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Physiologic complexity and aging: Implications for physical function and rehabilitation

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ABSTRACT

The dynamics of most healthy physiological processes are complex, in that they are comprised of fluctuations with information-rich structure correlated over multiple temporospatial scales. Lipsitz and Goldberger (1992) first proposed that the aging process may be characterized by a progressive loss of physiologic complexity. We contend that this loss of complexity results in functional decline of the organism by diminishing the range of available, adaptive responses to the innumerable stressors of everyday life. From this relationship, it follows that rehabilitative interventions may be optimized by targeting the complex dynamics of human physiology, and by quantifying their effects using tools derived from complex systems theory. Here, we first discuss several caveats that one must consider when examining the functional and rehabilitative implications of physiologic complexity. We then review available evidence regarding the relationship between physiologic complexity and system functionality, as well as the potential for interventions to restore the complex dynamics that characterize healthy physiological function.

1. Introduction

A hallmark of healthy physiologic function is the capacity to detect, respond and adapt to the innumerable perturbations and stressors of daily life. This capacity is achieved via complex interactions between multiple control systems, feedback loops, and regulatory processes that operate over multiple scales of time and space (Lipsitz and Goldberger, 1992), and interact with one another in nonlinear fashion (Goldberger et al., 2002a). As a result of this rich organization, the seemingly irregular dynamics of most physiological outputs are "complex;" i.e., they contain "meaningful structural richness (Grassberger, 1991)" marked by a degree of non-random fluctuations over multiple temporospatial scales (Costa et al., 2002; Goldberger et al., 2002a). In recent years, the study of physiologic complexity, using the theory and quantitative tools derived from complex systems biology, has shown great promise for improving our understanding of aging, monitoring senescence, and evaluating novel interventions that treat age-related disease and promote healthy aging.

The conventional view of aging is that it is a linear process of physical and cognitive decline that occurs over time as one progresses from adulthood into senescence. Lipsitz and Goldberger (1992) first proposed that the aging process can be defined by a progressive loss of complexity within the dynamics of physiologic outputs. Although important exceptions have been reported and are described elsewhere (Duarte and Sternad, 2008; Hartman et al., 1994; Vaillancourt and Newell, 2002; Vaillancourt and Newell, 2003), numerous studies have since demonstrated that biological aging and numerous age-related diseases and syndromes are characterized by a loss of physiologic complexity in the dynamics of the cardiovascular (Beckers et al., 2006; Costa et al., 2008; Iyengar et al., 1996; Kaplan et al., 1991; Pikkujamsa et al., 1999), respiratory (Peng et al., 2002), central nervous (Yang et al., 2012) and motor control (Costa et al., 2007; Manor et al., 2010; Thurner et al., 2002) systems, among others. Importantly, this loss of information content is often independent of age- and/or disease-related changes in signal variability (Manor et al., 2010). Fig. 1, as an example, illustrates the dynamics of anterioposterior (i.e., fore-aft) postural sway recorded as four individuals stood with their eyes open on a stationary force platform. Compared to the healthy young adult, the fluctuations in postural sway were less complex in each older adult and in particular those suffering from peripheral or central nervous system impairment.

An age-related loss of physiologic complexity is believed to stem from gradual deterioration of underlying structural components of physiological systems, as well as alterations within the nonlinear coupling between these systems (Lipsitz, 2002, 2004). We therefore contend that 1) relatively low physiologic complexity in the dynamics of a system under basal conditions (i.e., resting or free-running) underlies the diminished capacity of that system to respond and adapt to stressors, and 2) preventative and/or rehabilitative interventions may be optimized

Abbreviations: MSE, multi-scale entropy; MEG, magnetoencephalography; BOLD, blood-oxygen level dependent; MRI, magnetic resonance imaging.

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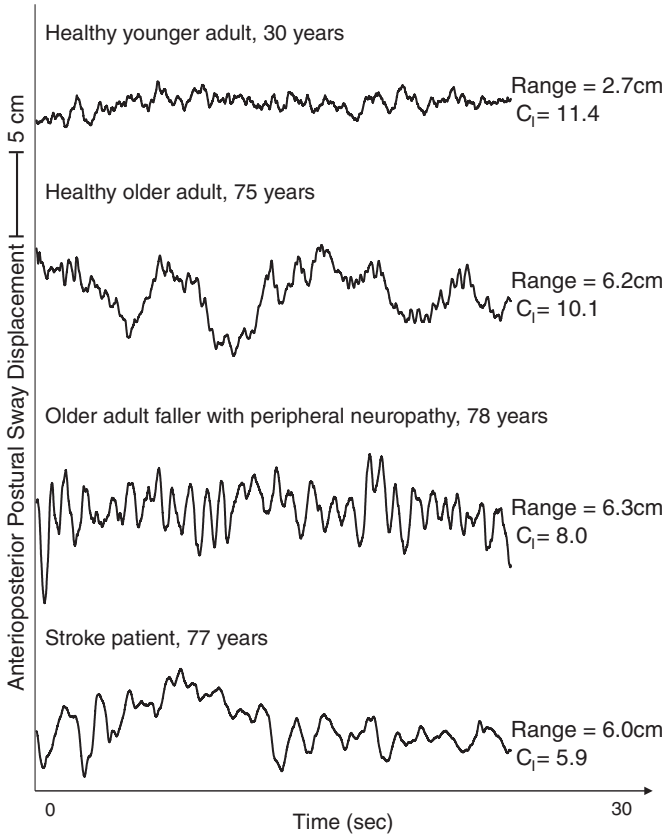

Fig. 1. Representative anterioposterior postural sway time-series during standing with eyes open. Age- and disease-related changes to the neuromuscular system are often associated with unique alterations to the dynamics of postural sway. Presented here are unfiltered postural sway (i.e., center-of-pressure) dynamics of four individuals differing in age and/or disease status. Multiscale entropy analysis (of high-pass filtered data) was used to derive the complexity index (C_I), for which higher values reflect a greater degree of irregularity across multiple scales of time (i.e., greater complexity). The C_I was highest in the healthy young adult and lowest in the older adult with chronic brain damage due to a history of a hemispheric middle cerebral artery infarction (i.e., stroke). It is also of note that C_I was independent of the traditional measure of maximum sway range.

by targeting the physiologic complexity that often characterizes healthy system function.

In this paper we aim to provide empirical evidence regarding the relationship between measured physiologic complexity and system functionality, as specifically defined by the capacity to adapt to physiologic stresses or perturbations. We then examine the potential for and functional implications of interventions designed to restore the loss of physiologic complexity with advancing age. First, however, we discuss several important caveats regarding measurement and task constraints that one must consider when interpreting this research.

2. Physiologic complexity: measurement issues and task constraints

When examining the relationship between the complexity of a system's dynamics and the functionality of that system, one must consider 1) the metric(s) used to quantify complexity, 2) the sampling frequency and window of observation, 3) the impact of task constraints, and 4) the type of stimulus, stressor or perturbation being examined.

First, there are numerous metrics available that each quantify different aspects of the complex, nonlinear properties of physiologic time-series, including entropy (Pincus, 1991) and multiscale entropy analyses (MSE) (Costa et al., 2002), detrended fluctuation analysis (Peng et al., 1995), fractal dimension (Higuchi, 1988) and recurrence plot analysis (Webber and Zbilut, 1994), among others. It is of note that traditional entropy-based metrics estimate the degree of regularity or orderliness of a time-series *on a single scale of time*. As discussed in depth by Costa et al. (2002), these metrics do not capture the structural characteristics of a signal over multiple scales of time, and thus, may fail to characterize physiologic complexity. To overcome this issue, new metrics have been developed such as MSE, which utilizes a technique called "coarse-graining" to enable estimation of a signal's regularity over multiple time scales (Fig. 2). Still, Goldberger et al. (2002b) has argued that no single statistical measure can fully capture the complexity of a physiological system. Insensitivity of a particular metric to the effects of group, experimental condition or intervention does not necessarily imply that other metrics will also lack meaningful relationships to the functionality or rehabilitative potential of the system in question.

Second, estimation of a signal's complexity is dependent upon both the sampling frequency and window of observation. The contribution of high-frequency fluctuations may be omitted if the sampling frequency is not sufficiently high, whereas the contribution of low-frequency fluctuations may be overlooked if the measurement window is not sufficiently long. An example of the latter can be seen in the regulation of heart rate. Endogenous circadian rhythms influence heart rate on time scales of approximately 24 h. When measured over days or weeks, these low-frequency fluctuations contribute to the physiologic complexity of heart rate dynamics (Hu et al., 2008). On the other hand, if heart rate is observed over an observation window of several hours, circadian influences will cause a "drift" or "nonstationarity" in heart rate; i.e., the statistical distribution of the signal will change over time. Such nonstationarities—whether stemming from important physiological processes, measurement error or noise—significantly affect complexity metrics and should be detrended (Peng et al., 2009). In addition to clouding inter-study comparisons, therefore, these issues must be considered when drawing conclusions regarding the functional implications of complexity as estimated from finite physiological time-series.

Third, the constraints within which a system operates may influence the functional implications of physiologic complexity. For example, in several studies examining the dynamics of force output of the finger (Sosnoff and Newell, 2008; Vaillancourt and Newell, 2002, 2003), subjects were asked to match either constant or time-varying target forces with their index finger by pressing on a load cell, and were provided with real-time continuous visual feedback from a computer screen. Younger adults performed each task with less error than older adults. Yet, compared to older adults, the force dynamics produced by younger adults were also *more* complex in the constant force condition, and *less* complex in the time-varying force condition, as quantified by approximate entropy

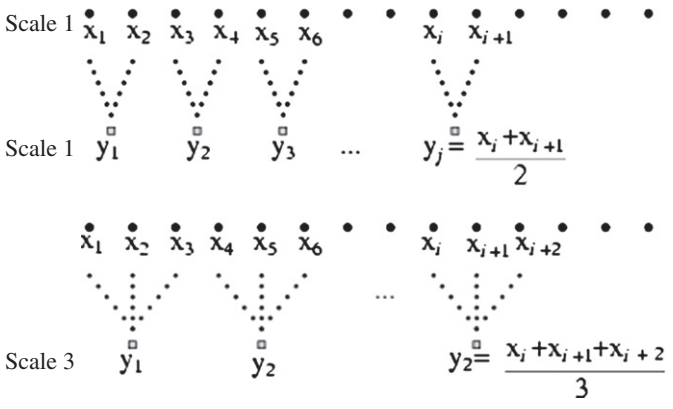

Fig. 2. Schematic illustration of the coarse-graining procedure utilized in multiscale entropy analysis (adapted from Costa et al., 2002). Consecutive time-series are constructed from the original time-series (scale 1) by averaging successively increasing number of data points in non-overlapping windows. Here, coarse-grained time-series capturing time scale two and three are shown. Entropy of each coarse-grained series is then calculated to estimate the degree of irregularity over multiple scales of time. See Fig. 3 for an example of multiscale entropy analysis of physiological data.