The Continuum from Temperament to Mental Illness: Dynamical Perspectives

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Keywords

Temperament · Mental illness · Continuum · Dynamics · Time series · Dynamical phases · Phase transitions · Process algebra

Abstract

Temperament in healthy individuals and mental illness have been conjectured to lie along a continuum of neurobehavioral regulation. This continuum is frequently regarded in dimensional terms, with temperament and mental illness lying at opposite poles along various dimensional descriptors. However, temperament and mental illness are quintessentially dynamical phenomena, and as such there is value in examining what insights can be arrived at through the lens of our current understanding of dynamical systems. The formal study of dynamical systems has led to the development of a host of markers which serve to characterize and classify dynamical systems and which could be used to study temperament and mental illness. The most useful markers for temperament and mental illness apply to time series data and include geometrical markers such as (strange) attractors and repellers and analytical markers such as fluctuation spectroscopy, scaling, entropy, recurrence time. Temperament and mental illness, however, possess fundamental

characteristics that present considerable challenges for current dynamical systems approaches: transience, contextuality and emergence. This review discusses the need for time series data and the implications of these three characteristics on the formal study of the continuum and presents a dynamical systems model based upon Whitehead's Process Theory and the neurochemical Functional Ensemble of Temperament model. The continuum can be understood as second or higher order dynamical phases in a multiscale landscape of superposed dynamical systems. Markers are sought to distinguish the order parameters associated with these phases and the control parameters which describe transitions among these dynamics.

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Introduction

Existing approaches to the classification of mental illness have come under considerable criticism of late, and there is an urgency to identify biomarkers of mental illness that will facilitate diagnosis and individualized treatment. Temperament of healthy individuals and mental illness have been conjectured to lie along a continuum of neurobehavioral regulation [1–5]. Temperament refers

to the biological basis of consistent patterns of normative neurobehavioral regulation. Mental illness, in contrast, refers to dysfunctional or pathological patterns of neurobehavioral regulation, and in both classes of behavioral patterns neurochemistry plays a crucial role.

Early attempts to explore this possible continuum between temperament and mental illness focused on establishing correlations between individual temperament traits and the presence or absence of (symptoms of) mental illness. A search for causal relationships involves an examination of the underlying neurobehavioral regulatory systems (NBRS), and in particular the neurochemical regulatory systems (NCRS) upon which the phenomena of temperament and mental illness are thought to supervene. The NCRS include monoamine, acetylcholine, neuropeptide and opioid receptor systems.

The most detailed neurochemical model describing the contribution of NCRS to consistent behavioral patterns is the Functional Ensemble of Temperament (FET) model. The FET summarizes experimental studies in neurochemistry and psychopharmacology that have demonstrated a central role for the NCRS in determining those consistent behavioral patterns known as temperament traits [6–11]. It describes 12 traits, 9 traits classified by dynamical features (endurance, variability, orientation) and by domain (intellectual, physical-motor, social-verbal), together with 3 emotionality traits (self-confidence, neuroticism, impulsivity). Every trait within the FET model is associated, not with a single neurotransmitter system, but with a specific, distinct ensemble of NCRS.

A useful metaphor for conceptualizing the continuum between temperament and mental illness comes from meteorology, a field in which many modern concepts in nonlinear and complex systems dynamics originated and which deals with dynamics across multiple time scales: very short, short and long duration. Behavior *per se* occurs at very short time scales, resembling individual instances of weather. Temperament and chronic mental illness both describe long-term patterns of behaviors. In that they resemble climate, which also describes long-term dynamical patterns. Acute mental illness resembles frontal weather and storms, in that they all represent short duration pathological or outlier dynamical patterns. The transition from temperament, which is normative, to mental illness, which is pathological, is analogous to climate change.

Multiple temperament traits such as impulsivity, sensation seeking, neuroticism, endurance, plasticity, sociability have been linked to NCRS [6–14]. Likewise, several DSM symptoms have been linked to these NCRS. For ex-

ample, psychomotor retardation has been shown to be regulated mostly by dopaminergic systems [15] which receive modulatory influences from mu-opioid receptor [16, 17] and delta-opioid receptor systems [18, 19]. Closely related, fatigue has been linked to serotonin systems which are major regulators of the energetic maintenance of behavior [10, 11]. Long held to play a role in depression [20], the serotonin system has been implicated in the endurance aspects of activities [21–23]. Impulsivity appears linked to interactions between delta opioid systems and dopamine and mu opioid systems [18, 19, 24, 25]. Dysphoria shows links to dysregulation in the mu-opioid receptor systems [16, 26]. Anxiety appears also to be linked to impaired regulation of kappa opioid receptor systems by mu opioid receptor systems and arises due to their effect upon GABA [26, 27], noradrenaline release and HPA axis arousal [27–34].

Since temperament and some psychopathology appear to share NCRS, a model of temperament that is sensitive to changes in NCRS should show differential effects in the presence of mental illness if the continuum hypothesis is valid [5, 35]. In fact, the FET has shown differential effects in the presence of several categories of mental illness (depression, anxiety, personality disorders) with much more differential power than lexical approach models (such as Big Five) or Positive/Negative Affect models [4, 35–37]. Temperament profiles obtained using the FET-related Structure of Temperament Questionnaire 77 (STQ-77) [9, 38–41] using samples of patients suffering from specific mental illnesses showed distinct patterns in the presence of: Major Depression (lower scores on physical/motor traits) [4, 37], Generalized Anxiety Disorder (lower scores on social/verbal traits) [4, 36], Comorbid Depression and Anxiety (significantly lower scores on cortical traits) [4, 35] and a range of other disorders [38].

The FET model is notable for describing traits that refer to the dynamics of behavior, particularly endurance and variability, which may account for its sensitivity to alterations in the dynamics of the NCRS. The effects mentioned above are intriguing and lend support to the hypothesized continuum between temperament and mental illness. However, although mental illness does appear to impact on temperament in a differential manner, the altered temperament scores are still within the normative range. A simplistic dimensional interpretation of the continuum is not supported. Missing are specific biomarkers for pathological states that could be used to determine whether or not an individual is functioning within normative, at-risk, or pathological regimes [5, 42, 43], as well

as recognition of the different effects on the dynamics of behavior which occur in the expression of temperament and mental illness. The goal of the dynamical approach described herein is to identify dynamical biomarkers whose presence or absence provides information about the dynamics of these NCRS and which can then be used to determine whether an individual's functioning is normative, at-risk, or pathological [5, 42, 43].

Dynamics and Time Series

Cross-disciplinary research inevitably encounters differences in the use of terminology. In biology, the term behavior generally refers to the motor activities of an organism. In dynamical systems theory, the term behavior refers simply to whatever it is that a dynamical system does over time, regardless of the nature of its individual states. The study of complex systems which consist of multiple subsystems extending across multiple spatio-temporal scales and layers of organization inevitably faces the problem that various disciplines have laid claim to these different subsystems and developed their own terminologies and methodologies. Dynamical systems theory offers a generic language describing temporal change within any domain – motor, sensory, cognitive, affective, electrophysiological, neurochemical. The same language can thus be used across multiple spatio-temporal scales and across multiple neural systems. In what follows, the term behavior should be understood in this generic sense.

A behavioral act is by definition dynamical in nature, referring to a pattern in time of states (which could be physical or psychological) of an individual (referenced to a specific context), having finite duration and satisfying some ecological or functional criteria. Behavior refers to a set of individual behavioral acts which possess the same ecological and functional properties. Temperament and mental illness do not refer to specific behaviors (as broadly conceived here) but rather to distinct *patterns* of behavior which persist over extended periods of time and impact on the functional capacity of the individual. Temperament and mental illness refer to second (or higher) order dynamics (patterns of patterns), which determine the temporal patterning of behaviors, which are in turn generated by the lower level dynamics of NCRS (NBRS more generally) responsible for determining individual behavioral acts.

The pioneering work of Gottschalk et al. [44] demonstrated the existence of these second order dynamical patterns in their seminal study of mood variation in normal

and bipolar subjects. There are striking differences in time series between bipolar and control subjects in terms of the size and frequency of fluctuations, the spectral structure of fluctuations, the entropy, complexity and degree of persistence. Qualitatively, the time series of normal controls look much like white noise, while those of clinical subjects show periods with prolonged dwell times, recurrence and persistence, intermittency, slow wave and long wave patterning. These dynamical features clearly distinguish the two sets of subjects, but are not addressed with commonly used assessment tools, which are mostly self-report questionnaires referencing either single points in time or the subjective estimation of averages. It is unlikely that these dynamical features can be assessed by an individual subject, let alone represented by means of a simple Likert scale. It is now possible to acquire real time data about behavior and mood using personal monitoring devices such as Fit Bits and smartphone apps. However, the effectiveness of such time series depends upon the models developed to explain the time series and the analytical tools used to examine them.

Formally, a dynamical system consists of a space X of states, a space T of times and a function f , the dynamic, which maps from $X \times T$ to X . The state $f(x, t)$ represents the state of the system after a duration t and which began in the state x . A time series represents the succession of states of a dynamical system over discrete times (e.g., $f(x, t_0), f(x, t_1), f(x, t_2), f(x, t_3), \dots$) [44–48]. A time series may also be formed from measurements on states. Since behaviors are sets of behavioral acts, what is truly needed is a dynamics of sets [49, 50], but this is not yet available, the standard approaches dealing only with trajectories of individual states.

The formal study of dynamical systems seeks out symmetries and universal characteristics of dynamics in general. The classification of trajectories forms the basis for the *geometrical* approach to dynamical systems. Trajectories may be described in terms of their final destination, their *attractors*. The most common attractors are (1) fixed point, (2) periodic, (3) quasiperiodic, (4) strange (chaotic). Trajectories which do not trend towards an attractor may be divergent, transient, recurrent or ergodic.

The *analytical* approach has been effectively applied to the analysis of time series data [46–48]. Analytical tools, currently in widespread use and suitable for studying behavioral data, include: (1) fluctuation spectroscopy, (2) fluctuation distributions (these tend to be power law rather than Gaussian), (3) Lempel-Ziv complexity, (4) Hurst exponent, (5) Lyapunov exponent, (6) Shannon and Renyi entropy, (7) Ap entropy, (8) mutual information, (9)

recurrence and dwell times, (10) correlation, Hausdorff and Box dimensions, (11) scaling, (12) order parameters [41, 42].

Time series methods have been applied in neuroscience [48, 51] and have been applied to animal behavioral data with considerable success [52].

Since Gottschalk et al. [44], time series methods are being used more frequently in the study of bipolar disorder [53–59] and also in schizophrenia [57], obsessive compulsive disorder [52], generalized anxiety disorder [60–62] and social stress [63]. A few studies have employed time series methods in the study of temperament, personality [53, 54] and monoamine systems [63–65].

Time series data have been derived from measures of heart rate variability [62], EEG signals [57], mood ratings [56] and levels of various neurotransmitters and their metabolites [64]. A wide variety of analytical tools have been employed: wavelet analysis [65], entropy [56, 60, 62], detrended fluctuation analysis [62], fluctuation distributions [58], scaling [61]. Time series have been used as a basis for forecasting future mood states [59]. There have also been some early attempts to take into account the role of environmental context [66].

The use of time series methods has matured over time, engendering quite sophisticated technical debates around data collection and analytical methodologies. The interested reader is directed to the literature for details. The studies mentioned here should be viewed as illustrative examples of what is possible, even if imperfect, and not as providing any “final answers.”

The use of time series methods in the study of bipolar disorder has been quite promising. Ortiz et al. [56] showed that first-degree relatives of patients with bipolar disorder had entropies of mood and energy time series that were more similar to those of the patients than the controls. Nonlinear analyses have shown that correlations within mood time series tend to be very short range. Mehraei and Akcay [67] were able to predict future mood based on a current time series of mood ratings as have other groups [53, 59]. The work of Bonsall et al. [68, 69] is particularly interesting as they have not only demonstrated some important aspects of the dynamics (nonlinearity, identification of regions or stability/instability, separation of mood and noisy dynamics) but have also shown the usefulness of time series methods in guiding and measuring outcomes in treatment [70].

Mandell and Selz [71] applied nonlinear dynamical times series methods to the analysis of time series data from subjects with either borderline or obsessive compulsive personality disorders. They found differences be-

tween them in terms of spatial entropy and largest Lyapunov exponent. Their model focuses on dynamical patterns in behavior as providing the essential differentiation between disorders.

Heart rate variability is an easily accessible physiological measure that can sometimes serve as a proxy for a true order parameter distinguishing between normative and pathological states. Goldberger showed that important information about physiological functioning can be found by examining the complexity of time series data. In particular, he showed that the complexity of the R-R interval in the ECG is altered during senescence and the transition into pathological states [72]. Fiskum et al. [62] examined time series of heart rate variability in children and found correlations between sample entropy and internalizing psychopathology and negative affect, and between detrended fluctuation analysis and internalizing psychopathology. Bornas et al. [60] examined heart rate variability in high and low anxious adolescents and found that the fractal dimension and entropy were lower in the high-anxiety group. This is similar to the cardiac results where complexity declined in the context of illness. Heart rate variability thus serves as a marker for distinguishing between different states of dynamics.

There has been some work to develop formal models of various NCRS, particularly dopamine and serotonin [63–79]. Most studies have focused on the dynamics of the metabolism of the neurotransmitter within a neuron or at a single receptor [73–78]. Stratmann et al. [79] studied the functional role played by monoamines within the CNS, though only for locomotor systems. They found that serotonergic systems scale ionotropic signals, enabling fast responses to changing contexts. There have been a number of papers exploring models of psychopathology at the symptom level [80–85]. These use a wider variety of methods, including neural network modeling [80] and general systems theory [84]. Some papers have explored the personality level in the context of cocaine addiction [86] as well as normative function [87]. There have also been models that have explicitly incorporated ideas from dynamical systems theory, nonlinear dynamics and chaos theory [40, 64–67, 87–90].

Challenging Dynamical Features of NBRs

Understanding the continuum between temperament and mental illness requires bridging the explanatory gap between the behavioral level and the level of the NCRS upon which psychological phenomena supervene. The

use of dynamical systems theories in this endeavor faces a formidable challenge due to the presence of three striking characteristics of complex adaptive systems which must be considered in any realistic model. These are transience, contextuality and emergence.

Transience of NBRS Generators

Behavioral acts are not merely transient in duration, they are transient in their expression. This was demonstrated experimentally by Bernstein [91] who showed that specific behavioral acts are not constructed in a stereotypical manner, endlessly repeated like a film clip, but are instead constructed anew each and every time they are expressed by an organism. Different neurons, different neural pathways enter into each construction of the behavioral act. This constructive nature of neurobiological regulation led to the development of the functional constructivism approach in several biopsychological disciplines [92]. Trofimova [92, 93] has proposed several process algebra-based formalisms for describing the principles of transience which govern processes in functional constructivism. Her approach to process algebra uses several functional differentiation classes, a concept of “performance” and several universal process trends. From this perspective, there is no one-one correspondence between behavioral acts and the dynamics of lower level entities. Instead, many different processes give rise to similar sets of behavioral acts, so that there is no simple correspondence by means of which one can formally move up or down the hierarchy of dynamical systems of the organism. In many respects, a behavioral act is like a play, which can be performed with many different actors or many different stages.

This form of transience (sometimes referred to as metastability) has been observed in the place cell system in the rat hippocampus. The correspondence between individual place cells and actual spatial locations may change over time, in spite of the animal being able to accurately perform the same spatially dependent tasks [94, 95]. A similar phenomenon has been observed in hippocampal regions involved in long-term memory, where regions of supporting neurons appear to change over time, migrating along the hippocampus [96].

Contextuality of NBRS Activities

Phenomena such as temperament and mental illness, which are thought to be enduring features of behavior, whether normative or pathological, are also contextual. Jung [97] noted that the expression of certainly personality traits was contextual. Although the entire behavioral repertoire is accessible to any individual, each tends to fall

back upon default patterns, but context can induce shifts in these patterns. Context includes immediately past experience, present conditions and future expectations. Organisms do not merely react to their environments but also to internally generated predictions and expectations concerning those environments [98].

The NCRS underlying temperament and mental illness, particularly the monoamine systems, are known to have complex feedback relationships among themselves and cannot be considered to be statistically independent of one another [5, 10, 11, 79, 84, 92, 93]. Correlations among these systems may be time and context dependent, local or global [5, 51, 92, 93, 99]. Correlational and dimensional analyses are likely to miss these subtleties altogether. Classical probability and statistics are framed within a single context and thus often misapplied when multiple contexts are in play. A significant advance in this area is the contextual probability theory of Khrennikov [100] which is being applied to problems in psychology, economics and biology.

Emergence of NBRS Actions

Emergence refers to dynamics exhibited at a higher level that is not a direct consequence of the lower level dynamics. Emergence demands a multilevel, multiscale approach to theory building, modeling and analysis. The whole is quite often greater than the sum of the parts. For example, studies of nest emigration in *Temnothorax albipennis* [101, 102] have shown that while an individual worker's decision making may be subject to the non-rational decoy effect, the decision making of the colony as a whole is protected against this effect, remaining rational in the absence of any central authority.

The hippocampal place cell system is also emergent, being not an inherent property of individual hippocampal neurons, but rather of the brain-body as a whole [94, 95]. So too is long term memory retrieval, a process of reconstruction “on the fly” which is created on demand, emergently, with different top-down and bottom-up components contributing each time [96].

Dynamical Phase Transitions

In addition to the considerable challenges involved in trying to access the dynamics of the NCRS directly in humans, transience, contextuality and emergence present additional complexities that must be addressed both experimentally and theoretically. Contextuality implies non-stationary time series, which must be subdivided

into short duration transients, each defined by local context. Emergence, coupled with transience, imply that likely there is no simple relationship between the dynamics of the NBRS and that of the behaviors that they generate.

Faced with such complexity, physicists have sought out effective approaches targeting robust, global and if possible, universal features of the system under study so that phenomena can be studied in an approximate (or effective) manner at a single level, with the effect of higher and lower levels on the dynamics modeled as perturbations or fluctuations [103]. Transitional behavior is sought in the distribution of fluctuations and rare events [104]. Over time, two level and then multi-level models are developed. In the context of behavior, this suggests a shift from studying specific behaviors to studying *patterns* of behaviors. Contextually stable patterns of behavior are referred to here as dynamical phases. These phases may be short lived or long lived depending upon the global context but persist long enough to make a difference. Context is thought to induce a dynamical phase, while changes in context induce transitions between these phases. Fluctuations at stable regimes usually obey a Gaussian law, but fluctuations near a critical point often follow a power law. A $1/f$ power law distribution is often taken as an indicator of complexity.

This can be illustrated with a simple model, the iterated logistic map, given by $f = \mu x(1-x)$ where x lies within the interval $[0, 1]$ and μ lies within the interval $[0, 4]$. Each value of μ (control parameter) determines a particular dynamics, given by f . Given an initial value of x , the action of f is to generate a time series, $x, f(x), f(f(x)), f(f(f(x))), \dots$. As μ increases from 0 to 4, the time series changes from fixed point (period 1) to period 2, period 4, period 8 and so on until a critical value is reached and a non-periodic time series appears, following which time series of all periods or aperiodic series begin to occur. Below the critical value, each period is associated with a small interval of μ values, so that these are dynamical phases. Above the critical value, each value of μ merely determines a dynamics as change occurs too frequently. The periodicity of the time series serves as a marker of its dynamical phase.

In physics, phase transitions frequently show *universality* [105, 106], whereby the *form* of the scaling laws describing various physical properties near the transition's critical point is independent of the mechanism underlying the transition. The values of specific parameters in the scaling law reflect the mechanism. The presence of universality allows for the creation of general models into which more precise details of mechanism can be added as knowledge is acquired.

The idea of dynamical phases and their transitions have been applied to neurodynamics [107, 108] (where phase is often taken literally to mean phase-locked synchronization of a group of neurons) but only recently have they been applied to the study of large-scale behavior. In the context of neural systems, dynamical phases are frequently recognized as short duration, synchronized bursts of neuronal activity, which may be localized or distributed. Phase transitions are marked by spatially and temporally distributed phase gradients, "*phase cones*." The identification of dynamical phases with phase-locking works at the level of neurons, but more complex and subtle forms of coordination have been observed in models of complex networks of neurons (and complex adaptive systems more generally). For example, in exogenously stimulated networks, a low-frequency external stimulus can induce the network to produce a stable (across different initial conditions and local dynamics), reproducible, patterned global network output without synchronization among the agents [109–112]. This is termed transient induced global response synchronization (TIGoRS).

Freeman pioneered much of the research into dynamical phases and the role of chaotic dynamics in information processing by the brain [113–116]. He carried out extensive neurophysiological studies, particularly of olfaction in insects [113], demonstrated the existence of these phase synchronized dynamical phases, introduced the concept of phase cones and their relationship to phase transitions and observed them experimentally. The responses of the insect to distinct odors appeared to take the form of phase transitions between dynamical phases corresponding to each odor [113, 116]. He introduced the idea of *patterned attractors* [113] which bear some similarity to TIGoRS.

Freeman promoted the important idea that the brain maintains a state of criticality which enables rapid transitions between dynamical phases [117]. This improves information processing capability. The idea of criticality has gained prominence over time [118–120]. Signatures of criticality have been proposed as markers indicating the existence of a potential to transition from one dynamical phase to another [121, 122]. A recent paper used such markers to provide an early warning sign of sudden change in the context of psychotherapy [123]. Jiang et al. [124] have developed a set of network-based biomarkers which can be used in neuroimaging studies to assess the level of functional criticality observed in fMRI imagery. They have applied this to the setting of Alzheimer's disease and have demonstrated changes in functional criticality, which appear to distinguish between normal cog-

nition, mild cognitive impairment and Alzheimer's disease [125].

The idea of criticality has not been met uncritically [126]. Fluctuations in correlated activity in the critical state can be expected to vary widely, and in particular very strong correlations are expected to occur. Recently, the simultaneous recordings of 155 cortical motor neurons in macaque monkeys revealed surprisingly weak correlations but wide dispersion, which argues against the standard model of criticality [127]. The authors, however, argue for the presence of a second form of criticality that is dominated by inhibition yet is nearly unstable due to heterogeneous connectivity [127]. Moreover, recent work has suggested that the brain may exist instead at a subcritical state, which still provides information processing flexibility but avoids runaway states such as may occur in epilepsy [128].

Process Approaches to Dynamics

Currently, there are two complementary dynamical approaches to the problems of transience, contextuality and emergence: the functional constructivism model of Trofimova [92, 93] and the process algebra model [129–131]. Standard approaches assume that systems are enduring, objective, isolated and closed, with fixed dynamics and thus are deeply unsuited to understanding transient, emergent and contextual complex adaptive systems acting, reacting and interacting. Whitehead's Process Theory [132] was developed as a theory of organism. In Whitehead's view, processes generate informational primitives called actual occasions which come into being, exist briefly, just long enough toprehend the information of previous occasions, then fade away. Processes possess transient, contextual and emergent aspects [92, 93, 106, 129–131].

The functional constructivism approach of Trofimova [92, 93] is a process-oriented approach designed specifically to take into account the transience, contextuality and emergent nature of behavior and its generation (and other systems as well). It is a global level model to be applied across the multiplicity of scales from the neurochemical to the sociological. Fundamental are concepts of action generation, contingency cycles and the existence of several universal processes whose actions generate multiscale behavior. These include expansion or diversification, selection or integration, maintenance or replication processes, acting over multiple spatiotemporal scales in a vertical, horizontal or diagonal manner.

The Process Algebra is a specific algebraic system which describes the various ways that processes may couple or interact [129–131]. Couplings describe the timing of the generation of actual occasions by each contributing process. In couplings, processes may generate actual occasions sequentially (sums) or concurrently (products), share information among occasions (free) or never share (exclusive). Two processes may be independent. Interactions result in the activation or inactivation of process or the creation of new processes. Interactions are described by functions which map from collections of processes back to the set of processes. Processes interact according to their compatibility [133], dependent upon their attributes and functionalities. Interactions among processes create superordinate processes. Causal linkages [134] across generations between processes are denoted by concatenation. In addition, there is the zero process, O , which represents the process which does nothing. The appendix provides a brief example of how the process algebra may be used to construct a dynamical landscape.

A Dynamical Perspective on the Continuum

Temperament and mental illness are not specified by any particular behavior or set of behaviors but rather by specific dispositions or preferences for, and patterns of, behaviors which manifest in different contexts. Recall that the term behavior is used here in the generic sense and refers to temporal change in any of motor, cognitive or affective domains. Temperament and chronic mental illness refer to long term, dynamically stable *patterns* of such behavior manifesting across a variety of contexts and which are normative or pathological, respectively. Acute mental illness refers to a *transient pattern* of dysfunctional or outlier behavior, which may leave the person unchanged or induce a dynamical phase transition from a normative to a long-term pathological state. These patterns of behavior may be short term or long term, but most importantly, they exhibit a degree of robustness and stability, and thus appear to be better candidates as phenomena for study.

In dynamical terms, a meta-level approach is needed. To begin, each behavioral act (or more generally behavior) may be considered to be an individual state, and a sequence of behaviors becomes a trajectory. A homology of trajectories represents a specific dynamical phase. Next, let finite duration trajectories of behaviors (representative of short duration dynamical phases) become the new states, and sequences of trajectories (or patterns of

short term dynamical phases) become the new trajectories. This yields a meta-meta-level description. This coarse graining can be continued to higher levels. Equally, one can fine grain to ever lower levels of dynamics. The appendix shows how this might be carried out within the process algebra framework. Such a multilevel description is essential when dealing with any complex adaptive system due to the complexity of the feedback relationships that exist between the various subsystems of the global system and the hierarchical organization of these subsystems.

The transient nature of neural and psychological phenomena allows dynamical transients to serve as legitimate, ecologically meaningful states of behaving systems. This is certainly true of the NBRS and NCRS that underlie the generation of behavior in humans. The monoamine and acetylcholine systems exhibit complex feedback relationships, and these systems are in turn modulated by opiate and other neuropeptide systems, which in turn possess multiple feedback relationships among themselves [10, 11, 135, 136]. They act primarily through G-protein coupled receptors which modify the dynamics of target neurons, thus acting as control parameters [135]. Disentangling such relationships is a difficult, if not intractable, problem and a global approach is required such as suggested by Freeman in his notion of “circular causality” [114].

Meteorologists have developed considerable expertise in studying long-term dynamical phases (climate), their short-term phases (weather) and pathologies (storms) and their phase transitions (climate change) [137]. They have made extensive use of time series methods, many of which could be adapted for use in neuroscience [138–141].

The utility of a focus upon markers of dynamical phases has already been alluded to previously in the analysis of fluctuations. These methods have already yielded results for forecasting mood [59, 67, 70], for forecasting the possibility of sudden change in therapy [123] and for distinguishing between disease states [53, 56, 60, 124, 125]. Thus, although still early, the use of concepts such as dynamical phases and phase transitions, and the measurement of their attributes such as fluctuation distributions, scaling laws, order parameters, show promise in bringing about an understanding of the continuum between temperament and mental illness.

The continuum between temperament and mental illness is hypothesized as a multiscale landscape of second (and higher) order dynamical phases reflecting the activity of NBRS (and NCRS) in interaction with their envi-

ronment (which consists of other neural systems, somatic systems and the external environment). Temperament and chronic mental illness represent distinct long duration dynamical phases, while acute mental illness is viewed as consisting of short-duration outlier states.

Behaviors correspond to first level dynamical phases, of which individual behavioral acts constitute specific instances of these phases. In keeping with the FET model [10, 11], these phases are determined by the activities of the NBRS, which itself is a complex adaptive system and so possesses its own dynamical phases. The FET model suggests that many temperament traits result from ensemble interactions among monoamine systems, which in turn are regulated by opiate receptor systems, among other neuropeptides [10, 11]. This suggests that long-duration dynamical phases are determined principally by NCRS. The precise features of NCRS which give rise to such long duration dynamical phases are a matter for future research. They could be grounded in genetics, local and global connectivity, receptor densities, neurotransmitter metabolism among many other possibilities. Short-duration dynamical phases would be expected to be determined by those systems which exert a regulatory influence upon the NCRS, in particular opiate and other neuropeptide receptor systems. These are again complex adaptive systems with their own complicated feedback interactions and so possess their own dynamical phases which could determine short- and long-duration dynamical phases.

Functional constructivism provides one approach to modeling dynamical phases. Its core ideas are based upon neurophysiological research, and it addresses transience, contextuality and emergence, which are fundamental aspects of neurodynamics. Thus, it appears well suited from the kind of multi-scale modeling necessary to fully capture an embodied neurodynamics. The process algebra approach, on the other hand, provides a very general formal framework for describing and analyzing the concept of process, which lies at the heart of naturally occurring dynamical systems such as the human nervous system. Unlike standard dynamical systems theory which begins with a state space and examines a single dynamic on that space, the process algebra begins with a space of dynamics, in the form of processes, and examines a dynamics on these dynamics. It is thus well suited for studying the specific questions addressed here, namely the characterization of dynamical phases (as coherent sets of processes) and their phase transitions (process dynamics and interactions). It provides a nuanced unifying language for describing multi-scale processes, their constituent sub-processes and their interactions. It is hoped that from such a

study, generic or universal features of dynamical phases and their transitions can be discovered and used in the study of neurodynamics at any level.

The dynamical phase approach can be illustrated using research involving an animal model of obsessive-compulsive disorder [52]. Long term treatment of rats with the D₂/D₃ quinpirole induced behavioral changes which exhibited characteristics consistent with compulsive checking. Single injections of quinpirole induced short-duration locomotor behavior, but long-term injections, twice weekly for 5 weeks, resulted in a persistent change in several dynamical characteristics. The rats returned to two sites in the open field approximately 5 times more often than saline-treated rats. Moreover, the recurrence time to these two sites was approximately 1/20th that of the saline-treated rats and the dwell time increased. In addition, there was a contextual effect in that when an object was placed at a site which previously had not been preferred by the rat, the recurrence time to that site decreased and the frequency of visits and dwell time both increased (approximately 5-fold for each). In comparing the Lempel-Ziv complexity of the saline and treated rats, there was a significant decline in complexity (0.95 ± 0.16 vs. 1.20 ± 0.01 , $p < 0.001$). Likewise, there was a decline in entropy between the treated and saline rats (0.709 ± 0.005 vs. 0.888 ± 0.003). Both levels were elevated in both treated and saline animals showing that the paths of the animals in the open field were fairly random, but there appeared to be more structure overall in the treated animals. This suggested that the chronic quinpirole-treated animals were in a distinct dynamical phase from that of the saline animals. This phase was characteristic by a somewhat contextually dependent orientation of the animal's behavior on two specific sites within the open field possessing significantly shorter recurrence times, significantly higher dwell times and frequencies of visits, and slightly greater structure in their paths. This appears in keeping with the FET model which attributes a role for dopamine in motor tempo, plasticity and orientation to probabilities.

It can be debated whether or not the chronic quinpirole model represents an induction of an acute or chronic illness state. It does illustrate that this state represents a distinct dynamical phase from that of the control animals, suggesting the validity of the dynamical phase perspective. Unfortunately, a fluctuation analysis was not carried out during the induction phase which might have shed some light on the underlying nature of the dynamical phase transition.

The goal of the dynamical approach is to study dynamical phases and phase transitions at multiple time

scales corresponding to individual behaviors, contextually dependent short-term patterns of behaviors and long-term patterns of behaviors. This can be carried out using proxies, such as heart rate and locomotor activity, collected via smart phone or Fit Bit type technology supplemented with formal modeling using a process-based approach which takes into account the aforementioned features of transience, contextuality and emergence. The appendix provides a suggestion for how such a system might be framed within the process algebra. The resulting time series can be analyzed using a variety of measures but with a particular focus upon fluctuation analysis and the search for order parameters for the various dynamical phases. The focus upon phases and phase transitions arises because of the possible presence of universality in the phase transitions, which can be used to simplify formal models, which need not capture all of the details of the dynamics but only the most relevant features.

Conclusions

Temperament and mental illness have been postulated to lie along a continuum of neurobehavioral regulation. This continuum has been hypothesized, from a dynamical systems perspective, as a second or higher order landscape of dynamical processes, grouped together into distinct phases. Each phase in turn consists of distinct patterns of behaviors, that is, distinct patterns of first order dynamical phase. These phases should be marked by order parameters and linked through control parameters. These could be sought empirically through fluctuation analysis of appropriate time series of behavioral measures, and theoretically through the analysis of suitable formal models. The functional constructivism and process algebra approaches provide promising candidate frameworks for such models. The identification of these order and control parameters would facilitate the diagnosis and individualized treatment of mental illness and refine the separation between normative temperament and illness.

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Appendix

Process Algebra Construction of Dynamical Landscape

A landscape of dynamics can be constructed within the Process Algebra as follows. One begins with a “ground” level of processes Π^0 . The choice depends upon the number of levels to be included in the analysis and the limits of efficacy expected of the model. This

ground level could refer to that of fundamental physical processes, neurochemical processes, axo-dendritic processes, neural processes, neural assembly processes, neurobehavioral regulatory processes, regional processes, behavioral processes or sociocultural processes, to name a few. Regardless, there is posited a ground level and a set of ground processes, ${}^0P_1, {}^0P_2, {}^0P_3, \dots$. Let S be a set of algebraic expressions involving the 8 coupling operations. For example, one such expression might be $(Y \times Z) + (Z \times W)$. Each expression contains variables and constants. The variables imply universality, the constants specificity. Next, let F be a set of functions from tuples of processes to processes which define the interaction operations. For example, $f({}^0P_1, {}^0P_2, {}^0P_3) = {}^0P_2 \times {}^0P_4$ means if ${}^0P_1, {}^0P_2, {}^0P_3$ interact, then during the next-generation cycle, ${}^0P_1, {}^0P_3$ become inactive while 0P_2 remains active and 0P_4 becomes active. Finally, there might be superselection rules which are formulae of the form $S(x,y,z,a,b,c) = O$ which states that the combination represented by the form $S(x,y,z,a,b,c)$ never occurs. Using these rules, a next level of processes, Π^1 can be constructed. This procedure can be repeated to create ever higher levels of processes. One can express the dependency upon lower levels by using a functional form. For example, $\Pi^2(\Pi^1)$ indicates that the second level involves only combinations or operations on first-level processes, an expression of vertical emergence. $\Pi^2(\Pi^1, \Pi^0)$ indicates that the second level involves combinations of both first and ground processes, an expression of diagonal emergence [69, 70].

References

- 1 Hirschfeld RM, Klerman GL. Personality attributes and affective disorders. *Am J Psychiatry*. 1979 Jan;136(1):67–70.
- 2 Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. *J Abnorm Psychol*. 1994 Feb;103(1):103–16.
- 3 Watson D, Naragon-Gainey K. Personality, emotions, and the emotional disorders. *Clin Psychol Sci*. 2014 Jul;2(4):422–42.
- 4 Trofimova I, Sulis W. The lability of behavior as a marker of comorbid depression and anxiety. *Adv Biosci Biotechnol*. 2010;1(3):190–9.
- 5 Sulis W. Assessing the continuum between temperament and affective illness: psychiatric and mathematical perspectives. *Philos Trans R Soc Lond B Biol Sci*. 2018 Apr;373(1744):20170168.
- 6 Depue RA, Morrone-Strupinsky JV. A neurobehavioral model of affiliative bonding: implications for conceptualizing a human trait of affiliation. *Behav Brain Sci*. 2005 Jun;28(3):313–50.
- 7 Gray JA. The neuropsychology of anxiety: an enquiry into the functions of the septo-hippocampal system. Oxford: Oxford University Press; 1982.
- 8 Kagan J. Galen's prophecy: Temperament in human nature. Westview Press; 1997.
- 9 Rusalov VM, Trofimova IN. Structure of Temperament and its Measurement. Toronto: Psychological Services Press; 2007.
- 10 Trofimova I. The interlocking between functional aspects of activities and a neurochemical model of adult temperament. In: Arnold MC, editor. *Temperaments: Individual Differences, Social and Environmental Influences and Impact on Quality of Life*. New York: Nova Science Publishers; 2016. pp. 77–147.
- 11 Trofimova I, Robbins TW. Temperament and arousal systems: A new synthesis of differential psychology and functional neurochemistry. *Neurosci Biobehav Rev*. 2016 May;64:382–402.
- 12 Cloninger CR. A unified biosocial theory of personality and its role in the development of anxiety states. *Psychiatr Dev*. 1986;4(3):167–226.
- 13 Heath AC, Cloninger CR, Martin NG. Testing a model for the genetic structure of personality: a comparison of the personality systems of Cloninger and Eysenck. *J Pers Soc Psychol*. 1994 Apr;66(4):762–75.
- 14 Zentner M, Shiner R, editors. *Handbook of Temperament*. New York: Guilford; 1992.
- 15 Bennabi D, Vandel P, Papaxanthis C, Pozzo T, Hatten E. Psychomotor Retardation in Depression: A Systematic Review of Diagnostic, Pathophysiological, and Therapeutic Implications. *Biomed Res Int*. 2013;2013:158746.
- 16 degli Uberti EC, Petraglia F, Bondanelli M, Guo AL, Valentini A, Salvadori S, et al. Involvement of mu-opioid receptors in the modulation of pituitary-adrenal axis in normal and stressed rats. *J Endocrinol Invest*. 1995 Jan;18(1):1–7.
- 17 Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. *J Neurosci*. 1992 Feb;12(2):483–8.
- 18 Comer SD, Hoenicke EM, Sable AI, McNutt RW, Chang KJ, De Costa BR, et al. Convulsive effects of systemic administration of the delta opioid agonist BW373U86 in mice. *J Pharmacol Exp Ther*. 1993 Nov;267(2):888–95.
- 19 Jutkiewicz EM, Rice KC, Traynor JR, Woods JH. Separation of the convulsions and antidepressant-like effects produced by the delta-opioid agonist SNC80 in rats. *Psychopharmacology (Berl)*. 2005 Nov;182(4):588–96.
- 20 Blazer D, Steffens D. *Textbook of geriatric psychiatry*. Washington: APA Publishing; 2009.
- 21 Harrington ME. Neurobiological studies of fatigue. *Prog Neurobiol*. 2012 Nov;99(2):93–105.
- 22 Krishnan V, Nestler EJ. Linking molecules to mood: new insight into the biology of depression. *Am J Psychiatry*. 2010 Nov;167(11):1305–20.
- 23 Strüder HK, Weicker H. Physiology and pathophysiology of the serotonergic system and its implications on mental and physical performance. Part I. *Int J Sports Med*. 2001 Oct;22(7):467–81.
- 24 Olmstead MC, Ouagazzal AM, Kieffer BL. Mu and delta opioid receptors oppositely regulate motor impulsivity in the signaled nose poke task. *PLoS One*. 2009;4(2):e4410.

- 25 Pradhan AA, Befort K, Nozaki C, Gavériaux-Ruff C, Kieffer BL. The delta opioid receptor: an evolving target for the treatment of brain disorders. *Trends Pharmacol Sci*. 2011 Oct; 32(10):581–90.
- 26 Bodnar RJ. Endogenous opiates and behavior: 2010. *Peptides*. 2011 Dec;32(12):2522–52.
- 27 Tanaka M, Yoshida M, Emoto H, Ishii H. Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies. *Eur J Pharmacol*. 2000 Sep;405(1-3):397–406.
- 28 Takahashi M, Senda T, Tokuyama S, Kaneto H. Further evidence for the implication of a kappa-opioid receptor mechanism in the production of psychological stress-induced analgesia. *Jpn J Pharmacol*. 1990 Aug;53(4):487–94.
- 29 Schwarzer C. 30 Years of Dynorphins – New insights on their functions in neuropsychiatric diseases. *Pharmacol Ther*. 2009 Sep; 123(3):353–70.
- 30 Simonin F, Gavériaux-Ruff C, Befort K, Matthes H, Lannes B, Micheletti G, et al. kappa-Opioid receptor in humans: cDNA and genomic cloning, chromosomal assignment, functional expression, pharmacology, and expression pattern in the central nervous system. *Proc Natl Acad Sci USA*. 1995 Jul;92(15): 7006–10.
- 31 Wittmann W, Schunk E, Rosskoth I, Gaburro S, Singewald N, Herzog H, et al. Prodynorphin-derived peptides are critical modulators of anxiety and regulate neurochemistry and corticosterone. *Neuropsychopharmacology*. 2009 Feb;34(3):775–85.
- 32 Reyes BA, Johnson AD, Glaser JD, Commons KG, Van Bockstaele EJ. Dynorphin-containing axons directly innervate noradrenergic neurons in the rat nucleus locus coeruleus. *Neuroscience*. 2007 Mar;145(3):1077–86.
- 33 Reyes BA, Chavkin C, van Bockstaele EJ. Subcellular targeting of kappa-opioid receptors in the rat nucleus locus coeruleus. *J Comp Neurol*. 2009 Jan;512(3):419–31.
- 34 Filliol D, Ghazizadeh S, Chluba J, Martin M, Matthes HW, Simonin F, et al. Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. *Nat Genet*. 2000 Jun;25(2):195–200.
- 35 Trofimova I, Sulis W. There is more to mental illness than negative affect: comprehensive temperament profiles in depression and generalized anxiety. *BMC Psychiatry*. 2018 May; 18(1):125.
- 36 Trofimova I, Sulis W. Benefits of distinguishing between physical and social-verbal aspects of behaviour: an example of generalized anxiety. *Front Psychol*. 2016 Mar;7:338.
- 37 Trofimova IN, Sulis W. A study of the coupling of FET temperament traits with Major Depression. *Front Psychol*. 2016 Nov;7:1848.
- 38 Trofimova I, Christiansen J. Coupling of temperament traits with mental illness in four age groups. *Psychol Rep*. 2016 Apr;118(2):387–412.
- 39 Trofimova I. Questioning the “general arousal” models. *Open Behav Sci Psychol*. 2010;4: 1–8.
- 40 Trofimova I; IRINA TROFIMOVA. An investigation into differences between the structure of temperament and the structure of personality. *Am J Psychol*. 2010;123(4):467–80.
- 41 Trofimova I, Sulis W. Is temperament activity-specific? Validation of the Structure of Temperament Questionnaire – Compact (STQ-77). *Int J Psychol Psychol Ther*. 2011; 11(3):389–400.
- 42 Venkatasubramanian G, Keshavan M. Biomarkers in Psychiatry– a critique. *Ann Neurol*. 2016 Mar;23(1):3–5.
- 43 Nelson B, McGorry P, Wichers M, Wigman J, Hartmann J. Moving from static to dynamical models of the onset of mental disorder: a review. *JAMA Psychiatry*. 2017 May;74(5):528–34.
- 44 Gottschalk A, Bauer MS, Whybrow PC. Evidence of chaotic mood variation in bipolar disorder. *Arch Gen Psychiatry*. 1995 Nov; 52(11):947–59.
- 45 Guastello S, Koopmans M, Pincus D. Chaos and complexity in psychology. Cambridge: Cambridge University Press; 2011.
- 46 Small M. Applied nonlinear time series analysis: applications in physics, physiology and finance. Singapore: World Scientific; 2005.
- 47 Kantz H, Schreiber T. Nonlinear time series analysis. Cambridge: Cambridge University Press; 2003. <https://doi.org/10.1017/CBO9780511755798>
- 48 Pourahmadi M, Noorbaloochi S. Multivariate time series analysis of neuroscience data: some challenges and opportunities. *Curr Opin Neurobiol*. 2016 Apr;37:12–5.
- 49 Aubin JP, Frankowska H. Set valued analysis. Boston: Birkhauser; 2009. <https://doi.org/10.1007/978-0-8176-4848-0>
- 50 Dufort PA, Lumsden C. Dynamics, complexity and computation. In: Lumsden C, Brandts W, Trainor EH, editors. Physical Theory in Biology. Singapore: World Scientific; 1997. p. 69–106.
- 51 Sulis W, Gupta A. Nonlinear dynamics in psychiatry. In: Sulis W, Trofimova I, editors. Nonlinear Dynamics in Life and Social Sciences. Amsterdam: IOS Press; 2000.
- 52 Szechtman H, Sulis W, Eilam D. Quinpirole induces compulsive checking behavior in rats: a potential animal model of obsessive-compulsive disorder (OCD). *Behav Neurosci*. 1998 Dec;112(6):1475–85.
- 53 Perez Arribas I, Goodwin GM, Geddes JR, Lyons T, Saunders KE. A signature-based machine learning model for distinguishing bipolar disorder and borderline personality disorder. *Transl Psychiatry*. 2018 Dec;8(1):274.
- 54 Tsanas A, Saunders KE, Bilderbeck AC, Palmius N, Osipov M, Clifford GD, et al. Daily longitudinal self-monitoring of mood variability in bipolar disorder and borderline personality disorder. *J Affect Disord*. 2016 Nov; 205:225–33.
- 55 Ortiz A, Bradler K, Garnham J, Slaney C, Alda M. Nonlinear dynamics of mood regulation in bipolar disorder. *Bipolar Disord*. 2015 Mar; 17(2):139–49.
- 56 Ortiz A, Bradler K, Garnham J, Slaney C, McLean S, Alda M. Nonlinear dynamics of mood regulation in unaffected first-degree relatives of bipolar disorder patients. *J Affect Disord*. 2019 Jan;243:274–9.
- 57 Cutler CD, Neufeld RW. Nonlinear Indices with Applications to Schizophrenia and Bipolar Disorder. *Nonlinear Dynamics Psychol Life Sci*. 2019 Jan;23(1):17–56.
- 58 Sree Hari Rao V, Raghavendra Rao C, Yeragani VK. A novel technique to evaluate fluctuations of mood: implications for evaluating course and treatment effects in bipolar/affective disorders. *Bipolar Disord*. 2006 Oct;8(5 Pt 1):453–66.
- 59 Moore PJ, Little MA, McSharry PE, Geddes JR, Goodwin GM. Forecasting depression in bipolar disorder. *IEEE Trans Biomed Eng*. 2012 Oct;59(10):2801–7.
- 60 Bornas X, Balle M, De la Torre-Luque A, Fiol-Veny A, Llabrés J. Ecological assessment of heart rate complexity: differences between high- and low-anxious adolescents. *Int J Psychophysiol*. 2015 Oct;98(1):112–8.
- 61 Tolkunov D, Rubin D, Mujica-Parodi L. Power spectrum scale invariance quantifies limbic dysregulation in trait anxious adults using fMRI: adapting methods optimized for characterizing autonomic dysregulation to neural dynamic time series. *Neuroimage*. 2010 Mar; 50(1):72–80.
- 62 Fiskum C, Andersen TG, Bornas X, Aslaksen PM, Flaten MA, Jacobsen K. Non-linear Heart Rate Variability as a Discriminator of Internalizing Psychopathology and Negative Affect in Children With Internalizing Problems and Healthy Controls. *Front Physiol*. 2018 May;9:561.
- 63 Summers CH. Social interaction over time, implications for stress responsiveness. *Integr Comp Biol*. 2002 Jul;42(3):591–9.
- 64 Fetissov SO, Meguid MM, Chen C, Miyata, G. Synchronized Release of Dopamine and Serotonin in the Medial and Lateral Hypothalamus of Rats. *Neuroscience*. 2000;101(3):657–63.
- 65 Salomon RM, Johnson BW, Schmidt DE. Central neurochemical ultradian variability in depression. *Dis Markers*. 2006;22(1-2):65–72.
- 66 Adolf JK, Voelkle MC, Brose A, Schmiedek F. Capturing Context-Related Change in Emotional Dynamics via Fixed Moderated Time Series Analysis. *Multivariate Behav Res*. 2017 Jul-Aug;52(4):499–531.
- 67 Mehraei M, Akcay N. Mood and emotional states prediction by time series methods. Conference paper. Research Gate;2016.
- 68 Bonsall MB, Wallace-Hadrill SMA, Geddes JR, Goodwin GM, Holmes EA. Nonlinear time-series approaches in characterizing mood stability and mood instability in bipolar disorder. *Proc Biol Sci*. 2012 Mar;279(1730): 916–24.

- 69 Bonsall MB, Geddes JR, Goodwin GM, Holmes EA. Bipolar disorder dynamics: affective instabilities, relaxation oscillations and noise. *J R Soc Interface*. 2015 Nov;12(112): L20150670.
- 70 Holmes EA, Bonsall MB, Hales SA, Mitchell H, Renner F, Blackwell SE, et al. Applications of time-series analysis to mood fluctuations in bipolar disorder to promote treatment innovation: a case series. *Transl Psychiatry*. 2016 Jan;6(1):e720.
- 71 Mandell AJ, Selz KA. Nonlinear dynamical patterns as personality theory for neurobiology and psychiatry. *Psychiatry*. 1995 Nov; 58(4):371–90.
- 72 Kaplan D, Goldberger A. Chaos in cardiology. *J Cardiovasc Electrophysiol*. 1991;2(4):342–54.
- 73 Flower G, Wong-Lin K. Reduced computational models of serotonin synthesis, release and uptake. *IEEE Trans Biomed Eng*. 2014 Apr;61(4):1054–1.
- 74 Cullen M, Wong-Lin K. Analysis of a computational model of dopamine synthesis and release through perturbation. *IEEE Int Conf Bioinformatics Biomedicine*, Belfast, 2014, p. 1–7. <https://doi.org/10.1109/BIBM.2014.6999252>
- 75 Best J, Reed M, Nijhout HF. Models of dopaminergic and serotonergic signaling. *Pharmacopsychiatry*. 2010 May;43(Suppl 1):S61–6.
- 76 Best JA, Nijhout HF, Reed MC. Homeostatic mechanisms in dopamine synthesis and release: a mathematical model. *Theor Biol Med Model*. 2009 Sep;6(1):21.
- 77 Best J, Nijhout HF, Reed M. Serotonin synthesis, release and reuptake in terminals: a mathematical model. *Theor Biol Med Model*. 2010 Aug 19;7:34.
- 78 Qi Z, Miller GW, Voit EO. Computational systems analysis of dopamine metabolism. *PLoS One*. 2008 Jun;3(6):e2444.
- 79 Stratmann P, Albu-Schäffer A, Jörntell H. Scaling our world View: how monoamines can put context into brain circuitry. *Front Cell Neurosci*. 2018 Dec;12:506.
- 80 Looijestijn J, Blom JD, Aleman A, Hoek HW, Goekoop R. An integrated network model of psychotic symptoms. *Neurosci Biobehav Rev*. 2015 Dec;59:238–50.
- 81 Maia TV, Huys QJ, Frank MJ. Theory-based computational psychiatry. *Biol Psychiatry*. 2017 Sep;82(6):382–4.
- 82 Adams RA, Huys QJM, Roiser JP. Computational psychiatry: towards a mathematically informed understanding of mental illness. *J Neurol Neurosurg Psychiatry*. 2016 Jan;87(1): 53–63.
- 83 Huys QJ, Moutoussis M, Williams J. Are computational models of any use to psychiatry? *Neural Netw*. 2011 Aug;24(6):544–51.
- 84 Tretter F, Albus M. Systems biology and psychiatry – modelling molecular and cellular networks of mental disorders. *Pharmacopsychiatry*. 2008 Sep;41 Suppl 1:S2–18.
- 85 Montague PR, Dolan RJ, Friston KJ, Dayan P. Computational psychiatry. *Trends Cogn Sci*. 2012 Jan;16(1):72–80.
- 86 Caselles A, Micó JC, Amigó S. Cocaine addiction and personality: a mathematical model. *Br J Math Stat Psychol*. 2010 May; 63(Pt 2):449–80.
- 87 Revelle W, Condon D. A model for personality at three levels. *J Res Pers*. 2015;56:70–81.
- 88 Boldrini M, Placidi G, Marazziti D. Applications of chaos theories to psychiatry: a review and future perspectives. *CNS Spectr*. 1998;3(1):22–9.
- 89 Bystritsky A, Nierenberg A, Feusner J, Rabinovich M. Computational non-linear dynamical systems theory to psychiatry: a new methodological paradigm for diagnosis and course of illness. *J Psychiatr Res*. 2012 Apr;46(4):428–35.
- 90 King R, Barchas JD, Huberman B. Theoretical psychopathology: An application of dynamical systems theory to human behaviour. In: Basar E, Flohr H, Haken H, Mandell AJ, editors. *Synergetics of the brain*. Springer Series in Synergetics. Volume 23. Berlin: Springer; 1983. https://doi.org/10.1007/978-3-642-69421-9_27
- 91 Whiting H, editor. Human motor actions: Bernstein reassessed. New York (NY): North-Holland; 1984.
- 92 Trofimova I. *Functional constructivism: In search of formal descriptors*. *Nonlin Dynam Psychol Life Sci*; 2017. pp. 441–74.
- 93 Trofimova I. Phenomena of functional differentiation and fractal functionality. *Complex Systems Theory and Applications*. WIT Press; 2016. <https://doi.org/10.2495/DNE-V11-N4-508-521>.
- 94 Quirk GJ, Muller RU, Kubie JL. The firing of hippocampal place cells in the dark depends on the rat's recent experience. *J Neurosci*. 1990 Jun;10(6):2008–17.
- 95 Ziv Y, Burns LD, Cocker ED, Hamel EO, Ghosh KK, Kitch LJ, et al. Long-term dynamics of CA1 hippocampal place codes. *Nat Neurosci*. 2013 Mar;16(3):264–6.
- 96 Barry DN, Maguire EA. Consolidating the case for transient hippocampal memory traces. *Trends Cogn Sci*. 2019 Aug;23(8): 635–6.
- 97 Jung C. *Psychological types*. Princeton: Princeton University Press; 1971.
- 98 Buzsaki G. *The brain from inside out*. Oxford: Oxford University Press; 2019. <https://doi.org/10.1093/oso/9780190905385.001.0001>.
- 99 Sulis W. Transients as the basis for information flow in complex adaptive systems. *Entropy (Basel)*. 2019;21(1):94.
- 100 Khrennikov A. *Ubiquitous quantum structure*. New York: Springer; 2010. <https://doi.org/10.1007/978-3-642-05101-2>.
- 101 Sulis W. Collective intelligence: Observations and models. In: Guastello S, Koopmans M, Pincus D, editors. *Chaos and complexity in psychology*. Cambridge: Cambridge University Press; 2009. pp. 41–72.
- 102 Sasaki T, Pratt S. Emergence of group rationality from irrational individuals. *Behav Ecol*. 2011;22(2):276–81.
- 103 Ma T, Wang S. *Phase Transition Dynamics*. New York: Springer; 2019. <https://doi.org/10.1007/978-3-030-29260-7>.
- 104 Pérez-Espigares C, Hurtado PI. Sampling rare events across dynamical phase transitions. *Chaos*. 2019 Aug;29(8):083106.
- 105 Shpielberg O, Nemoto T, Caetano J. Universality in dynamical phases of diffusive systems. *Phys Rev E*. 2018;98(5):052116.
- 106 Popkov V, Schadschneider A, Schmidt J, Schütz GM. Fibonacci family of dynamical universality classes. *Proc Natl Acad Sci USA*. 2015 Oct;112(41):12645–50.
- 107 Steyn-Ross DA, Steyn-Ross M, editors. *Modeling phase transitions in the brain*. New York: Springer; 2010. <https://doi.org/10.1007/978-1-4419-0796-7>.
- 108 Lambertz M, Vandenhousten R, Grebe R, Langhorst P. Phase transitions in the common brainstem and related systems investigated by nonstationary time series analysis. *J Auton Nerv Syst*. 2000 Jan;78(2-3):141–57.
- 109 Sulis W. Driven Cellular Automata, Adaptation, and the Binding Problem. In: Moran F, Moreno A, Merelo JJ, Chacon P, editors. *Advances in Artificial Life, Lectures Notes in Artificial Intelligence* 929. New York: Springer-Verlag; 1995. pp. 824–40.
- 110 Sulis W. TIGoRS and Neural Codes. In: Sulis W, Combs A, editors. *Nonlinear Dynamics in Human Behaviour*. Singapore: World Scientific; 1995.
- 111 Sulis W. Synchronization, TIGoRS, and Information Flow in Complex Systems: Dispositional Cellular Automata. *Nonlinear Dynamics Psychol Life Sci*. 2016 Apr;20(2): 293–317.
- 112 Sulis W. Driven Cellular Automata. In: Nadel L, Stein D, editors. *Lectures on Complex Systems. Lecture Volume VI in the Santa Fe Institute Studies in the Sciences of Complexity*. New York: Addison-Wesley, 1993; pp. 565–578.
- 113 Freeman W. *Neurodynamics: An exploration in mesoscopic brain dynamics*. New York (NY): Springer; 2000. <https://doi.org/10.1007/978-1-4471-0371-4>.
- 114 Freeman W. *How brains make up their minds*. New York (NY): Columbia University Press; 2001.
- 115 Freeman WJ. A pseudo-equilibrium thermodynamic model of information processing in nonlinear brain dynamics. *Neural Netw*. 2008 Mar-Apr;21(2-3):257–65.
- 116 Kozma R, Freeman W. Cognitive phase transitions in the cerebral cortex: Enhancing the neuron doctrine by modeling neural fields. New York (NY): Springer; 2015.
- 117 Freeman WJ, Holmes M, West G, Vanhatalo S. Dynamics of human neocortex that optimizes its stability and flexibility. *Int J Intell Syst*. 2006;21(9):881–901.
- 118 Cocchi L, Gollo L, Zalesky A, Breakspear M. Criticality in the brain: A synthesis of neurobiology, models and cognition. *Prog Neurobiol*. 2017 Nov;158:132–52.

- 119 Werner G. Brain dynamics across levels of organization. Preprint cogprints.org/5275/1/braindynamics.pdf.
- 120 di Santo S, Villegas P, Burioni R, Munoz M. Laudau-Ginzburg theory of cortex dynamics: scale-free avalanches emerge at the edge of synchronization. *Proc Natl Acad Sci U S A*. 2018 Feb;115(7):E1356–65.
- 121 Scheffer M, Carpenter SR, Lenton TM, Bascompte J, Brock W, Dakos V, et al. Anticipating critical transitions. *Science*. 2012 Oct;338(6105):344–8.
- 122 Olthof M. 2019-10-28. <https://psych-networks.com/how-to-study-early-warning-signals-for-clinical-change>.
- 123 Olthof M, Hasselman F, Strunk G, van Rooij M, Aas B, Helmich M, Schiepek G, et al. Critical fluctuations as an early-warning signal for sudden gains and losses in patients receiving psychotherapy for mood disorders. *Clin Psych Sci*. 2020;8(1):25–35.
- 124 Jiang L, Qiao K, Sui D, Zhang Z, Dong H. Functional criticality in the human brain: Physiological, behavioural and neurodevelopmental correlates. *PLoS One*. 2019 Mar;14(3):e0213690.
- 125 Jiang L, Sui D, Qiao K, Dong HM, Chen L, Han Y. Impaired functional criticality of human brain during Alzheimer's disease progression. *Sci Rep*. 2018 Jan;8(1):1324.
- 126 Beggs J, Timme N. Being critical of criticality in the brain. *Front Physiol*. 2012 Jun 7;3:163.
- 127 Dahmen D, Grün S, Diesmann M, Helias M. Second type of criticality in the brain uncovers rich multiple-neuron dynamics. *Proc Natl Acad Sci USA*. 2019 Jun;116(26):13051–60.
- 128 Priesemann V. Self organization to sub-criticality. *BMC Neurosci*. 2015;16(Suppl 1):O19.
- 129 Sulis W. Completing Quantum Mechanics. In: Sienicki K, editor. *Quantum mechanics interpretations*. Open Academic Press; 2017. pp. 350–421.
- 130 Sulis W. A process algebra approach to quantum electrodynamics: physics from the top up. In: Martinez R, editor. *Complex systems: theory and applications*. New York: Nova Publishing; 2017. pp. 1–42.
- 131 Sulis W. A process algebra approach to quantum electrodynamics. *Int J Theor Phys*. 2017;56(12):3869–79.
- 132 Whitehead AN. *Process and reality*. New York: The Free Press; 1978.
- 133 Trofimova I. Sociability, diversity and compatibility in developing system: EVS approach. In: Nation J, Trofimova I, Rand J, Sulis W, editors. *Formal Descriptions of Developing Systems*. Dordrecht: Kluwer; 2002. pp. 231–48.
- 134 Sulis W. A process algebra approach to quantum electrodynamics. *Int J Theor Phys*. 2017;56:3869–79.
- 135 Kandel E, Schwartz J, Jessell T. Principles of Neuroscience, 4th edition. New York: McGraw-Hill, 2000.
- 136 Robbins TW. Opinion on monoaminergic contributions to traits and temperament. *Philos Trans R Soc Lond B Biol Sci*. 2018 Apr;373(1744):20170153.
- 137 Lutgens F, Tarbuck E. *The atmosphere: An introduction to meteorology*. New York: Pearson; 2011.
- 138 Krzyszczak J, Baranowski P, Zubik M, Kazandijev V, Georgieva V, Slawinski C, et al. Multifractal characterization and comparison of meteorological timeseries from two climatic zones. *Theor Appl Climatol*. 2019;137(3-4):1811–24.
- 139 Duchon CE, Hale R. Time series analysis in meteorology and climatology: an introduction. New York: Wiley; 2012. <https://doi.org/10.1002/9781119953104>.
- 140 Kargapolova N. Stochastic simulation of non-stationary meteorological time-series: daily precipitation indicators, maximum and minimum air temperature simulation using latent and transformed Gaussian processes. In Proceedings of the 7th International Conference on Simulation and Modeling Methodologies, Technologies and Applications. Vol 1: SIMULTECH 2017. pp. 173–9.
- 141 Horenko I. On clustering of non-stationary meteorological time series. *Dynam Atmospheres Oceans*. 2010;49:164–87.