Moving From Static to Dynamic Models of the Onset of Mental Disorder A Review

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Moving from static to dynamic models of the onset of mental disorder

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Abstract

Importance: In recent years there has been increased focus on sub-threshold stages of mental disorders, with attempts to model and predict which individuals will progress to full-threshold disorder. Given this considerable research attention and clinical significance of the issue it is timely to analyse the assumptions of the theoretical models in the field.

Observations: Psychiatric research into predicting onset of mental disorder has shown an overreliance on one-off sampling of cross-sectional data (i.e., a "snapshot" of clinical state and other risk markers) and may benefit from taking dynamic changes into account in predictive modeling. Cross-disciplinary approaches to complex system structures and changes, such as dynamical systems theory, network theory, instability mechanisms, chaos theory and catastrophe theory, offer potent models that can be applied to emergence (or decline) of psychopathology, including psychosis prediction but also to transdiagnostic emergence of symptoms.

Conclusions and Relevance: Psychiatric research may benefit from approaching psychopathology as a system rather than as a category, identifying dynamics of system change (e.g., abrupt versus gradual psychosis onset), identifying the factors to which these systems are most sensitive (e.g., interpersonal dynamics, neurochemical change), and individual variability in system architecture and change. These goals can be advanced by testing hypotheses that emerge from cross-disciplinary models of complex systems. Future studies require repeat longitudinal assessment of relevant variables through either, or a combination of, micro- (momentary, day-to-day) and macro- (months, years) level assessments. Ecological momentary assessment is a data collection technique appropriate for micro-level assessment. Relevant statistical approaches include joint modelling and time series analysis, including metric- and model-based methods that draw on the mathematical principles of dynamic systems. This next generation of prediction studies may more accurately model the highly dynamic nature of psychopathology and system change, as well as have treatment

implications, such as introducing a means of identifying critical periods of risk for mental state deterioration.

In recent years there has been increased focus on sub-threshold stages of mental disorders, with attempts to predict which individuals will progress to full-threshold (i.e., *DSM* or *ICD* diagnosable) disorder[1,2]. A prototype for this line of research has been prediction of onset of psychotic disorder in high risk cohorts defined through a combination of risk factors[3]. The standard research approach consists of assessing a range of variables (clinical, neurocognitive, neurobiological, etc.) at clinical service entry and investigating whether these variables predict the emergence of more severe psychopathology (i.e., onset of psychotic disorder) over time. In the case of psychosis prediction research this point of disorder onset has traditionally been defined as “transition” to first episode psychosis[4]. The assumption here is that a single baseline assessment of clinical variables (e.g., intensity of paranoid ideation or frequency of perceptual disturbances) may index level of risk for emergence of diagnosable mental disorder (schizophrenia, major depression, etc.) over time[5]. In other words, the approach assumes that a one-off sampling of cross-sectional data (i.e., a “snapshot” of clinical state and other risk markers) can reliably predict future emergence of a particular mental disorder or progression to more advanced stages of disorder[6,7].

However, there is increasing recognition of psychopathology as being highly dynamic and changeable in nature[8]. Symptoms can vary substantially over time both on a “macro” (months, years) level and a “micro” (momentary, day-to-day) level and also defy diagnostic boundaries, changing from one clinical picture to another, particularly in the early phases of disorder[9]. In addition, these patterns of symptom development can differ substantially between individuals, adding to the heterogeneous nature of emerging psychopathology. These characteristics of psychopathology suggest that the ‘static’ model of prediction described above (i.e., predictions based on single baseline assessments) may not be fit for purpose. This is also reflected in the modest accuracy and replicability of static prediction models in the psychosis prediction field[3,10]. Rather, theoretical models and associated analytic techniques built on the dynamic nature of psychopathology may be more powerful for predicting which individuals (and *when* such individuals) may change from one clinical state to another (sub-threshold to threshold states and vice versa)[8,9,11].

The purpose of the current article is exploratory and heuristic in nature. We briefly present a number of cross-disciplinary models of system change (dynamical systems theory, network theory, instability mechanisms, chaos theory and catastrophe theory) and suggest how these may be conceptually and empirically applied to psychopathology prediction research.

Dynamical systems theory[12], originating in the fields of mathematics and physics, aims to explain the behaviour of complex systems such as the climate, ecosystems and financial markets. It proposes that complex systems can have different types of constitutive architecture: some systems are made up of parts that are diverse and only marginally connected, while other systems consist of similar, highly interconnected components[13,14]. In the first type of system, change tends to occur gradually, while the second type of system may initially resist change and then reach a "tipping point" that involves a relatively sudden and dramatic shift to an alternative state (see Figure 1C and Figure 2). Particular system changes have been described that identify how close a system is to such transitions. While some system transitions occur gradually in response to changing conditions (Figure 1A), others may be triggered by a massive external shock (Figure 1B). Other system transitions are preceded by an increase in random variance and volatility or, alternatively, a "critical slowing down" of activity (Figure 1C). *Critical slowing down* refers to a system slowing down in returning to a state of equilibrium in response to disturbances ('perturbations') when it is close to a tipping point (Figure 2). This phenomenon has been demonstrated in mathematical models (e.g., in paleoclimatic transitions such as the Earth's shift from icehouse to greenhouse states) and has been demonstrated experimentally in biological systems (e.g., the food web of a lake and cyanobacterial population changes in response to increasing light stress)[15-17]. The concept has also been used in general medicine. Olde-Rikkert and colleagues[18], for example, argue that system slowing down can predict acute transitions in chronic diseases such as asthma, cardiac arrhythmias, migraine and epilepsy.

Several studies have applied this approach to mood disorders using ecological momentary assessment (i.e., frequently assessing individuals' mood states in the flow of their everyday life). In a large sample of healthy individuals and depressed patients, Van de Leemput and colleagues[19] found that shifts between depressed and normal states were preceded by increased connectivity of an emotional state with itself over time (increased temporal autocorrelation), increased variance in recorded emotions, and stronger positive correlation between emotions with the same valence (e.g., cheerful and content) and stronger negative correlation between emotions with different valences (e.g., cheerful and anxious). A very similar pattern of early warning signals was reported in a single person case study prior to a clinically and statistically significant transition to depression after discontinuation of antidepressant medication[20]. These findings are consistent with the notion of a critical slowing down in a person's response to perturbations (e.g., slower recovery from depressed affect after a life stressor, such as the end of an intimate relationship) as an early warning sign for a tipping point in mood state (from normal to depressed state and possibly vice versa; Figure 2)[20-24]. However, while related ideas have been applied to psychotic symptomatology[25-27], this approach to modeling critical transitions in complex systems has not been applied to predicting transitions in people at clinical high risk of psychosis. It would be of interest to investigate whether transitions in psychotic and other psychiatric disorders (e.g., transition from prodrome to first episode disorder or from remission/recovery to relapse) are foreshadowed by a critical slowing down in the system's (i.e., the person's) various domains of subjective experience and functioning (cognition, affect, corporeality, interpersonal functioning, etc.) in response to perturbations (e.g., life stressors, trauma, etc.). For example, a person at high risk of psychosis may describe becoming "stuck" in paranoid thoughts and may take longer to return to non-paranoid thinking in response to situational stressors as a signal of an imminent "tipping point" into first episode psychosis (Figure 1C and Figure 2). Critical slowing down may also apply to domains such as neurocognitive functioning and EEG patterns. It is also possible that the critical slowing down model is less applicable to some disorders, with gradual changes in a system (Figure 1A) or sudden shifts in response to a sudden strong external impact (Figure 1B), or possibly also increased variability and volatility in mental state, being more accurate models of disorder onset and relapse[28]. There may also be individual differences: some patients' transitions may be foreshadowed by a critical slowing down while others may follow alternative courses.

A related area of research that has already gained some traction in psychiatric research is that of network models. In network models, correlations between symptoms are not explained by a common cause (the underlying mental disorder), as in the traditional latent disease model (e.g., lung cancer being a common cause of symptoms such as shortness of breath, chest pain, and coughing up blood). Rather, mental disorders are seen as complex dynamic systems in which symptoms and psychological, biological and sociological components have autonomous causal power to influence each other[29-31]. By this account, symptoms are not passive expressions of an underlying disturbance but may actively trigger other symptoms (e.g., psychosocial circumstances may produce anxiety, which in turn may activate paranoid ideation)[32]. If symptoms engage in patterns of mutual reinforcement and feedback loops, the system as a whole may become trapped or "locked" in a state of extended symptom activation, a point at which a mental disorder may be diagnosed. Using a network approach, Isvoranu and colleagues[33], for example, recently showed that general psychopathological symptoms (anxiety, poor impulse control, motor retardation) connect different types of childhood trauma with positive and negative psychotic symptoms. This finding suggests that these general psychopathological symptoms may activate and reinforce psychotic symptoms in patients with a history of childhood trauma, which points towards mechanisms of onset of psychotic disorder and variables that may be incorporated into dynamic predictive models in those at high risk. Accordingly, the network perspective may be useful in predicting transition to frank disorder in those with emerging signs and symptoms (e.g., from clinical high risk state to psychotic disorder)[34].

Another relevant area of research is that of *instability mechanisms* identified in environmental geography[35-37]. In "unstable" systems small natural variations or disturbances are amplified through the operation of positive feedback loops, eventually disrupting consistency in a pattern. Mathematical analysis and computer modeling have established that instability mechanisms are responsible for many natural formations and patterns. For example, on an initially flat sand surface on a beach, a small variation in the sand thickness encourages the accumulation of local sediment and the sand thickness consequently grows. With regards to psychopathology, it is possible that analogous mechanisms drive the intensification of symptoms over time. For example, in the area of psychosis risk, such instability mechanisms may exacerbate minor anomalous subjective experiences (e.g., mild dissociative phenomena) into frank psychotic symptoms over time. Interestingly, many writers in the phenomenological tradition have posited an underling instability in basic processes of conscious awareness (awareness of time, space, body, self, intersubjectivity, etc.) as being *le trouble générateur*[38] (generative disorder or underlying causal mechanism) in schizophrenia spectrum disorders[39,40]. Although some work has applied the concept of instability to brain functioning in schizophrenia[25,41], the predictive value of such models has not yet been tested.

Finally, non-linear and chaos-based theories have been used to examine a wide array of phenomena ranging from biological population models to the functioning of modern work organisations. These theories posit that, although a series of observations over time or space may *appear* complex, relatively simple underlying "generators" may in fact be responsible for these seemingly complex observations or behaviors. Chaotic dynamical systems are characterised by a lawful but extreme sensitivity to initial conditions, which can lead to a striking divergence of behavioral patterns over time, popularly referred to as the "butterfly effect". In such systems, small differences in initial conditions yield widely diverging outcomes. "Initial conditions" in terms of psychosocial development, such as adverse childhood experiences, or effectiveness of treatment in early stages of illness may influence the ultimate trajectory of psychiatric symptoms and syndromes, or may set the basic parameters within which a system can develop. A similar approach is that of catastrophe theory, a mathematical theory that models how sudden changes may occur even though the underlying causal variables are essentially continuous[42]. The approach shows that phenomena or systems that show sudden quantitative shifts from one state to another may be under the influence of two or more independent mechanisms which themselves do *not* show any sudden shifts or jumps in magnitude. In the emergence of psychopathology it may be that the steady accumulation of a range of risk factors (e.g., obstetric complications, trauma, social adversity) forces the person to reach a rather sudden change ('catastrophe' or 'tipping point') in mental state. Again, although there has been some discussion of non-linear, chaos-based[43-45] or catastrophe-based[46] models of mental disorder, it has not yet been applied to prediction of transition from sub-threshold to full threshold psychopathology. For example, Scott[46] applies the mathematical principles of catastrophe theory to bipolar disorder, modeling how the variables of anxiety, self-esteem and aberrant salience of environmental stimuli may interact over time to produce depressive and manic episodes. Such dynamic models could be tested for their predictive utility in high risk samples.

These overlapping models each attempt to capture the dynamic and shifting nature of complex systems and may be fruitfully applied to psychopathological research. Psychosis and mood disorder prediction research, in particular, are at junctures where they could move beyond static or baseline "snapshot" prediction to modelling a complex system with resilience and fragilities built into its structure that can reach "tipping points" (transitions) in response to internal and/or external stressors. These dynamic models of emerging psychopathology require different methodological designs and analytical techniques from those to which we are accustomed and also indicate the value of cross-disciplinary collaboration, for example with mathematicians and physicists. Although machine learning methods[47,48] and a "high risk calculator"[49] have gained much attention in recent years, these methods are still built on prediction from "single snapshot" baseline data, albeit applied on an individual patient level, and tend not to take into account the time-to-event nature of prediction research. In order to examine the value of dynamic models, methodology that uses repeated longitudinal assessments of relevant features (time series methods) are required. This may be either, or a combination of, moment-to-moment ecological assessment (micro-level assessment of psychopathology) or repeated assessments over more extended periods of time (macro-level assessment; Figure 3)[24]. The most widely used method for the former are ecological momentary assessments techniques[50]. Techniques for the latter such as joint modelling of time-to-event outcome with time-dependent predictors, which can take into account the time-to-event nature of predicting onset of disorder, are also currently being developed[51]. Other applicable time series metric-based and model-based methods are also available[28]. Of course, one of the challenges of these time series methods of detecting imminent transitions is the large amount of repeat data required per research participant[20]. However, with an increased use of technology aiding data collection (e.g., mobile applications for ambulatory assessments, online surveys) and more than two decades of experience with engaging clinical high risk for psychosis populations, we are better equipped than ever to gather the required high-resolution, longitudinal data. In-depth qualitative methods with smaller samples (e.g., retrospective first person accounts of subjectively experienced changes associated with the onset of disorder) should also be considered.

There are a number of important questions raised by these models that can push the field of prediction research in psychiatry forward. All of these models emphasise *systems* rather than *categories*. While the notion of psychopathology/mental disorders as being disordered systems is not a new concept[52-54] it has not yet been directly applied to prediction of outcome in clinical high risk populations. What sort of system exactly is psychopathology, with what sort of constitutive architecture, and what factors is this architecture most sensitive to? Which of the overlapping but distinct concepts of dynamical systems theory, network models, instability mechanisms or non-linear/chaos- or catastrophe-based theories are most appropriate for modelling change in psychopathological states? As mentioned above, it may be that mental disorder cannot be characterised as a single type of system, but may consist of *different types* of systems (e.g., some disorders with high heterogeneity, others more homogenous in structure, which will influence response to stressors) and may vary between individuals[13]. Certainly, common psychiatric language (e.g., "flight into health", "psychotic break") suggests that system change can be quite abrupt for some individuals. It would be valuable to characterise and quantify the abrupt onset psychoses versus the gradual onset cases in clinical high risk samples (i.e., the 'psychotic break', Figure 1B and C vs. 'psychotic slide', Figure 1A) in order to improve our understanding of these issues, rather than simply categorise patients according to "transitioned" or "non-transitioned" cases. The nature of the early warning signals of system change will vary depending on the type of system: for some individuals or for some disorders the critical slowing down phenomenon (slowed reattainment of equilibrium in response to stressors; Figure 1C and Figure 2) may be predictive, whereas for others variability and volatility in the system (rapid cycling mood episodes, wildly fluctuating affective or mental states, etc.) or sensitivity to particular conditions (low thresholds for particular affective or cognitive responses, dissociation, etc.) may be predictive. A challenge for the next wave of research in this field is to determine which of these concepts is clinically useful, and to translate these models from group-level to individual-level prediction, which Wichers and colleagues have already shown is possible[20]. The theoretical richness of these dynamic models needs to be balanced with clinical applicability[55].

In a sense, these dynamic models are more sophisticated versions of diathesis-stress models, incorporating architectural features of a system, feedback loops and interactive effects between symptoms, which raises a number of issues: What factors determine why transitions occur at particular points in time? What is it about *particular* stressors and not others that trigger system change? Why does a system manifest particular clusters of symptoms (e.g., psychotic or mood symptoms) rather than other symptom clusters? There may be architectural features of the system and biopsychosocial interactions within the system (e.g., HPA axis dysregulation interacting with cognitive biases) that prime it for reacting to stressors in a particular way (resulting in emergence of a certain type or intensity of symptoms over others). Metacognition (i.e., the individual's *reaction* to symptoms) is also of relevance and may introduce cascading or self-reinforcing cycles, although possibly also present opportunities for recovery and resilience.

From a practical point of view, baseline prediction (the snapshot model) is appealing because it would provide an opportunity based on an initial assessment to inform a patient of their level of risk for a particular disorder. However, there may be a limit to the utility and accuracy of this approach as it may not do justice to the dynamic and complex nature of psychopathology and the progression or regression of the illness. It may ultimately be most effective to supplement baseline prediction with repeated assessment (a time series) of the person's psychopathology and other factors. From a treatment point of view such longitudinal modelling would facilitate being able to identify "danger times" or activate "alerts" for possible mental state deterioration, either in the context of in-person therapy or via tools such as mobile phone applications.

Conclusion

The models reviewed above show the benefits of engaging with cross-disciplinary approaches to modelling complex systems and present challenges to the current theoretical and analytical templates used in psychopathology prediction research. The ability to predict change from sub-threshold to threshold level disorder (on the group and individual level) may benefit from incorporating dynamic change into predictive modelling rather than relying on static data from a baseline assessment point. This requires enhanced understanding of the structural features of mental disorder and indicators of imminent system change. Future studies require study designs with repeat longitudinal assessment of relevant variables, achieved through either, or a combination of, micro- and macro-level assessments of psychopathology and other variables (e.g., neurocognition and neuroimaging). Ecological momentary assessment is a data collection technique appropriate for micro-level assessment. Relevant statistical approaches include joint modelling and time series analysis, including metric- and model-based methods that draw on the mathematical principles of dynamic systems.

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Figure Legends

Figure 1

Title: Dynamic models of symptom progression in the onset of mental disorders

Text.
A = Gradual deterioration in mental state in response to stressors
B = Transition to mental disorder triggered by a sudden major stressor
C = Transition to mental disorder foreshadowed by critical slowing down in response to stressors
EWS = Early warning signs
Sy = Symptoms
Green lightning bolt = stressor

Figure 2

Title: Critical slowing down as an early warning sign for transition in mental state

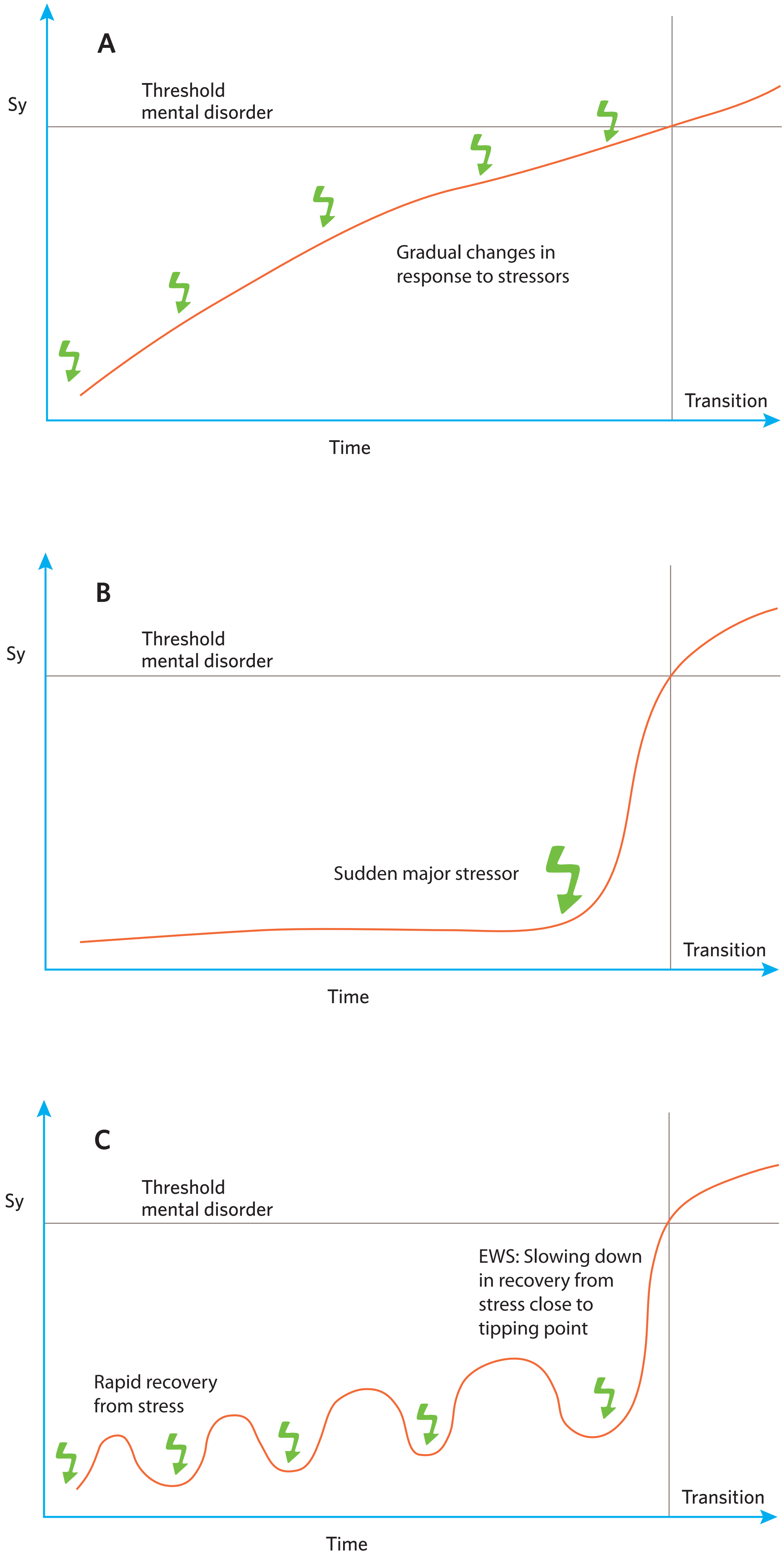
Text.

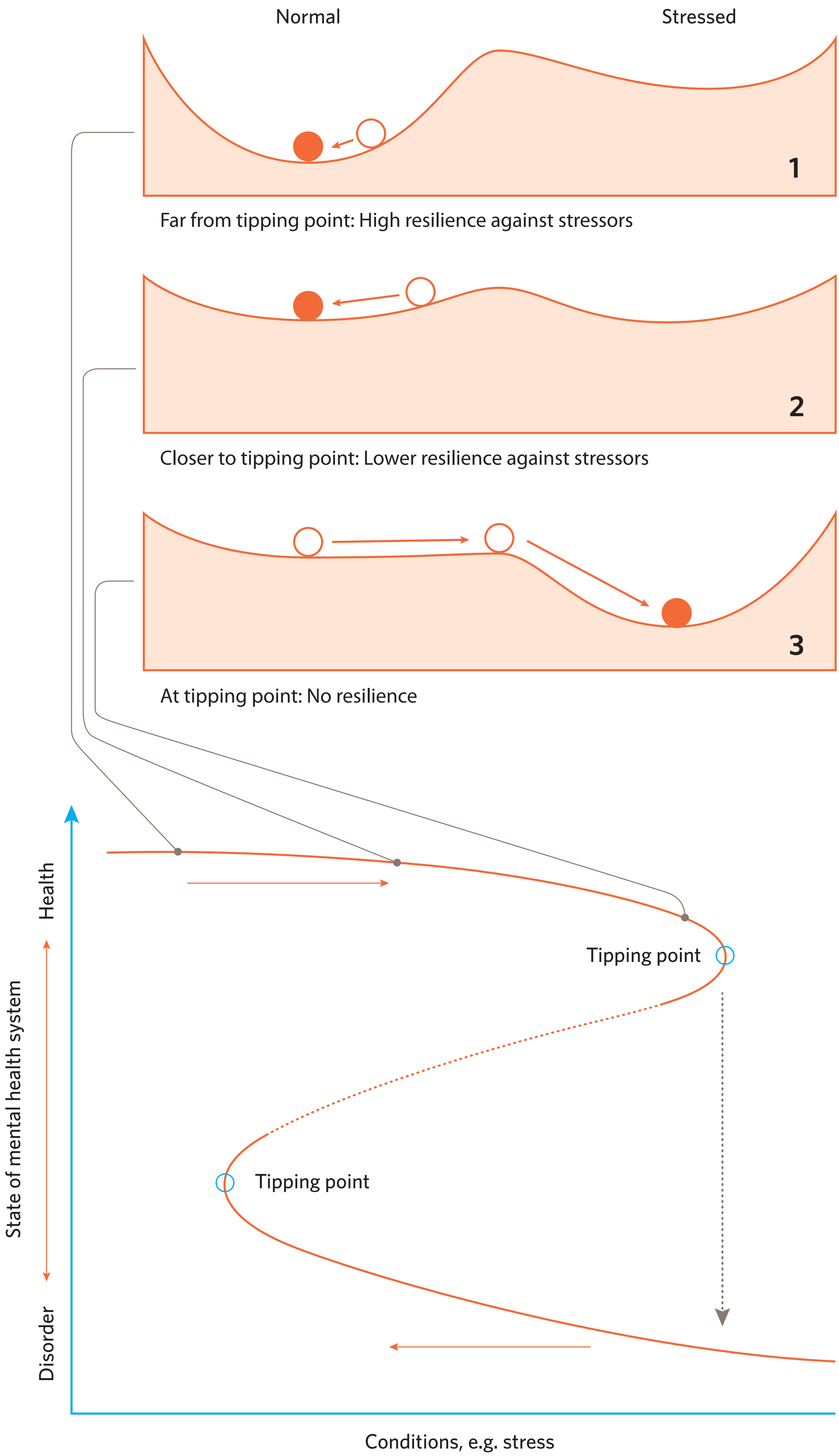
The figure shows a system with two states (e.g., well and psychotic). With changing conditions (e.g., increased stress) the system is pushed towards a critical point ("tipping point"). Far away from this threshold, the system is resilient (1). The closer it gets to the tipping point, the less resilient it becomes (2). In 3, even a small perturbation (e.g., an argument) can push the system beyond the threshold and trigger a change reaction: the whole system transitions towards a different state (e.g., into a psychotic state). Early warning signals are certain system properties that change when a system approaches a critical transition. The balls in panels 1, 2 and 3 demonstrate the principle of critical slowing down as an early warning sign. There are three principles to critical slowing down: 1. Slow recovery from perturbation (e.g., sleep loss: the closer a system is to a critical transition point, the slower it is to recover from the effects of a sleepless night, 2), 2. Increased autocorrelation (the state of the system becomes increasingly like its previous state, e.g., a depressed moment is likely to be followed by another depressed moment rather than return to a normal state), and 3. Increased variance (e.g., more mood fluctuation across the day). Figure adapted from Scheffer et al (2012).

Figure 3

Title. Measurement required in static and dynamic predictive models

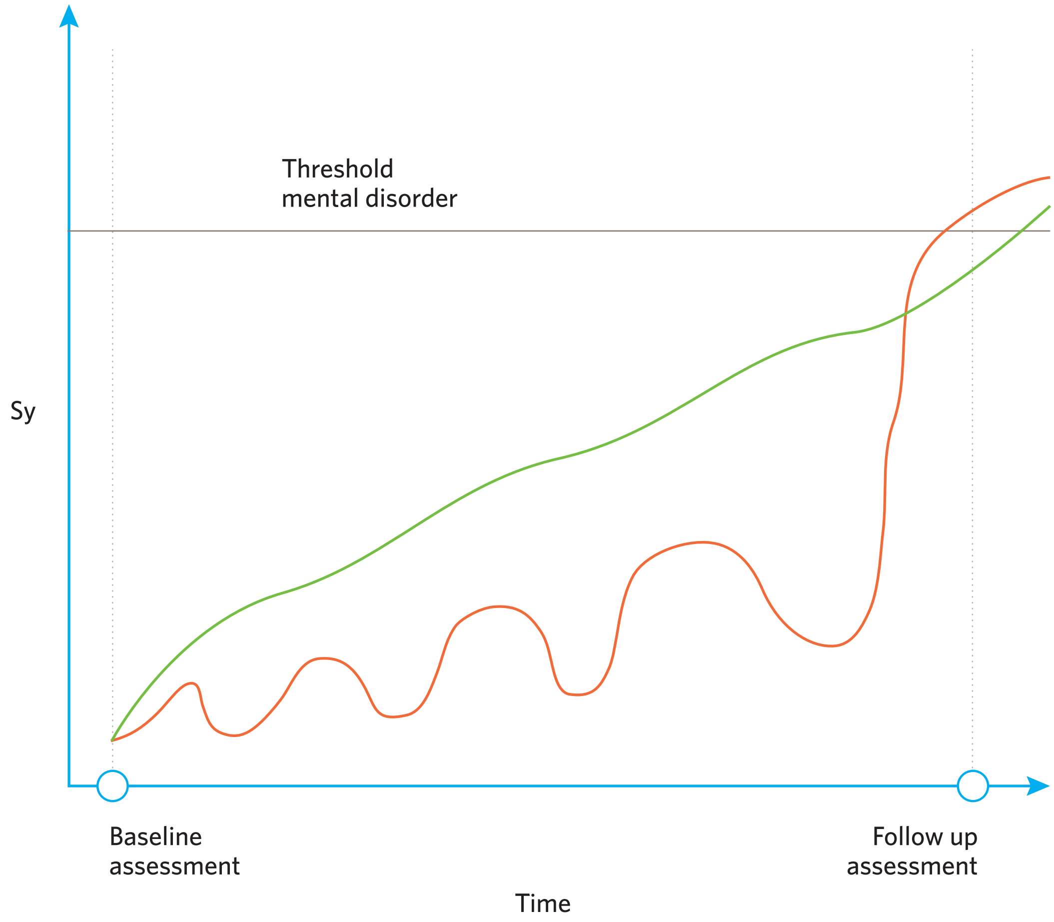
Text.
The green and orange lines represent different trajectories to threshold-level mental disorder. The blue circles on the x axis represent measurement time points. ‘Macro’ assessments involve repeated assessment time points, e.g. at monthly intervals. ‘Micro’ assessments are represented by the magnifying glass symbol. These assessments involve high resolution, granular level assessments (e.g., repeated assessments over the course of a day).
Sy = symptoms.


A
Sy
Threshold
mental disorder
Gradual changes in
response to stressors
Transition
Time
B
Sy
Threshold
mental disorder
Sudden major stressor
Transition
Time
C
Sy
Threshold
mental disorder
EWS: Slowing down
in recovery from
stress close to
tipping point
Rapid recovery
from stress
Transition
Time



Normal
Stressed
1
Far from tipping point: High resilience against stressors
2
Closer to tipping point: Lower resilience against stressors
3
At tipping point: No resilience
Health
State of mental health system
Disorder
Tipping point
Tipping point
Conditions, e.g. stress

Measurement for static prediction



Measurement for dynamic prediction