Maladaptation diseases as disorders of goal state integration and intraorganismal individuation

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Abstract

The present work introduces the hypothesis that various human maladaptation diseases including addiction, cancer, autoimmunity, fibrosis, depression, chronic pain and post-traumatic stress disorder share a universal functional pattern in that they are all caused by defects in goal state integration of physiological subsystems into whole-organism goal states and by the resulting emergence of new levels of individuality within the organism. In this framework, a general mechanism in ontogenetic maladaptation is the intraorganismal individuation of subsystems via physiological adaptation mechanisms, which results in these systems becoming uncoupled from the rest of the organism and pursuing a hyperoptimization of their own goals at the cost of whole organism health. A central mechanism for mediating continued dysfunction in these disorders is the formation and maintenance of maladaptive memories. A potential universal therapeutic principle for maladaptation disorders is to provide physiological integration pressure to force subsystems to integrate back into the functional organization of the whole organism.

Introduction

Several of humanity's most common and burdensome diseases can be described as ontogenetic maladaptations, i.e. processes in which adaptation mechanisms within an individual drive physiological systems into dysfunctional states [1-3]. Examples for maladaptation diseases include drug and behavioral addictions, cancer, fibrosis, anxiety, post-traumatic stress disorder (PTSD), autoimmunity, depression, chronic pain, hypertensive cardiovascular remodeling and diabetes. A unifying feature in these pathologies is that the induction of the diseased state usually happens after birth, oftentimes precipitated by defined environmental and/or intraorganismal stressors, and is dependent on physiological adaptation mechanisms. Examples include learning and memory cascades in addiction [4,5], adaptive immune mechanisms in autoimmunity [6], cellular survival and memory mechanisms in cancer [7,8], novel tissue formation and repair in fibrosis [9] and cellular plasticity mechanisms in diabetes [10]. These diseases are thus in many ways characterized by a hyperfunctional state of physiological systems as opposed to degenerative or hypofunctional mechanisms. I present here a framework that conceptualizes maladaptation diseases as disorders of goal state integration in physiological subsystems which leads to the individuation of these subsystems and a functional antagonism with the rest of the organism. The concept of maladaptive individuation provides a basis to generalize pathophysiological dynamics across different disease entities and suggests that various human diseases are caused by the same underlying maladaptation process with different characteristics depending on organ system physiology and anatomy.

Goal state disintegration and intraorganismal individuation

The hypothesis presented here is that a general property of maladaptation disorders is that physiological subsystems (e.g. organs, tissues, neural circuits, molecular pathways) become progressively uncoupled from the rest of the body and put the achievement of their own suborganism goals over goal integration into the rest of the organism. This is termed *intraorganismal individuation* and entails the emergence of novel levels of agency within the organism after a disintegration of goal states between a network and the rest of the organism. The novel maladapted subnetwork uncouples itself from regulatory feedback and acts on its own behalf, oftentimes in an adversarial manner to the rest of the organism. This can go so far as to the subnetwork being considered a distinct individual which uses the organism as its host, usually to the latter's detriment.

Under physiological conditions, every biological entity has to subordinate its function to the overarching goals of the organism, i.e. the organism functions as an integrated whole. Yet, subsystems such as cells and tissues have their own agency, and display adaptation and learning mechanisms to continuously optimize goal achievement at their level. In maladaptation disorders, oftentimes as a result of chronic stressor exposure, physiological subsystems uncouple themselves from constraints and integration stimuli (e.g. anti-growth or differentiation signals) imposed on them by other biological entities (e.g. other cell types and organs) and redirect organismal resources towards maximization of their own reward. Over time, this leads to a conflict in resource allocation between the subsystem and the rest of the organism, and causes a decline in health for the whole organism up to the point of death.

Several steps in this maladaptation process can be distinguished (Fig. 1). In health, the physiological whole-organism network consists of nodes (e.g. cells) and interactions between nodes (e.g. intercellular communication patterns) (Fig. 1, panel 1). Nodes form suborganism networks with distinct functional boundaries (e.g. organs). The whole organism is functionally delineated by the functional organism boundary which in conditions of health overlaps with the structural organism boundary (i.e. the organism is one functional and one anatomical individual). In the healthy state, the goal states of all subnetworks are integrated into whole-organism goal states and hence all subnetworks are contained within the functional boundary of the whole organism. Due to certain stimulation patterns either from outside or within the organism (usually classified as *stressors*), a subnetwork within the organism becomes maladaptive (Fig. 1, panel 2, red subnetwork in lower left corner). The interactions between the nodes of the maladaptive network become stronger and agency emerges at the level of the subnetwork, leading to a novel functional boundary. At this stage, the network is still functionally integrated into the whole organism and can serve physiological functions (e.g. cancer precursor cells still exerting some physiological tissue function). The next stage marks the individuation of the maladaptive network (Fig. 1, panel 3). The network functionally uncouples itself from the rest of the organism, giving rise to a novel individual boundary for the maladaptive network and to a shifted boundary for the organism network. The maladaptive network now has its own goal states, independent of the rest of the organism. The physiological interactions between the maladaptive network and the rest of the organism are dissolved. As both functional individuals (e.g. the organism and the maladaptive network) are still part of the same structural organism (i.e. anatomical body) they are contained within the structural organism boundary. Finally, the maladaptive network forms pathological connections to the rest of the organism to serve its own goals (Figure 1, panel 4). The maladaptive network has emerged as an independent functional individual which uses the rest of the organism

to maximize achievement of its own goals, usually to the detriment of whole-organism health. The whole process might thus be termed *adversarial individuation*. Note that some steps in this process can overlap (e.g. the dissolving of physiological connections and the formation of

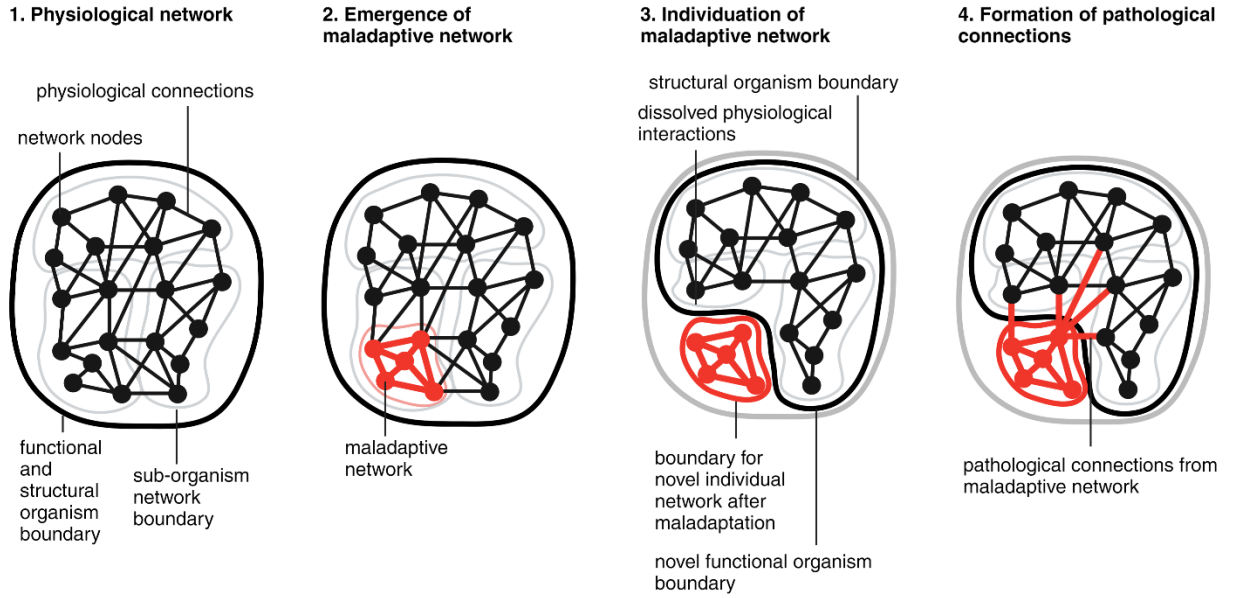

Figure 1. Maladaptation as a result of goal state disintegration and suborganism individuation of a physiological network. 1) Under physiological conditions, different nodes form suborganism networks with corresponding supranodal goal states (delineated by grey lines) which are connected to each other and together form the organism. The organism is delineated by the structural and functional organism boundaries which in conditions of health overlap. The functional whole-organism boundary is established via whole-organism goal states. 2) Due to stressor exposure and/or genetic predisposition, a maladaptive network (red nodes and connections) emerges within the organism. The maladaptive nodes are connected stronger to each other than to the rest of the organism (bold red lines) and the network begins to express its own goal states and agency (faint red lines delineating the maladaptive network). At this stage, the network is still connected to the rest of the organism and can exert physiological roles. 3) The maladaptive network uncouples its goal states from the rest of the organism and becomes a novel individual. Physiological connections to the rest of the organism are severed and the maladaptive network expresses its own functional boundary (bold red line). This also leads to a different functional boundary for the rest of the organism (shifted bold black line excluding the maladapted network). Both physiological individuals are still contained within the same anatomical body, delineated by the structural organism boundary (bold grey line). 4) The maladaptive network forms novel connections to the host organism (bold red lines connecting to black nodes) to further its own goals. It is now an adversary individual to the host organism.

pathological ones).

An interesting problem is how the maladapted network progressively establishes and maintains its identity. A hypothesis that I advance here is that this happens via the formation of a *maladaptive memory*. The maladaptive memory encodes and holds the diseased state. In this way, maladaptation diseases would be based on the formation and maintenance of “traumatic memories”, encoded in physiological subnetworks. Memory phenomena have been described in cancer [8], fibrosis [11], autoimmunity [12], addiction [4,5,13] and obesity [14] among others. Maladaptation diseases could thus perhaps also be described as learning disorders in physiological systems. Maladaptive memories would be the substrates of a particular disease, and could also be conceptualized as functional scars in that they represent a permanently altered functional state after injury or stress.

Application to human diseases

Several examples for this maladaptation process will be given in the following sections with drug addiction, cancer and autoimmunity among others to illustrate the principle of goal state disintegration and suborganism individuation.

A central biological substrate for mediating addiction behavior is the brain's reward circuitry [4,5,13], centering on the mesostriatal dopamine system. The output of this circuit controls many aspects of motivation, movement and habitual behavior [15]. Physiologically, this system is subjected to regulatory inputs that modulate reward-seeking. Drugs of abuse induce changes in reward-processing networks and over time, as addiction progresses through repeated drug exposure, these regulatory inputs become altered. Positive feedback which drives addiction-related behavior becomes strengthened (e.g. cocaine enhances excitatory transmission onto D1-MSNs [16,17] which have been shown to drive cocaine-induced behavior changes [18], and leads to enhanced dopamine release during subsequent cocaine administration [19]) and negative feedback which antagonizes addiction-related behavior becomes weakened (e.g. cocaine self-administration decreases LTD onto striatal neurons [20] and cocaine exposure decreases inhibitory drive onto D1-MSNs [17]). Anti-addiction mechanisms thus become weakened while pro-addiction mechanisms become strengthened. Subsequently, addiction-mediating neuronal circuits (e.g. midbrain-striatum connections) pursue their own reward maximization and exert more and more influence over the organism's behavior until everything is subsumed under the preoccupation with attaining and consuming drugs, even to the point of death of the organism. Thus, maladaptation of a relatively minor cell collective in the brain can disturb whole-organism physiology and behavior.

This pattern of an uncoupling from inhibitory signals, an amplification of positive feedback and a runaway effect in the pursuit of a basic local goal is also seen in cancer. Cancers uncouple themselves from anti-growth and anti-migration signals to start growing, invading and metastasizing at the cost of the rest of the organism [7]. Cancers use physiological learning and memory mechanisms to acquire and store malignancy phenotypes and thereby become individuals within an organism [8]. They start hyperoptimizing their own growth and reprogram the rest of the body towards their own goals (e.g. through manipulating the endocrine system [21] and functionally mimicking other cell types [22]). The result in most cancers is a deterioration of organism health and death of both the organism and the cancer it contains. Interestingly, in many cases, defined chronic stressors have been identified that can predispose or precipitate cancer development. For instance, in precancerous conditions such as Barretts esophagus, chronic stressor exposure (e.g. gastric acid) leads to a metaplastic reprogramming of tissues and cells [23]. If the stressor does not subside, in a subset of cases cancer develops.

In autoimmunity, a pattern of uncoupling from regulatory inputs and a runaway effect in pursuit of subsystem goals is observed. Lymphocytes start producing antibodies directed against endogenous antigens and start to expand and attack healthy host tissue [6]. They also become insensitive to regulatory signals (e.g. CTLA-4 [24] and PD-1 [25]). From the local perspective of the "autoimmune system", these actions make sense, as successful identification and elimination of antigens triggers cell survival [26] and potentially beneficial metabolic transitions for immune cells [27]. Exploiting this system selfishly, autoimmune cells and the autoimmune system gain an advantage over their healthy cellular competitors which, due to their healthy programming, have to suppress their activity or concede their life in apoptosis if they malfunction. Here again, the system seems to have encoded a maladaptive memory that keeps it in its diseased state.

In anxiety disorders, the overactivation of circuits mediating avoidance behavior leads to the achievement of a local goal (i.e. reduction in stress signals and activation of reward signals) while sacrificing whole-organism goals (e.g. by excluding the organism from vital social and foraging activities). In fibrosis, maladaptive activation of tissue repair systems, oftentimes after repetitive injury, leads to a harmful transition in the cellular phenotype and a remodeling of the extracellular matrix [9,28]. The tissue effects of initial fibrosis can lead to further exacerbation of the process thus creating a positive feedback loop [29] as outlined above. Interestingly, fibroblasts can maintain a fibrotic memory after being returned to healthy tissue conditions [11] demonstrating functional autonomy in the maladapted phenotype.

The pattern that is common to different instances of ontogenetic maladaptation is thus that bodily subsystems start pursuing their own goals while uncoupling themselves from feedback which would align them with higher-order organism goal states, usually as a result of chronic stressor exposure. One way to permanently hold the novel goal states and the altered identity of the subnetwork is via the formation of maladaptive memories.

Factors influencing goal state disintegration and maladaptation

One important set of problems is why and how the increase in agency at the suborganism level emerges. In general, the establishment of dysfunctional subnetworks relies on the activation of adaptation programs. Two options are that maladaptation emerges as determined by inherited factors over the life-history of the organism (i.e. even in the absence of any unphysiological stimulation) or that it is triggered by external stimulation (i.e. certain stimulation patterns trigger maladaptation in all organisms of that species regardless of heritable differences). In most instances, there is probably a mixture of these two factors and maladaptation is caused by an interplay between factors within the organism (e.g. genetic and epigenetic predispositions) and the nature of environmental stimuli (e.g. carcinogens, drugs of abuse, psychological stressors).

The two general factors that determine concrete maladaptation emergence within the organism are time (i.e. dynamics) and space (i.e. anatomical location of maladaptation). With regard to dynamics, it seems that chronic or extraordinarily high stimulus exposure facilitates or even causes maladaptation. Many maladaptations are caused by continuous and chronic stressor exposure including psychological stressors (e.g. social isolation increasing vulnerability to addiction [30]) and carcinogen exposure (e.g. lung cancer from chronic smoking [31])). In diseases such as PTSD, fibrosis and cancer, a single intense trigger can cause maladaptation (e.g. a traumatic event in PTSD [32], a single injury triggering fibrotic changes [33], a single carcinogen exposure triggering cancer [34]). Tissue-specificity could be related to location of exposure (e.g. lung cancer from smoking; cocaine influencing dopamine transporters in the brain) or hereditary influences (e.g. tissue-specific enhancer variants predisposing to cancer in that tissue).

Regarding potential mechanistic substrates, the same biological entities can drive different downstream effects depending on their activation patterns (e.g. MAPK activation in PC12 cells driving differentiation or proliferation [35]). It is possible that prolonged stress signaling leads to a remodeling of biological adaptation programs with increased baseline activity of certain signaling factors and reduced sensitivity to modulatory inputs.

An interesting similarity in cancer and addiction is that both can be conceptualized by a two-step model in which stressors lead to a vulnerability towards disease initiation and subsequent stimulation can precipitate the disease. Chronic stress can increase the vulnerability to addiction

[36] while a concrete substance (e.g. cocaine) then triggers and sustains disease progression. In cancer, certain substances or stimuli can prime cells for malignant transformation while subsequently different stimuli then initiate oncogenesis [37]. This principle even extends to the same stimuli in that psychological stress can predispose towards both addiction [36] and cancer [38]. Perhaps underlying genetic or epigenetic predispositions can lead to a generalized bodily susceptibility for maladaptation, explaining why several maladaptation disorders are positively correlated to each other. Cancer for instance is positively associated with anxiety [39], addiction [40] and autoimmunity [41,42].

While maladaptation is a central phenomenon in many individual diseases, it has also been proposed as a crucial driver of aging [2]. The *adaptation-maladaptation dilemma* describes the conundrum in which physiological adaptation mechanisms which counter stressors on the organism also mediate maladaptation and hence act as stressors themselves. Over the long-term, rising dysfunction within an organism is hence inevitable. Maladaptation might be a fundamental property of living systems and its tendency to increase during aging might explain why many individual maladaptation diseases including cancer, autoimmunity and cardiovascular remodeling increase with age. In aging, goal integration might become dysregulated within the whole organism leading to the emergence of maladaptive networks. An interesting line of research would be to investigate what surveillance mechanisms the body has to detect maladaptation. Just like the immune system can for instance detect cancer, perhaps neural circuits in the brain detect the emergence of maladaptive networks in addiction and anxiety to then counteract them.

Application of physiological integration pressure as a therapeutic principle

The fact that maladaptation is a common underlying principle in many diseases and is oftentimes even mediated by the same physiological mechanisms across disease entities (e.g. adaptive transcription [1]) suggests the possibility of developing universal therapeutic principles. One such principle proposed here is to apply *integration pressure* to the organism. In interventions such as physical exercise, different organ systems coordinate with each other and implement body-wide adaptations [43]. In the course of these adaptations, individual organ systems become aligned with the rest of the body and the overall physiological goals of the organism. Perhaps not surprisingly, exercise has preventative and curative effects in depression [44], addiction [45], cancer [46], autoimmunity [47], diabetes [48] and cardiovascular disease [49] among others. The same might be true for other whole-body interventions such as exposure to heat and cold, nutritional scarcity and social challenges.

Conclusion

In summary, an underlying pattern in many seemingly disconnected human diseases is the loss of goal state integration of physiological subsystems into whole-organism goal states via maladaptation which leads to the emergence of new levels of individuality within the organism (i.e. *intraorganismal individuation*). In addiction, cancer, autoimmunity and several other maladaptation disorders, certain subsystems start to gain functional autonomy and uncouple themselves from integrative feedback signals from the rest of the body. These subsystems then start to hyperoptimize the fulfillment of their own lower-level goals (e.g. reward error minimization in addiction, survival and spread in cancer, destruction of antigens in autoimmunity) at the expense of the rest of the organism. The diseased state is held in maladaptive memories which, after they

have been encoded, drive continuous chronic dysfunction. Maladaptation disorders could thus also be conceptualized as learning and memory disorders in physiological systems. A potential therapeutic counterstrategy could be to exert integration pressure on the whole system so that individual subsystems are forced to align with each other (and thereby overwrite their maladaptive memories) to maximize whole-organism performance.

Competing interests

The author declares no competing interest.

Author contributions

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