Supplemental Online Content

Scheffer M, Bockting CL, Borsboom D, et al. A dynamical systems view of psychiatric disorders—theory: a review. *JAMA Psychiatry*. Published online March 27, 2024. doi:10.1001/jamapsychiatry.2024.0215

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eAppendix 1. A graphical model of depression to illustrate the link between resilience and tipping points

To illustrate how resilience, alternative attractors and tipping points are connected, we use graphic models that show how major depressive disorder may be understood as a dynamical phenomenon (Fig. S1). As in all disorders, depression involves a complex web of symptoms with the potential for many intertwined feedback loops. However, for the sake of argument, we focus on a single one, the feedback between behavior and mood [1]. Put simply, depressed mood leads to reduced activity, which in turn depresses the mood. Grasping this graphical model takes some effort but as you will see it facilitates an understanding the universal principles of how tipping points relate to resilience.

We define activity (A) as the variable encompassing (physical and social) activity, and mood (M) as valence of the state of mind. Our graphical model is based on only two assumptions:

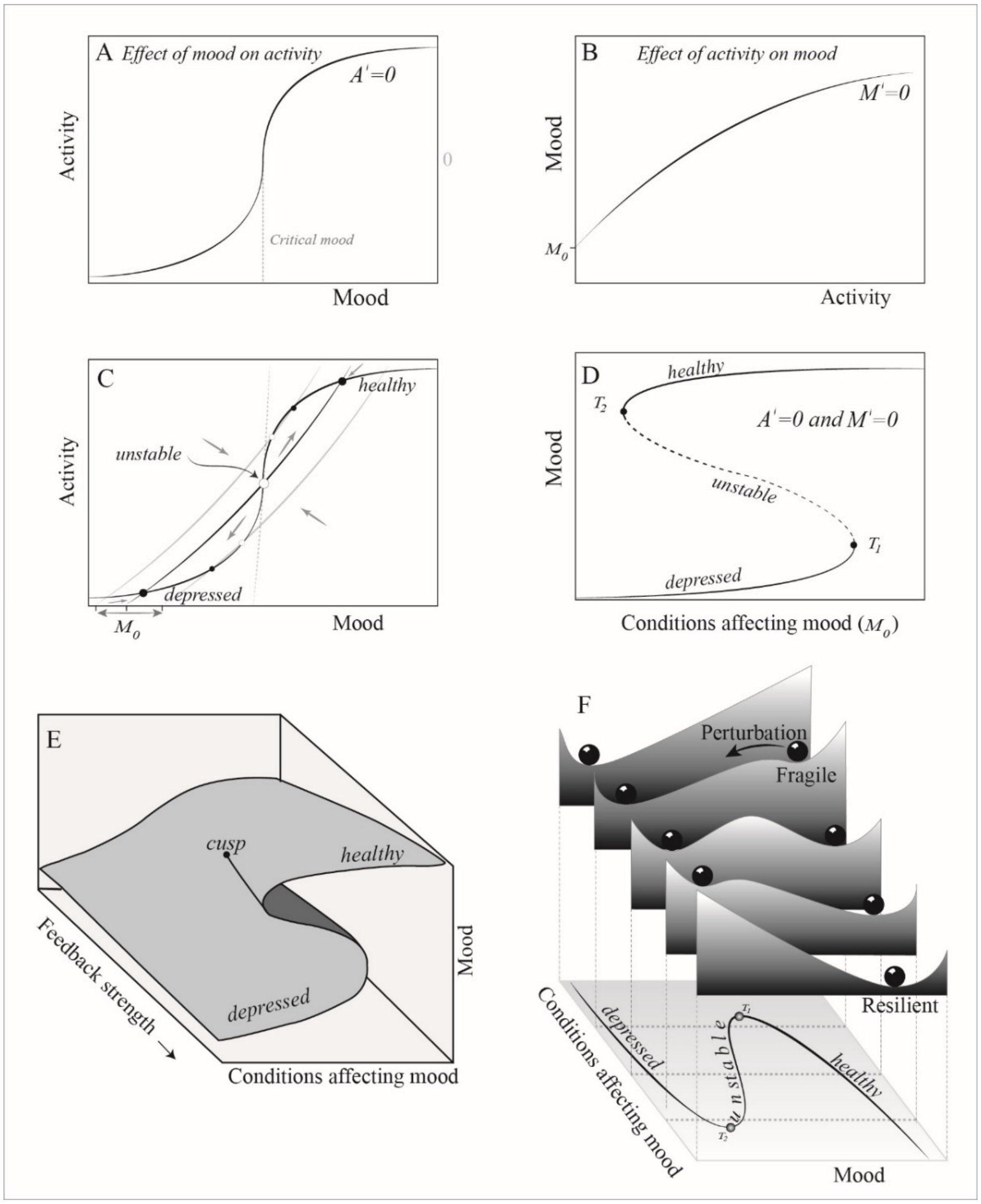
1) Individuals lose interest in activity below a critical mood level (Fig. S1A).
2) Mood increases in a saturating way with activity (Fig. S1B).

Now imagine that those hypothetical curves represent the dynamic equilibria of mood and activity level. Thus, for instance, the mood curve (Fig 2B) shows the equilibrium mood at each level of activity. As indicated by the arrows, mood on other points than those on the curve will increase or decrease until the mood level of the curve is reached. The same applies to the equilibrium activity level as a function of mood (Fig. S1B). As a next step we combine the two curves in one graph (Fig. S1C). Note that this requires exchanging the horizontal and vertical axes for the mood curve. The two equilibrium curves still separate the areas in the graphs where either of the variables will increase or decrease. Consequently, the equilibria of the interactive system as a whole (in which mood and activity affect each other mutually) are now the points where both mood and activity are in equilibrium. This condition is met only at the three interaction points of the curves that arise in this example. It can be seen from the arrows that the highest and the lowest point are stable points, as the system will return to this point upon a small perturbation away from it. Those points correspond to a stable healthy and a stable depressed state. By contrast, the middle intersection point (open dot) is an unstable equilibrium. Small perturbations will cause the system to move in the direction of either of the other two stable points.

Obviously, mood and activity depend on other factors as well. Therefore, as conditions change, imagine that the curves move. For example, the basal mood (M_0) may increase or decrease shifting the entire curve (Fig. S1C). As the basal mood increases, the unstable equilibrium and the depressed state will move together until they collide and disappear. In technical terms, this critical point at which the depressed state vanishes corresponds to a bifurcation point. Similarly, a bifurcation point at which the healthy state disappears is reached if basal mood decreases. Now, if one plots how the intersection points move as a function of basal mood, a famous sigmoidal curve known as the 'catastrophe fold' arises (Fig. S1D). This curve has two stable parts corresponding to the healthy and depressed states, and a dotted unstable part corresponding to the unstable middle intersection points in the upper panel. Tipping points occur where the stable and unstable parts meet (T_1 and T_2, technically known as saddle-node bifurcations).

The implications of this classical situation can be intuitively seen from stability landscapes (Fig. S1F). Here the valleys correspond to stable points ('attractors') and the hill tops to unstable points ('repellors') of the curve on the bottom plane representing the catastrophe fold for mood as a function of conditions affecting basal mood (M_0). If a healthy individual (front stability landscape) is exposed to changing conditions (e.g., an abusive interpersonal relationship) that affect their basal mood, we move to situations represented by stability landscapes in the background of the figure. Initially, the realized mood is only slightly reduced. However, the basin of attraction around this equilibrium shrinks. This implies a loss of resilience in the sense that only a small perturbation may eventually be enough to move the individual into the basin of attraction of the alternative depressed state (see supplementary video 1). If, subsequently, the conditions reverse (e.g., the end of the abusive interpersonal relationship), the individual will have a tendency to stay in the depressed mood, because of the mood-activity feedback that makes the depressed mood represent an alternative stable state over a range of conditions. Another perturbation (a life event, exercise program, drug treatment, etc.) can in principle induce a shift back to the healthy state if this state is stable.

The model also helps to see why self-reinforcing feedback is a necessary, but not a sufficient, condition to invoke alternative stable states. Tipping points arise only if the positive feedback is strong enough. For instance, if in our example mood is only marginally improved by activity, a nearly vertical equilibrium line for mood arises in figure S1D (it would be horizontal in 2C) and no multiple intersections with the equilibrium line for activity can exist. This dependency on the relative strength of feedback loops implies that in dynamical systems the response of a variable can often change from hysteretic to smooth (Fig. S1E). In terms of psychiatric disorders this leads to the prediction that while some persons may be trapped in a disorder and require major intervention before they eventually ‘flip’ to the recovered state, others will tend to enter the disorder and recover from it more incrementally and smoothly.



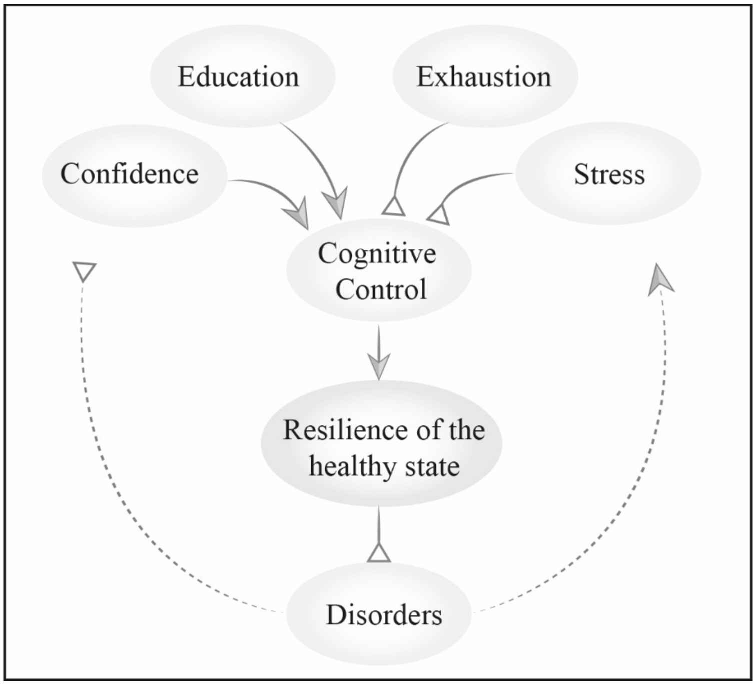
A graphical model of depression as an alternative stable state. A) Equilibrium activity level (where change is zero: A'=0) as a function of mood (M). B) Equilibrium mood (M'=0) as a function of activity (A). C) Three intersections represent states where both mood and activity are in equilibrium. The grey lines reflect how other conditions may affect the relationship between activity and mood. The dashed curve represents M'=0 for a person where the effect of activity on the mood is weak. D) A 'catastrophe fold' in the curve representing the equilibria derived as intersections in panel C plotted as a function of other conditions affecting mood. E) If the feedback is weaker, for instance in a person where the effect of mood on activity or that of activity on mood (near-vertical dashed curve in panel C) is weak, only one intersection of the curves is possible and the response to changing conditions becomes smooth rather than catastrophic. F) Resilience of the depressed and healthy state reflected in stability landscapes where valleys correspond to stable states and hilltop to the unstable equilibrium separating the basins of attraction.

eAppendix 2. A mechanistic example of how mechanisms may shape dynamic resilience of the healthy state

Clearly, to know how resilience of the healthy state may be enhanced (at the expense of resilience of disordered states), we need to know the different factors shaping this resilience. In this context we are less interested in the character traits that have been traditionally associated with psychological resilience, as such traits tend to be relatively rigid. Instead, we need to know which webs of mechanisms drive variations in resilience over time, as those could hint at ways to manage resilience, i.e., are more modifiable. It would go beyond the scope of this paper to review all potentially relevant mechanisms. However, as a mechanistic example to illustrate how a resilience-based approach could work, consider *cognitive control* as a time-varying mechanism that is disrupted across many mental disorders [2,3]. Cognitive control is the power to inhibit undesirable impulses. It depends on cognitive *system 2*, the deliberate, effortful, rational 'slow thinking' that can help to balance the outputs of the automatic, intuitive, and effortless 'fast thinking' *system 1*. The capacity for the slow thinking system to take control enables emotional regulation and willpower to resist impulsive tendencies [4,5]. It is correlated with personality traits including intelligence [6]. More importantly in the current context, various mechanisms may alter the power of cognitive control (Fig. 5).

At a fast timescale, stress can diminish cognitive control as it biases cognition towards the fast autopilot of system 1 [7,8]. On slower timescales social conditions and accumulative effects of life experiences may play a role. This is suggested for instance by correlations between the prevalence of psychiatric disorders and factors such as inequality [9] and the relation between brain function and poverty[10,11]. On the other hand, working memory needed for cognitive control may be promoted by education [12] and there is evidence that confidence in one's own capacity for control plays an important role. Research on animals as well as humans supports the 'learned helplessness' hypothesis stating that early life exposure to uncontrollable situations undermines the tendency to attempt taking control later in life (implying a self-reinforcing feedback that can lead to a 'belief-trap') [13]. One hypothesis is that the mind continuously monitors the need and scope for controllability allowing 'meta decisions' on recruitment of the computationally expensive system 2 (if working memory permits) [14,15]. As mentioned, *stress* and *exhaustion* tend to undermine cognitive control as they bias the mind to system 1 thinking. Coupled with this, the learned helplessness research implies that beliefs shaped by *life events* such as childhood abuse may lead to biased perception of uncontrollability, and thus to less effective cognitive control. Indeed, in the Dunedin cohort study, childhood abuse ranging from emotional neglect to violence or sexual abuse, was the single most predictive factor for the incidence of psychiatric disorders later in life [16].

The mechanisms affecting cognitive control (Fig. 5) illustrate how resilience of the healthy state may to some degree be manageable. Basic behavioral traits that may either foster resilience or increase vulnerability to a mental disorder are established during infancy and childhood, and are influenced by genetic and epigenetic factors [17,18]. Factors such as poor education and lack of confidence in controllability are not easily addressed later in life. Coordinated efforts of health care, educational and social support systems targeting children and their parents would therefore be expected to have the greatest impact in enhancing life-long resilience.



Some factors that may promote or erode resilience of the healthy state through their effect on cognitive control. Note that as in the specific example for depression some of the drivers tend to be correlated with socio-economic status [19].

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