatation to stressors	[135]
Genetic Models – over expression		
Glucorticoid receptor	Depression, increased anxiety	[136]
GSK-3β	Mania, reduced anxiety, hypophagia	[137]
mutPOLG	Mania-like bevhaviour	[82]
Pharmacological Models		
Cocaine	Mania, reversible by lithium	[138]
Amphetamine	Mania, reversible by lithium	[139]
Ampheatmine and chlorodiazepoxide	Mania, reversal by lithium, carbemazepine, valproate and lamotrigine	[140]

Table 2: Animal models of mania and depression