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EARLY WARNING SIGN FOR CRITICAL TRANSITIONS IN CHRONIC DISEASES

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BACKGROUND

In our aging societies a quickly increasing number of subjects is suffering from one or more chronic diseases such as asthma/COPD, heart failure, dementia, epilepsy, diabetes, and Parkinson's, which are partly characterized by reversible and recurrent states of changed disease activity being: an exacerbation of bronchial obstruction, cardiac decompensation, delirium, seizures, hypo- or hyperglycemia, and falling, respectively. Here we present evidence and examples of early warnings of critical transitions in chronic diseases.

METHODS

A focus group was organized of 11 internationally accredited experts both from medicine and psychology (n=5), ecology (N=3), and theoretical/mathematical medicine/biology (n=3) to discuss the question whether there are empirical data and/or theoretical notions that support the evidence of early warning signal for the approximation of tipping points in the human pathophysiology.

Next, a systematic literature review was carried out in PUBMED and MEDLINE. Combining 'exacerbations', and ('prediction' or, 'early warning') resulted in 109; 'prediction' and 'acute episode' in 134, 'tipping points' in 174 hits, and critical slowing down' in 244 hits (up to July 1st 2014). The titles and abstracts were screened for relevant studies on the prediction of exacerbations in chronic diseases. The snowball method was added, starting from relevant articles. Finally, a realist review was carried out on the same question according to the methods described by Shepherd at al. (PLoSMed2009:e1000086, and Pawson et al. www.ccsr.ac.uk/methods/publications/documents/RMPmethods2)

RESULTS

Risk prediction for acute (e.g. COPD) episodes or relapse (e.g heart failure) has been attempted by several authors using clinical scoring systems, considerations of environmental factors and measuring organ function (e.g. lung or heart function as FEV1 and ejection fraction), as well as genetic, inflammatory and immunological markers in induced sputum or exhaled air. However prediction of acute disease episodes in individual patients using this classical epidemiological methodology remains notoriously difficult, and at best sub-populations at risk for an exacerbation or acute relapse are identified. These techniques do not allow prediction of the timing of the relapse, though this also has great impact for the individual, as well as for healthcare services.

New models based on telemonitoring and time series in individual patients have recently been tested and are used to understand the complexity and timing of exacerbations in chronic diseases (e.g. in epilepsy and COPD), which are regarded as complex dynamic systems. The underlying paradigms are derived from mathematical modeling, statistical physics and systems biology.

Based on the science of dynamical modeling, the focus group supported the hypothesis that

slowing down (CSD) of recovery time probably is an early warning signal of approaching tipping points of critical transitions in complex systems of human (patho)physiology, and mentioned examples from health (e.g extended nodding before falling asleep), and disease (e.g. elongation of the QTC time in the cardiology before ventricular tachycardia).
The systematic literature search yielded firm empirical and experimental evidence of CSD as warning for transition points in physics, chemistry, climate changes and ecology, but no evidence from medicine.
Realist review resulted in papers on systems biology applications in epilepsy, electrocardiology, COPD/asthma and exercise physiology that supported the theoretical viewpoint that the robustness of a complex system is reflected by a shorter recovery time, and greater speed of early recovery of for example: light flashes, cardiac pacing, bronchial irritation, and exercise, respectively.
Empirical data were found that support the hypothesis that CSD of recovery following a stressor marks health and disease severity of an organ system in cardiology, pulmonology, ophthalmology, neurology, endocrinology, and peripheral vascular disease, in studies on sinus node and ventricular QTc recovery time, bronchial reactivity recovery time, macular photorecovery time, functional recovery time following cerebral ischemia, skin temperature recovery time, and transcutaneous oxygen recovery time following limb ischemia, respectively.
In cardiology, more severe ischemic disease may cause elongation of electrical recovery time, which increases the chances of recurrent ventricular tachycardia, which is in itself a tipping point phenomenon.
Additionally, empirical data were found in some medical fields that support the hypothesis that CSD of recovery following a stressor marks the approximation of a tipping point of relapse in:
-increased autocorrelation as marker of CSD in disturbed mood signals that proved to predict the relapse of depressions in subjects with major depressive disorder (vd Leemput et al, PNAS, 2013).
-sinus node recovery time increased by pacing or adenosine application with increasing likelihood of critical transition to atrial tachycardia and syncope (e.g. Fragakis et al. Euopace 2012;14: 859-64);
-ventricular QTc elongation by drugs or electrical pacing correlates with increased likelihood of critical transition to Torsade de pointes arrhythmia, though it is not a sufficient, nor a necessary sign of this transition (e.g. Fish et al, Circulation 2004;109:2136-42);
-minute ventilation recovery time (a stressor response during weaning from mechanical ventilation) is longer in patients who failed to be successfully extubated, evidencing lower resilience of the cardiopulomonary system (Seymour et al. J Intensive Care Med 2008;23:52-60; Hernandez et al Chest 2007;131:1315-22.
-slowing of early phase recovery of systolic blood pressure after an orthostatic manoeuvre in frail older subjects showed elevated risk for subsequent mortality (Lagro et al, 2013).

CONCLUSION
Classical epidemiological prediction rules can reasonably well identify the patients who are at a greater risk of future disease exacerbations, however, these methods cannot be used to predict the occurrence of such acute episodes.
Systems biology models are used to predict the timing of exacerbations, and have shown to be reasonably successful for example in epilepsy.

Critical slowing down of recovery may be used to rank complex organ systems on a broad scale from resilient to fragile, and may be used as early warning signals for closeness to a tipping point both in normal physiology and in chronic disease. Though stochasticity may prohibit prediction of the exact timing of critical transitions in human pathophysiology, our systematic review and focus group results suggest that indicators of critical slowing down of recovery are still underused in medicine as potential early warning signals of relapse and acute disease episodes.
Current innovation in monitoring systems greatly facilitates time-series analysis, which can be used to automatically signal CSD related to small stressors in patients with chronic disease. In addition, increasing autocorrelation in the spontaneous and subtle fluctuations of the system's state may signal that patients are moving towards their tipping point, as an indirect indicator of slowing down.
Translation of theoretical notions and empirically collected evidence on CSD from systems biology to medicine may result in a breakthroughs on warning for the occurrence of hazardous tipping points in human disease, and opens a new exciting and promising field of research.