Physiological complexity: influence of ageing, disease and neuromuscular fatigue on muscle force and torque fluctuations

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Running title: Complexity of neuromuscular output

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New findings

What is the topic of this review?

We review physiological complexity in muscle force and torque fluctuations; specifically, we focus on the quantification of complexity, how neuromuscular complexity is altered by perturbations and the potential mechanism underlying changes in neuromuscular complexity.

What advances does it highlight?

We highlight the necessity to calculate both magnitude- and complexity-based measures for the thorough evaluation of force/torque fluctuations. We also highlight the need for further research on neuromuscular complexity, particularly how it relates to the performance of functional activities (e.g. manual dexterity, balance, locomotion).

Abstract

Physiological time-series produce inherently complex fluctuations. In the last 30 years, methods have been developed to characterise these fluctuations, and have revealed that such fluctuations contain information about the function of the system producing them. Two broad classes of metrics are used: 1) those which quantify the regularity of the signal (e.g. entropy metrics); and 2) those which quantify the fractal properties of the signal (e.g. detrended fluctuation analysis). Using these techniques, it has been demonstrated that aging results in a loss of complexity in the time-series of a multitude of signals, including heart rate, respiration, gait and, crucially, muscle force or torque output. This suggests that as the body ages, physiological systems become less adaptable (i.e. the systems' ability to respond rapidly to a changing external environment is diminished). More recently, it has been shown that neuromuscular fatigue causes a substantial loss of muscle torque complexity, a process that can be observed in a few minutes, rather than the decades it requires the same system to degrade with aging. The loss of torque complexity with neuromuscular fatigue appears to occur exclusively above the critical torque (at least for tasks lasting up to 30 minutes). The loss of torque complexity can be exacerbated with previous exercise of the same limb, and reduced by the administration of caffeine, suggesting both peripheral and central mechanisms contribute to this loss. The mechanisms underpinning the loss of complexity are not known but may be related to altered motor unit behaviour as the muscle fatigues.

Key words: ageing, complexity, neuromuscular fatigue, fractal, muscle force/torque

Introduction

One of the great challenges of the life sciences in the 21st century is to understand the 'emergent' properties of biological systems. Emergent phenomena are those producing system behaviours that cannot be predicted or explained by examining the system's components in isolation (Macklem, 2009). The concept of emergence is of importance to physiology, because system level function is an expression of the interactions of a large number of component parts. These interactions can produce unexpected and often nonlinear system behaviours (Lipsitz and Goldberger, 1992). The neuromuscular system, in particular, expresses these features, as it is composed of various types of excitable cells (motor cortical neurones, spinal motoneurons, muscle fibres, muscle afferents) whose purpose is to generate the muscular forces required to successfully perform motor tasks. Ideally, this results in smooth and accurate force (or torque) production across a joint, and thus the desired movement patterns. However, even in health, joint torque fluctuates in a seemingly random fashion during muscle contraction. These fluctuations have long been regarded as unwanted system noise, or a reflection of an underlying pathology (such as Parkinsonian tremor; Vaillancourt *et al*., 2001). More recently, however, the 'structure' or 'complexity' of these fluctuations have been acknowledged to provide key information about the state of the system (Vaillancourt and Newell, 2003; Pethick *et al*., 2015). In short, healthy physiological systems fluctuate in a predictably complex fashion (Peng *et al*., 2009). Understanding how these fluctuations change when the neuromuscular system is perturbed, particularly during neuromuscular fatigue, is a central aim of this review.

In this review, we provide a detailed examination of complexity measures as they relate to neuromuscular outputs and function. In doing this, we do not assume any underlying mathematical knowledge and aim to provide a gentle introduction to the field. We first describe

the quantification of complexity, and how this differs from traditional magnitude-based measures of time-series fluctuations. We then provide evidence regarding how neuromuscular output complexity is altered with various acute and chronic perturbations and outline potential mechanisms for such changes in neuromuscular output complexity. We finish by addressing future research directions necessary to increase our understanding of complexity in neuromuscular output and the implications of changes in neuromuscular output complexity.

1. What is physiological complexity?

Healthy physiologic systems are characterised by the interaction of multiple components and feedback loops operating over a range of temporal and spatial scales (Goldberger *et al*., 2002a). This results in outputs characterised by constant inherent fluctuations, even under resting conditions (Lipsitz and Goldberger, 1992). Such fluctuations have long been regarded as unwanted noise, which disturbs the balance of the system of origin and is associated with pathology (Goldberger *et al*., 2002a). However, it is now increasingly recognised that these fluctuations are not noise and, instead, contain "hidden information" regarding the underlying state and functionality of the system of origin (Goldberger *et al*., 2002a; Peng *et al*., 2009).

Traditionally, fluctuations in physiological outputs have been quantified according to their *magnitude*, using measures such as the standard deviation and coefficient of variation (Slifkin and Newell, 1999). These magnitude-based measures assume that fluctuations are random, with each data point completely independent of past and future values. However, fluctuations in physiological outputs can also be quantified according to their structure (i.e. how the output evolves over time; Pincus, 1991), with this quantification of structure being independent from the magnitude of fluctuations. Analysis of the structure, or "complexity", of physiological

123 outputs began with the study of heart rate (Kaplan *et al*., 1991), which demonstrates irregular,
124 self-similar fluctuations over multiple orders of temporal magnitude (i.e. seconds, minutes,
125 hours) under resting conditions. Subsequent studies have found numerous other physiological
126 outputs (including, *inter alia*, respiratory frequency and gait) to be characterised by irregular
127 non-random fluctuations, temporal irreversibility and long-range (fractal) correlations under
128 basal conditions (Hausdorff *et al*., 1995; Bruce, 1996). Importantly, these characteristics cannot
129 be quantified by traditional magnitude-based metrics. Thus, complexity measures can provide
130 information additional to, and distinct from, that provided by magnitude-based measures
131 (Slifkin and Newell, 1999). Indeed, complexity measures are capable of detecting subtle
132 changes undetected by more classical time-series measures, e.g. changes in heart rate with
133 ageing (Lipsitz and Goldberger, 1992), postural tremor in Parkinson's disease (Vaillancourt
134 and Newell, 2000) and torque output during neuromuscular fatigue in otherwise healthy adults
135 (Figure 1) can occur in the absence of any change in the magnitude of variability. Moreover,
136 the observation that non-random fluctuations are seen across a wide range of healthy
137 physiological outputs under basal conditions indicates that such fluctuations are not noise, but
138 rather contain an underlying structure, which may have a role in system control (Goldberger *et*
139 *al*., 2002a).
140
141 The ubiquity of "complex" fluctuations in physiological outputs has led to the suggestion that
142 complexity is a hallmark of healthy physiological systems (Peng *et al*., 2009). The presence of
143 a complex output is believed to be *adaptive*, conferring the system with the flexibility to react
144 to physiologic stresses in an ever-changing environment (Lipsitz, 2002). For example, low
145 complexity in heart rate dynamics has been demonstrated to be a predictor of death after acute
146 myocardial infarction (Mäkikalio *et al*. 1999), while low complexity in postural sway has been
147 demonstrated to predict increased postural sway speed when increasing task difficulty (Manor

148 *et al*., 2010). Interestingly, it has been repeatedly demonstrated that ageing and disease can be
149 characterised by a progressive loss of complexity within the dynamics of physiological outputs
150 (for reviews see: Lipsitz and Goldberger, 1992; Manor and Lipsitz, 2013). This loss of
151 complexity is thought to be indicative of reduced system functionality and a diminished
152 capacity to respond to perturbations; in other words, a loss of adaptability (Peng *et al*., 2009;
153 Manor and Lipsitz, 2013).
154
155 One system for which constant fluctuations in its output are of particular relevance is the
156 neuromuscular system, where the presence of these fluctuations influences an individual's
157 capacity to achieve a desired force and produce an intended movement trajectory (Figure 2;
158 Enoka *et al*., 2003). Indeed, in sporting performance variability is thought to serve as a measure
159 of success in realising task goals (Slifkin and Newell, 1998). High variability is typically
160 thought of as being indicative of inconsistent and poor performance, whereas the absence of
161 variability is thought of as necessary for successful performance. Moreover, certain
162 pathologies, such as Parkinson's disease, are characterised by overt increases in neuromuscular
163 variability (Vaillancourt and Newell, 2000), which can compromise the ability to perform
164 activities of daily living. Fluctuations in neuromuscular output were long considered random
165 noise superimposed on the signal (Fitts, 1954), though research has now demonstrated that both
166 muscle force/torque (Slifkin and Newell, 1999) and the surface electromyogram (EMG; Gitter
167 and Czerniecki, 1995) are, in fact, characterised by a complex temporal structure. This
168 complexity is believed to reflect the ability to modulate motor output rapidly and accurately in
169 response to alterations in task demands (Vaillancourt and Newell, 2003). Any change in the
170 complexity of neuromuscular output therefore has the potential to compromise motor control
171 and limit task performance in a range of populations and contexts (Morrison and Newell, 2012;
172 Pethick *et al*., 2016). Recently, research has extended the "loss of complexity" hypothesis from

173 the chronic perturbations of ageing and disease to the more acute perturbation of neuromuscular
174 fatigue (Cashaback *et al*., 2013; Pethick *et al*., 2015).
175
176
177 **2. Quantifying complexity**
178
179 It is important to acknowledge the difference between magnitude-based and complexity-based
180 measures of fluctuations and variability. This is illustrated in Figure 1, which shows two
181 isometric torque time-series. Both time-series have nearly identical means and variances, but
182 very different *dynamics*. It is only through the use of measures examining the temporal
183 structure, or complexity, of these time-series (in this case approximate entropy and detrended
184 fluctuation analysis) that these signals can be differentiated.
185
186 Traditional measures of the magnitude of variability provide an index of the degree of deviation
187 from a fixed point within a time-series independently from the order of distribution (Slifkin
188 and Newell, 1999); with the standard deviation quantifying the absolute amount of variability
189 and the coefficient of variation quantifying the amount of variability normalised to the mean
190 of the time-series. However, such measures cannot quantify the temporal irregularity, time
191 irreversibility and long-range fractal correlations exhibited by physiological outputs (Pincus,
192 1991; Goldberger *et al*., 2002a). Measures of complexity, on the other hand, characterise the
193 moment-to-moment relationship between successive points in a time-series (Slifkin and
194 Newell, 1999). These complexity measures derive from non-linear dynamics and include those
195 drawn from information theory, which provide a measure of the apparent randomness or
196 regularity of an output (e.g. entropy statistics), and those drawn from fractal geometry, which
197 quantify the long-range correlations present in an output. These measures provide information

198 additional to, and distinct from, magnitude-based measures and are able to detect differences
199 in the dynamics of outputs that magnitude-based measures are insensitive to (Figure 1; Lipsitz
200 and Goldberger, 1992). No single statistical measure can, however, fully capture the
201 complexity of a physiological output, and it is recommended that multiple metrics, quantifying
202 different aspects of the output, are used to characterise complexity (Goldberger *et al*., 2002b).
203 The main variability and complexity measures used to characterise muscle force are
204 summarised in Table 1. For a comprehensive review of complexity measures and their
205 calculation, see Seely and Macklem (2004).
206
207 **2.1. Entropy statistics**
208
209 Entropy is embodied in the Second Law of Thermodynamics as a measure of disorder or
210 randomness that tends towards a maximum in an isolated system (Seely and Macklem, 2004).
211 Entropy in the present context is different. Specifically, Claude Shannon (1948) extended the
212 concept of entropy to his "information theory", in which entropy is thought of as the rate at
213 which information is produced. In information theory, a highly predictable/regular output has
214 low entropy, because little information is conveyed. For example, the output "HHHHH" has
215 low entropy compared to the output "HELLO", as there is less predictability, more irregularity
216 and more information conveyed in the letters of the second output.
217
218 Approximate entropy (ApEn) derives from Kolmogorov-Sinai entropy and was developed to
219 quantify the apparent randomness or regularity of an output (Pincus, 1991). The development
220 of ApEn was necessary because Kolmogorov-Sinai entropy and statistics derived from it
221 theoretically required noise-free data of infinite length. The ApEn family of statistics was
222 developed specifically to quantify the regularity of finite, noisy data sets often encountered in

biology. To measure the complexity of an output, ApEn evaluates time-series for patterns that recur. This is accomplished by evaluating a data sequence of length *m* (termed the template) and determining the likelihood that other sequences of the same length are similar (within a specific tolerance, *r*). Once the frequency of occurrence of repetitive runs is calculated, a measure of their prevalence (the negative natural logarithm of the conditional probability) is determined. ApEn measures the difference between the logarithmic frequencies of similar runs of length *m* and runs with length *m+1*. Low values (close to zero) indicate a smooth and/or periodic time-series (e.g. a sine wave), while higher values (close to 2) correspond to greater irregularity and complexity. It is important to note that high entropy values, such as that of white noise, are not necessarily *physiologically* complex. White noise, for example, is a random signal (each value is completely independent of previous and future values), in which all nonlinear interactions have been destroyed (Goldberger *et al*., 2002b) As such, other metrics that can detect and quantify the presence of long-range correlations in a time-series (see below) are required to fully characterise physiologic complexity (Goldberger *et al*., 2002b).

It has been acknowledged that an inherent bias exists within the ApEn calculation, because the algorithm counts each sequence as matching itself. As such, ApEn can be heavily dependent on the run length *m*, making it uniformly lower than expected for short runs, and resulting in it lacking relative consistency (Richman and Moorman, 2000). To reduce this bias, Richman and Moorman (2000) developed sample entropy (SampEn), which does not count self-matches. As with ApEn, a run length *m* and tolerance window *r* must be specified to compute SampEn. SampEn is precisely the negative natural logarithm of the conditional probability that two sequences similar for *m* points remain similar at the next point, without allowing self-matches. As with ApEn, SampEn quantifies a continuum from 0 to 2, with values close to zero indicating high regularity and low complexity, and values approaching 2 indicating low regularity and

high complexity. Practically, SampEn is more consistent for short data lengths (<1000; Yentes *et al*., 2013), but for acquisition of more than 1000 data points, there is no meaningful difference between ApEn and SampEn: the use of either will yield the same interpretation. Results from our laboratory have indicated that, in the case of isometric muscle torque output, ApEn and SampEn do not differ when 5000 data points are used in their calculation (Pethick *et al*., 2015).

Traditional entropy statistics, such as ApEn and SampEn, evaluate the regularity of a time-series on only one timescale, the shortest one, and ignore other scales. Such metrics are, therefore, unable to capture the structural characteristics of a time-series over the multiple time scales inherent to healthy physiologic dynamics (Costa *et al*., 2002). To overcome this limitation, multiscale entropy (MSE) has been developed. In MSE, the original time-series is coarse-grained to derive multiple signals, each of which captures system dynamics on a given scale (Kang *et al*., 2009) The SampEn of each of these signals is then calculated in the same way as described above. The MSE curve is then obtained by plotting each of the SampEn values as a function of scale, with the area under this curve constituting the complexity index. As with ApEn and SampEn, high values over a wide range of time scales indicate high complexity.

2.2. Fractal geometry

It was Benoit Mandelbrot who first realised that principles of fractal geometry (seen, for example, in the von-Koch snowflake) could be applied to the complex shapes and forms of nature. The classic example he proposed was the coastline of Britain, which appears to maintain the same degree of "ruggedness" regardless of the size or detail of the map studied (Mandelbrot, 1967). In other words, the coastline is self-similar across multiple length-scales. (Strictly

speaking, the coastline possesses self-affinity, since the details of the coastline are not exact copies as the scale changes). From a physiological point of view, it was realised that many anatomic structures, such as the bronchial tree and vascular system, exhibit fractal-like geometry and self-similarity (Lipsitz and Goldberger, 1992). Applied to physiological outputs, an output is fractal if, as a function of time, it undergoes characteristic changes that are similar regardless of the time interval over which the observations are made. Fractal outputs are said to generate irregular fluctuations across multiple timescales (Figure 2), analogous to objects possessing geometrically similar structures across multiple length-scales (Goldberger *et al*., 2002a).

Detrended fluctuation analysis (DFA) is a measure of the long-range fractal correlations within a physiological output that are due to the intrinsic properties of the system (Peng *et al*., 1994). In the DFA algorithm, the time-series of interest is integrated, then divided into boxes of equal length, n, and a least squares line (representing the trend in each box) is fitted. The integrated time-series is detrended by subtracting the local trend in each box, and the root mean square of this integrated, detrended series, $F(n)$, is calculated. This calculation is then repeated over all timescales or box-sizes. The slope of the line relating $\log F(n)$ to $\log n$ determines the DFA α scaling exponent (Goldberger *et al*., 2002a). The DFA α exponent provides a measure of the noise "colour" and "roughness" of a time-series and theoretically ranges from ~0.5 to ~1.5 for physiological outputs (Goldberger *et al*., 2002a). For a more in-depth explanation of the calculation of DFA, please refer to Seely and Macklem (2004). When $\alpha < 0.5$, values are anti-correlated and when $\alpha = 0.5$, each value in a time-series is completely random and independent from previous values (i.e. white noise). When $\alpha > 0.5$, each value is not completely random and is correlated, to some extent, with previous values. An α exponent of 1.0 is consistent with statistically self-similar fluctuations, long-range correlations and 1/f (pink) noise, where power

298 is inversely proportional to frequency. An α exponent of 1.5 is indicative of Brownian noise,
299 and a smooth output with long-term memory (a so-called "random walk"; Goldberger *et al*.,
300 2002a).
301
302
303 **3. Evidence of complexity in neuromuscular output**
304
305 It has long been known that the force (or torque) produced by a contracting muscle is neither
306 smooth nor steady; rather, it constantly fluctuates around an average value (Enoka *et al*., 2003).
307 It has been repeatedly demonstrated that the magnitude of force fluctuations, measured using
308 the standard deviation, increases in proportion to the mean force exerted and as more motor
309 units are recruited (Jones *et al*., 2002). The coefficient of variation, on the other hand, is greatest
310 at low contraction intensities, decreases as the force exerted increases and then remains
311 constant over much of the operating range of the muscle (Jones *et al*., 2002; Hamilton *et al*.,
312 2004). Furthermore, the magnitude of these fluctuations is affected by ageing (Enoka *et al*.,
313 2003) and neuromuscular fatigue (Hunter and Enoka, 2003). The presence of such fluctuations
314 has significant functional impact, decreasing our ability to achieve a desired force and produce
315 intended movement trajectories (Enoka *et al*., 2003). As such, fluctuations in force output have
316 usually been interpreted as unwanted noise superimposed upon a signal (Stergiou and Decker,
317 2011). If these fluctuations were noise, then it would be anticipated that each point in a time-
318 series would be independent of the next point and the structure of that time-series would
319 approximate Gaussian noise (Slifkin and Newell, 1999). However, numerous studies over the
320 last 20 years have demonstrated that this is most certainly not the case.
321
322 The first evidence that fluctuations in muscle force output were distinguishable from noise
323 came from a study by Slifkin and Newell (1999), who demonstrated that the temporal structure

of isometric index finger flexion force was dependent on contraction intensity. During contractions ranging from 5-95% of participants maximum voluntary contraction (MVC), the magnitude of fluctuations (measured using the standard deviation) exhibited the well-established increase as force requirements increased, whilst there was an inverted-U shaped relationship between contraction intensity and complexity. Specifically, ApEn increased (indicating increasing complexity) as contraction intensity increased, reaching a projected maximum at ~40% MVC, and then decreased (indicating decreasing complexity) with further increases in contraction intensity (Figure 4 in Slifkin and Newell, 1999). The authors suggested that up to 30-40% MVC, force was increased solely by increasing the number of active motor units and thereafter the generation of further force was dependent solely on modulation of discharge rates. They went on to speculate that the peak in complexity at 40% MVC was the point of maximum system adaptability and information transfer because at this point force could be modulated by either motor unit recruitment or rate coding. However, De Luca *et al*. (1982) demonstrated that, in the case of the first dorsal interosseous, below 40% MVC increased force occurs via concurrent modulation of both recruitment and discharge rates, whereas above that point increased discharge rates are the dominant (but not only) means of force increase (De Luca *et al*., 1982). Nevertheless, Forrest *et al*. (2014) also reported differences in ApEn in the first dorsal interosseous below and above 40% MVC that were concomitant with the previously reported change from concurrent modulation of recruitment and discharge rates to dominance of discharge rates. However, whether changes in ApEn are actually caused by changes in force gradation strategies or are simply coincident with them has yet to be tested experimentally.

A similar inverted-U shaped relationship has been demonstrated for isometric elbow flexion (Svendsen and Madeleine, 2010), though further studies have called into question the exact

shape of the contraction intensity-complexity relationship. We have, for example, observed that complexity decreases linearly with an increase in target force in the knee extensors (Pethick *et al*., 2016; Pethick *et al*., 2021a). Forrest *et al*. (2014) have demonstrated that differences in the shape of the relationship between studies can be attributed to different ApEn signal acquisition/processing choices (e.g. sampling frequency and the value of *r*, the tolerance of accepting matches). Nevertheless, it is clear that the fluctuations in muscle force are not, as once assumed, random noise, but rather have a complex temporal structure that is thought to be indicative of a flexible and adaptive output (Figures 1, 2 and 3).

Studies have also shown that the EMG output is a complex signal composed of both deterministic and stochastic components (Potvin and Brown, 2004). Initial studies demonstrated that the surface EMG interference pattern possessed a fractal dimension which increased with increasing contraction intensity, indicating an output becoming more complex and less self-similar (Gitter and Czerniecki, 1995). This finding has subsequently been confirmed using entropic measures, with McManus *et al*. (2019) finding increases in SampEn for increasing contraction intensities between 10 and 40% MVC, and Cashaback *et al*. (2013) finding greater MSE during contractions at 70% compared to 40% MVC. It has, however, been suggested that surface EMG, particularly in bipolar configuration, is not appropriate for determination of complexity (Pethick *et al*., 2019). Indeed, amplitude cancellation and summation in the EMG signal results in a significant loss of signal content (Keenen *et al*., 2006). Thus, it has been suggested that either intramuscular or high-density EMG, from which individual motor unit spike trains can be decomposed, may represent the optimal way to analyse the complexity of EMG output. Accordingly, it has been demonstrated that the ApEn of individual motor unit discharge rates, measured using intramuscular EMG, increases with increasing contraction intensity and increasing discharge rates (Vaillancourt *et al*., 2002).

The complex output exhibited by muscle force is purported to confer the neuromuscular system with the adaptability and flexibility to react to physiological stresses (Lipsitz, 2002). Specifically, it reflects the ability to modulate motor output rapidly and accurately in response to alterations in task demands (Vaillancourt and Newell, 2003). It must be noted that, despite the purported significance of neuromuscular output complexity, there is currently limited empirical evidence linking it to system functionality. For example, no study to date has sought to determine how much variance in the performance of functional tasks force complexity accounts for. This is in contrast to the magnitude of force variability, which has been demonstrated to account for significant variance in the performance of manual dexterity (Feeney *et al*., 2018) and balance tasks (Davis *et al*., 2020). Importantly, the adaptive significance of complexity has been demonstrated for other physiological outputs, which suggests that it will also have significance for the neuromuscular system. For example, Manor *et al*. (2010) demonstrated that lower postural sway complexity during quiet standing predicted greater increases in postural sway speed when going from quiet standing to a dual task condition (i.e. when increasing task difficulty).

The lack of empirical evidence relating neuromuscular output complexity to clinical tests of motor function has, arguably, limited the uptake of complexity measures in research. As discussed at the end of this review, addressing this issue represents an important and necessary goal of future research. Nevertheless, changes in neuromuscular output complexity have been demonstrated concomitant to a variety of perturbations, both acute and chronic, and are speculated to contribute to the reduced functionality characteristic of these perturbations.

4. Loss of complexity hypothesis

A complex physiological output (e.g. muscle force/torque, heart rate, respiration, gait, etc.) is thought to be a hallmark of a healthy system (Lipsitz and Goldberger, 1992; Peng *et al*., 2009), conferring the system with the adaptability and flexibility to react to physiological stresses in an ever-changing environment (Lipsitz, 2002). Whilst healthy physiological systems exhibit complex outputs, systems under greater relative stress exhibit decreased complexity (Goldberger *et al*., 2002a). This was first observed in cardiovascular dynamics and ageing (Kaplan *et al*., 1991), with old adults (aged 62-90 years) displaying reduced ApEn in R-R interval compared to young adults (aged 21-35 years). Such findings led Lipsitz and Goldberger (1992) to propose the "loss of complexity" hypothesis, which states that the ageing process from adulthood to senescence is characterised by a progressive loss of complexity within the dynamics of physiological outputs. It has subsequently been demonstrated that this loss of complexity is not just evident in ageing, but also in disease (Goldberger *et al*., 2002a).

4.1. Loss of neuromuscular complexity with ageing

In the context of the neuromuscular system, ageing from adulthood to senescence is characterised by a compromised ability to generate task-relevant and precise levels of force (Morrison and Newell, 2012). Indeed, there have been numerous investigations demonstrating an age-related increase in the magnitude of force fluctuations (see Enoka *et al*., 2003 and Oomen and van Diëen *et al*., 2017 for reviews).

The first study to consider the importance of potential age-related changes in the complexity of muscle force fluctuations was by Vaillancourt and Newell (2003). They observed a progressive decline in the complexity of index finger abduction force (measured using ApEn

and DFA α) during low-intensity isometric contractions (performed at 5, 10, 20 and 40% MVC) from young adults (aged 20-24 years) to old adults (aged 60-69 years) and older-old adults (aged 75-90 years). These findings have been confirmed by several subsequent studies (Sosnoff and Newell 2006a; 2008) and extended to low-intensity (15-40% MVC) isometric knee extension contractions (Fiogbé *et al*., 2018). Taken together, these findings indicate that an age-induced loss of muscle force complexity affects both small upper limb muscles associated with fine motor skills and large lower limb muscles associated with locomotion. Furthermore, Challis (2006) demonstrated decreased muscle torque complexity in older adults (aged ~73 years) compared to young adults (aged ~23 years) during maximal isometric plantarflexion contractions. This is particularly important as age-induced increases in the magnitude of force fluctuations are typically only seen at low contraction intensities (Enoka *et al*., 2003; Oomen and van Diëen *et al*., 2017), suggesting that complexity-based measures may exhibit greater sensitivity to changes in force/torque fluctuations than magnitude-based measures. It has also been demonstrated that unilateral strength training can increase force complexity (measured using SampEn) in both the trained and untrained limbs in older adults (Keogh *et al*., 2007), indicating that muscular and neural adaptations may both contribute to age-related changes in complexity.

Interestingly, it has been demonstrated that the age-related change in complexity can be *bi-directional*, depending on the constraints and requirements of the action performed. Whilst older adults demonstrate decreased muscle force complexity during constant-force (i.e. isometric) tasks, they demonstrate increased complexity during sine-wave tracking tasks (Vaillancourt and Newell, 2003; Vaillancourt *et al*., 2004). It has been suggested that in tasks where the dynamic is constant, more complexity is required to maintain optimal output. During such tasks, an age-related decrease in complexity is evident because additional degrees of

freedom must be introduced in order to realise the goal of no motion; something which older adults find difficult to accomplish (Vaillancourt and Newell, 2003). In contrast, in tasks where the dynamic is oscillatory, less complexity is required to closely track oscillations and reduce error (Vaillancourt and Newell, 2003).

Similar age-induced losses of complexity have been observed in the surface EMG of various muscles. Arjunan and Kumar (2013) found that the fractal dimension of biceps brachii surface EMG was reduced in older adults during maximal and submaximal isometric contractions. Moreover, Kang and Dingwell (2016) observed lower complexity, measured using MSE, in the vastus lateralis and biceps femoris surface EMG during treadmill walking. Importantly, this extends the loss of complexity from isometric contractions to the type of dynamic contractions characteristic of activities of daily living.

4.2. Loss of neuromuscular complexity with disease

Numerous disease processes are associated with changes in neuromuscular output, with an obvious example being Parkinson's disease, which is characterised by increased tremor (McAuley and Marsden, 2000). Research has demonstrated decreased complexity, measured by decreased ApEn and SampEn, in both tremor and isometric force output in Parkinson's disease patients (Vaillancourt and Newell, 2000; Rose *et al*., 2013). Importantly, such decreases in complexity have been observed in the absence of differences in the magnitude of tremor/force (Vaillancourt and Newell, 2000; Vaillancourt *et al*., 2001), providing further evidence that complexity-based measures may be more sensitive than magnitude-based measures. Moreover, such findings suggest that complexity-based measures could be a useful tool in the detection of Parkinson's disease, particularly in its early stages. Furthermore, an inverse correlation between decreases in the SampEn of knee extensor surface EMG and

476 increases in the Movement Disorders Society Unified Parkinson's Disease Rating Scale has
477 recently been observed (Flood *et al*., 2019). Importantly, this is, to date, the only clinical motor
478 function measure that has been correlated with changes in neuromuscular output complexity,
479 though this does come with the caveats associated with analysing complexity of bipolar surface
480 EMG discussed above. Further neurological conditions, such as stroke (Chow and Stokic,
481 2014) and Multiple Sclerosis (Morrison *et* al., 2013), have been demonstrated to result in
482 decreased force complexity compared with healthy controls. It has also recently been observed
483 that the peripheral neuropathy associated with diabetes results in decreased complexity of
484 muscle force and surface EMG outputs during lower limb contractions (Suda *et al*., 2017).
485
486
487 **4.3.Loss of neuromuscular complexity with neuromuscular fatigue**
488
489 During submaximal contractions performed to the limit of tolerance, maximal force generating
490 capacity decreases, consequent to central and peripheral perturbations (Gandevia, 2001). This
491 loss of force generating capacity necessitates an increase in the number of activated motor units
492 and their firing frequency in order to sustain the demands of a submaximal task (Carpentier *et*
493 *al*., 2001; Adam and De Luca, 2005). Such compensatory adjustments have long been
494 associated with an increase in the magnitude of force fluctuations (Hunter and Enoka, 2003).
495 Recent research has extended these changes in the magnitude of force fluctuations to the
496 structure of fluctuations, thus further extending the "loss of complexity" hypothesis from
497 ageing and disease to acute neuromuscular fatigue.
498
499 We conducted the first study to investigate neuromuscular fatigue-induced changes in muscle
500 torque complexity during both maximal and submaximal (40% MVC) intermittent isometric
501 contractions, observing a decrease in knee extensor torque complexity (measured using ApEn,

SampEn and DFA α; Figure 1; Pethick *et al*., 2015). This study demonstrated, based on the purported significance of complexity, that the impact of neuromuscular fatigue is not limited to force-generating capacity but extends to the adaptability of the neuromuscular system to external perturbation. We postulate that the development of neuromuscular fatigue makes targeting errors more difficult to correct, thus limiting the ability to explore control solutions (i.e. a loss of adaptability) and, consequently, to maintain task demands. Subsequently, we demonstrated that muscle torque complexity decreases only during contractions above the critical torque (i.e. in the severe exercise domain). No changes were observed during contractions below the critical torque (i.e. in the heavy exercise domain; Figure 3A; Pethick *et al*., 2016). Such results provided the first evidence that metrics derived from non-linear dynamics are able to identify changes in neuromuscular behaviour coincident with the critical torque. Moreover, the muscle metabolic profile and the development of peripheral fatigue cannot be stabilized above the critical torque/power (Poole *et al*., 2016). In other words, the response of muscle torque complexity to exercise below and above the critical torque is strikingly similar to other variables implicated in the development of fatigue. Whether these similarities reflect causal relationships between peripheral fatigue and motor control remains to be established.

We have also demonstrated that circulatory occlusion following a bout of fatiguing knee extensor contractions completely abolishes recovery of muscle torque complexity (Pethick *et al*., 2018a). Indeed, at the end of the occlusion, when a second bout of contractions commenced, muscle torque complexity was no different than at task failure following the first bout of contractions. Given that circulatory occlusion holds the muscle ischaemic, preventing the recovery of the muscle metabolic milieu, this finding seems, at first glance, to support the supposition that the failure of complexity to demonstrate any recovery was mediated by this

maintained peripheral fatigue. However, both voluntary activation and vastus lateralis average rectified EMG (arEMG) also failed to demonstrate any recovery at the onset of the second bout of contractions. This suggests that the neuromuscular fatigue-induced loss of muscle torque complexity is an integrated response to both peripheral and central processes.

Various ergogenic aids and interventions have been found to affect the neuromuscular fatigue-induced loss of muscle torque complexity. Caffeine ingestion has been demonstrated to slow the loss of muscle torque complexity (Figure 3C), consequent to a slowed rate of decrease in torque generating capacity and a slowed development of central fatigue (i.e. attenuated the decrease in voluntary activation; Pethick *et al*., 2018b). Similarly, ischaemic pre-conditioning (an intervention consisting of alternating bouts of muscle ischaemia and reperfusion prior to exercise) has been demonstrated to slow the loss of muscle torque complexity (Figure 3D), which was accompanied by a slowing in the rates of increase in muscle oxygen consumption and arEMG (Pethick *et al*., 2021b). Such findings indicate that the loss of muscle torque complexity, and the adaptability of the neuromuscular system it reflects, is tightly coupled to the neuromuscular fatigue process (i.e. loss of torque generating capacity, development of central and peripheral), even after experimental manipulation. It has also been demonstrated that a neuromuscular fatigue test performed with an additional cognitive load (a self-regulated mathematical task) decreased muscle force complexity during the beginning and middle of the task, compared with the same test performed with no cognitive load (Cruz-Montecinos *et al*., 2018).

Interestingly, in our work on the neuromuscular fatigue-induced loss of muscle torque complexity, the point of task failure (i.e. exhaustion) has been associated with consistently low levels of complexity (Pethick *et al*., 2015; Pethick *et al*., 2016; Pethick *et a*., 2018a). Such

552 consistently low levels of complexity at task failure suggests that a loss of complexity could be
553 a contributor to the "sensory tolerance limit" being reached at task failure (Hureau et al., 2018).
554 The "sensory tolerance limit" proposes that the termination of severe-intensity exercise is
555 associated with substantial and consistent changes in the muscle metabolic profile, which has
556 been hypothesised to activate group III and IV afferent fibres (Amann and Dempsey, 2008).
557 These, in turn, inhibit central motor drive. Recent work by Martinez-Valdes *et al*. (2020)
558 observed an increase in motor unit recruitment and firing rate as task failure was approached
559 during sustained isometric knee extensor contractions at 30% MVC. However, the peak firing
560 rate at task failure did not reach levels seen during a non-fatiguing contraction at 50% MVC,
561 suggesting firing rate saturated at a lower frequency compared with the higher force non-
562 fatiguing contraction.
563
564 Further research has demonstrated differing recovery kinetics of muscle torque complexity
565 following fatiguing isometric exercise and muscle damaging eccentric exercise that reduced
566 MVC torque to the same extent (Pethick *et al*., 2019b). Following fatiguing isometric exercise,
567 recovery of muscle torque complexity was complete 10 minutes after the cessation of exercise.
568 In contrast, muscle torque complexity remained depressed for 60 minutes following the
569 cessation of eccentric exercise and only recovered back to its baseline level 24 hours after
570 exercise (Figure 3B). These findings indicate that, in addition to the prolonged depression of
571 muscle force/torque that follows muscle damaging eccentric exercise, there is also a prolonged
572 loss of adaptability in neuromuscular output.
573
574 Research from our laboratory has observed no change in ApEn or DFA α of surface EMG
575 during either fatiguing maximal or submaximal isometric contractions (Pethick *et al*., 2019a).
576 This led us to speculate that the bipolar surface EMG setup and analysis of the rectified EMG

we used were not appropriate for analysing complexity and that analysing motor unit spike trains (obtained via either intramuscular or high-density EMG) would be necessary for such analysis. Nevertheless, neuromuscular fatigue-induced losses of complexity have been observed in the surface EMG of various muscles. Cashaback *et al*. (2013) demonstrated a decrease in MSE near exhaustion during a fatiguing biceps brachii contraction and concluded that neuromuscular fatigue degraded fast-acting regulatory mechanisms of force control. The authors went on to speculate that this degradation of regulatory mechanisms could result from a combination of decreases in motor unit action potential velocity and amplitude, and reductions in motor unit discharge rates.

Alterations in neuromuscular complexity have been also been observed during dynamic exercise. Enders *et al*. (2015) observed increased regularity of surface EMG, measured using entropic half-life (a variant of SampEn), with increased power output during cycling. It was concluded that the increased difficulty of higher workloads led to a more constrained solution space, allowing less randomness in the execution of the task and fewer available solutions for the neuromuscular system to successfully complete the task. This decreased complexity with increased absolute task demands is similar to the decreased complexity with the increased relative task demands imposed by the development of neuromuscular fatigue.

5. Mechanistic basis for the loss of neuromuscular complexity

Motor units are the functional unit of the neuromuscular system, transducing synaptic input from the central nervous system into muscle force and movement. Motor neurons receive both independent and common synaptic input from a multitude of sources, though the independent

components are filtered out and only the common component is transmitted to the output of the motor neurons (Farina and Negro, 2015). The common input comprises the exact command for optimal force generation and a noise component (termed common noise) that determines oscillations of discharge rates of motor neurons at a common low frequency (Farina and Negro, 2015). Force fluctuations, and accuracy of force control, are determined mainly by variance in common noise (Negro *et al*., 2009; Farina and Negro, 2015). Indeed, it has been demonstrated that the magnitude of fluctuations in isometric force output are coherent with the common component of the cumulative motor unit spike train (Negro *et al*., 2009; Thompson *et al*., 2018). It has been speculated that common synaptic input must also contribute to the temporal structure of neuromuscular output (Taylor *et al*., 2003; Pethick *et al*., 2016). However, to date, no study has *directly* explored the relationships between common synaptic input and muscle force/torque complexity.

The first (indirect) evidence for the role of common synaptic input in the age-related decrease in neuromuscular output came from Sturman *et al*. (2005), who demonstrated a progressive decrease in the complexity of loaded postural tremor across young and three groups of progressively older adults. This decrease in tremor complexity was accompanied by, and linearly related to, an increase in peak-tremor EMG coherence, which provides a predictive measure of motor unit synchronisation (Halliday *et al*., 1999). As such, the authors speculated that the ageing process enhanced motor unit synchronisation, which then decreased the complexity of postural tremor. It must be noted, though, that measures of motor unit synchronisation are a poor proxy of common synaptic input (Farina and Negro, 2015).Nevertheless, common synaptic input to muscle has been demonstrated to increase with

626 increasing age and to be highly coherent with the age-related increased magnitude of force
627 fluctuations (Castronovo *et al*., 2018).
628
629 Further evidence of a relationship between motor unit synchronisation and neuromuscular
630 complexity comes from a study on simulated EMG signals, which found that decreases in the
631 fractal dimension (corresponding to decreased complexity) were highly related to simulation-
632 induced increases in motor unit synchronisation (Mesin *et al*., 2009). Subsequent experimental
633 studies demonstrated decreases in the fractal dimension of surface EMG with neuromuscular
634 fatigue, which were interpreted as increases in motor unit synchronisation (Beretta-Piccoli *et*
635 *al*., 2015; Boccia *et al*., 2015). More recently, it has been shown that common synaptic input
636 to muscles increases when the net excitatory drive to muscle increases, whether this is a
637 consequence of increased contractile intensity or the development of neuromuscular fatigue
638 (Castronovo *et al*., 2015). We have, therefore, speculated that at any neuromuscular fatigue-
639 induced (or contraction intensity-induced) increase in common synaptic input should be
640 reflected in a decrease in muscle torque complexity (Pethick *et al*., 2018a). As common
641 synaptic input increases with the development of neuromuscular fatigue, there is an increase in
642 common oscillations of motor neuron discharge rates (Castronovo *et al*., 2015) which would
643 result in increased regularity (i.e. decreased complexity) of the force output. However, direct
644 measurement of individual motor unit spike trains (using high-density EMG) is necessary to
645 confirm this link between common synaptic input and muscle torque complexity.
646
647 The observation of a neuromuscular fatigue-induced loss of muscle torque complexity only
648 during contractions performed above the critical torque suggests that fatigue mechanisms
649 particular to such contractions, i.e. metabolite-mediated peripheral fatigue (Burnley *et al*.,
650 2012), are involved. However, a loss of muscle torque complexity is likely to be a consequence

651 of changes in common synaptic input to motor neurons (Pethick *et al*., 2016). As such, in the
652 case of neuromuscular fatigue above the critical torque, we have postulated that metabolite-
653 mediated peripheral fatigue is a pre-requisite for central adjustments that act on the motor unit
654 pool, which are then responsible for the increase in common synaptic input and loss of torque
655 complexity (Pethick *et al*., 2016; Pethick *et al*., 2018a).
656
657
658 **6. Future research directions**
659
660 The presence of a complex output is purported to reflect the ability of a system to explore and
661 achieve a variety of control solutions (Peng *et al*., 2009). Low levels of complexity are,
662 therefore, reflective of a decreased ability to adapt to perturbation (Peng *et al*., 2009), with this
663 empirically demonstrated in the ageing postural control system (Manor *et al*., 2010). The
664 changes in the complexity of neuromuscular output seen with ageing from adulthood to
665 senescence, disease and neuromuscular fatigue are similarly thought to reflect a reduction in
666 the adaptive capacity and exploratory freedom of the neuromuscular system. As such, reduced
667 levels of complexity have been hypothesised to negatively impact motor control and co-
668 ordination (Cortes *et al*., 2014) and increase the risk of failing motor tasks (Pethick *et al*., 2018).
669 This could result in poorer performance of skilled movements in athletic and sporting events
670 (Forestier and Nougier, 1998), and perhaps more importantly, have a detrimental effect on
671 functional movements, such as gait, in older adults (Buzzi *et al*., 2003). However, no research
672 to date has investigated whether this might occur. It is imperative that future research establish
673 empirical relationships between neuromuscular output complexity and the performance of
674 motor tasks, such as manual dexterity, balance and locomotion, which represent the

675 fundamental motor skills from which all other motor skills are thought to derive (Newell,
676 2020).
677
678 Several studies on ageing and disease have demonstrated changes in complexity in the absence
679 of changes in the magnitude of fluctuations (Vaillancourt and Newell, 2000; Fiogbé *et al*.,
680 2018), suggesting that they may hold potential in detecting sub-clinical changes in motor
681 control. Furthermore, complexity measures have been demonstrated to be tightly coupled to
682 the neuromuscular fatigue process (Pethick *et al*., 2018) and exhibit the same exercise intensity
683 domain-specific behaviours as measures such as $\dot{V}O_2$, blood [lactate] and pH (Poole *et al*.,
684 2016; Pethick *et al*., 2016; Pethick *et al*., 2020). Taken together, such findings indicate that
685 muscle force/torque complexity may provide a sensitive index of the state of the neuromuscular
686 system, providing information in addition to, and in some instances beyond, traditional
687 measures of signal variability. However, to date research has only demonstrated empirically
688 that EMG complexity provides an index of the state of the neuromuscular system in
689 Parkinson's disease. This does, however, come with the caveat that surface EMG may not be
690 appropriate for characterising complexity due to the loss of signal content brought about by
691 amplitude cancellation and summation (Keenan *et al*., 2006; Pethick *et al*., 2019a). Further
692 research is necessary to determine to what extent complexity of either muscle force or EMG
693 actually reflect the state of the neuromuscular system and whether this extends to other
694 perturbations.
695
696
697 Just as important as determining the functional relevance of neuromuscular output complexity
698 is determining the mechanism responsible for it and for its decrease with perturbation. We
699 speculate common synaptic input to be responsible, based on the observation that it increases

(Castronovo *et al*., 2015; Castronovo *et al*., 2018) as a result of perturbations that decrease muscle force/torque or EMG complexity (Vaillancourt *et al*., 2003; Pethick *et al*., 2015). No study has, however, simultaneously measured both complexity and common synaptic input. Future studies must simultaneously measure motor unit spike trains (using high-density EMG), from which common synaptic input can be estimated, and muscle force/torque output. As mentioned previously, analysing complexity of the motor unit spike trains may also provide useful insight. Assuming common synaptic input is responsible for neuromuscular output complexity, a further challenge is determining what exactly causes it to change. For example, the mechanism responsible for the increased common synaptic input with ageing remains to be determined (Castronovo *et al*., 2018).

In our work on the neuromuscular fatigue-induced loss of muscle torque complexity, the point of task failure (i.e. "exhaustion") is associated with consistently low levels of complexity (Pethick *et al*., 2015; Pethick *et al*., 2016). This suggests that low complexity in neuromuscular output might be responsible, in part, for the inability to continue physical tasks (Pethick *et al*., 2016; Pethick *et al*., 2018b). Although the evidence is so far correlative, there are physiologically plausible mechanisms that explain this, and which can be viewed in the following way. Low torque complexity indicates low adaptability in motor control. Targeting errors in isometric contractions are more difficult to correct, and the additional effort of doing so may be beyond the neuromuscular system's capabilities or the participant's willingness to continue. From this perspective, task failure could be better described as a neuromuscular fatigue-induced loss of motor control rather than a loss of motor "capacity" (as reflected in the task-specific MVC torque; Pethick *et al*., 2018a). To test this intriguing possibility, future research could create a regression model for predicting endurance time based upon complexity.

7. Conclusion

In this review, we have shown that fluctuations in neuromuscular output can be altered by ageing, disease and neuromuscular fatigue. Quantification of time-series regularity (entropy metrics) and noise colour (detrended fluctuation analysis) provides crucial additional information about the state of the system producing these fluctuations. Such fluctuations appear to be an emergent property of physiological function, born of the multiplicity of components involved in system control. Ageing degrades the complexity of physiological outputs generally by reducing system capacity and connectivity. Disease states also have this effect but often for a much more specific set of system components (e.g. the loss of specific neuronal populations in Parkinson's disease). Neuromuscular fatigue also appears to reduce physiological complexity, but in this case without any loss of system structure. Instead, the changes in complexity appear to be related to a loss of peripheral function and the central adjustments made in order to compensate for the loss of force-generating capacity.

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Declarations

Funding: This work was supported by a Research Project Grant from the Leverhulme Trust (RPG-2016-440).

Conflicts of interest/competing interests: None.

Authors' contributions: All authors were involved in the conception of the review and contributed to the writing and critical revision of the manuscript.

Figure legends

Figure 1. Torque time series from the beginning (top panel) and end (bottom panel) of a time to task failure test in a young participant. Note the substantial loss of complexity (shown by the decrease in ApEn and the increase in DFA α) despite unchanged mean and SD torque. Such changes in complexity in the absence of a change in variability indicates that complexity measures may be more sensitive to subtle changes than classical time-series measures.

Figure 2. Representative knee-extensor torque time series during intermittent isometric contractions at a target of 40% MVC. Each panel shows the same contraction with decreasing time and torque scales. Panel A shows a series of five contractions. Panel B zooms in to focus on the second of the five contractions. Panel C zooms further in to focus on just the fluctuations around the target torque in the that contraction. Notice the fluctuations evident in the time-series in spite of the participant attempting to maintain a constant torque output and the self-similarity of these fluctuations are the time and torque scales are changed.. In panel C, the fluctuations can clearly be seen to vary in amplitude and frequency (i.e. they contain a complex temporal structure). Complexity metrics (e.g. ApEn, SampEn, DFA α) are used to characterise the structure in such time-series.

Figure 3. Key findings from experimental studies on the effect of neuromuscular fatigue on the complexity of knee extensor torque output. Panel A shows the influence of exercise intensity on the time course of torque complexity (Pethick *et al*., 2016). In this study, a fatigue-induced loss of complexity was only observed during contractions above the critical torque, suggesting that peripheral fatigue is a prerequisite for such losses. In Panel B, long-lasting

peripheral derangements wrought by eccentric contractions depressed torque complexity for more than 60 min, whereas complexity following isometric contractions recovered within 10 min of task failure (TF; Pethick *et al*., 2019b). Panel C shows the influence of caffeine administration on the progressive loss of torque complexity (Pethick *et al*., 2018b). In this study, both voluntary activation and torque complexity were elevated at TF with caffeine ingestion compared to placebo, suggesting a small but significant role for central processes in the loss of complexity with neuromuscular fatigue. Finally, in Panel D, ischaemic preconditioning resulted in a blunting of the rate of loss of torque complexity with fatigue (Pethick *et al*., 2021). Collectively, these results suggest that the fatigue-induced loss of torque complexity is a response that is peculiar to exercise performed in the severe-intensity domain (above CT), but that both central and peripheral factors contribute to such losses.

Figure 1

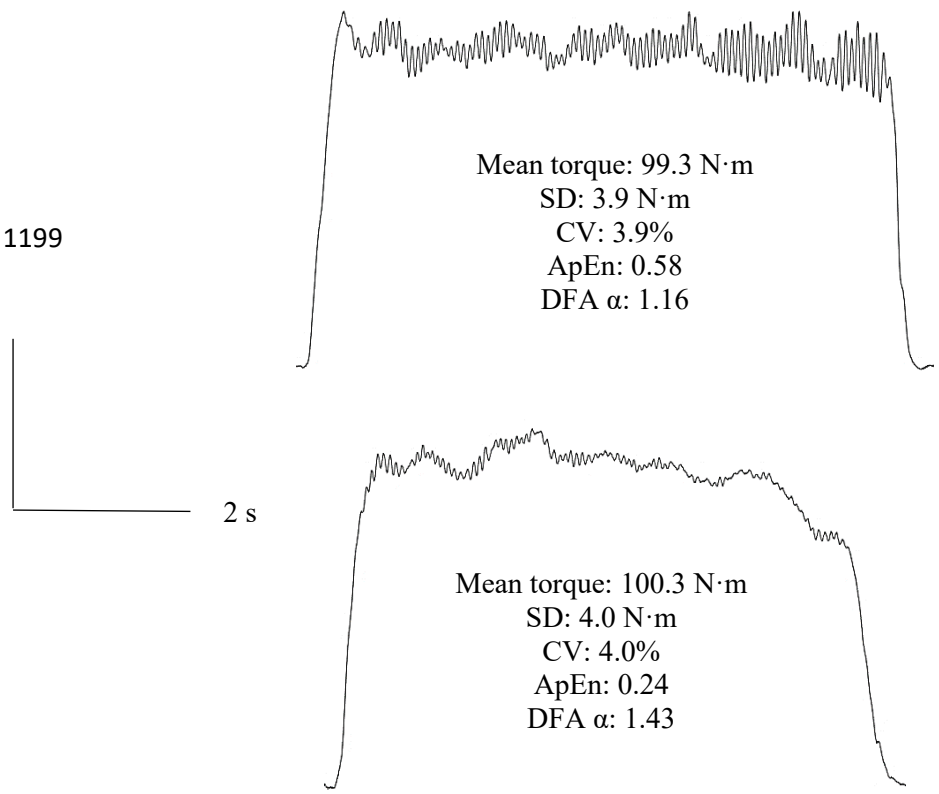

Mean torque: 99.3 N·m
SD: 3.9 N·m
CV: 3.9%
ApEn: 0.58
DFA α: 1.16
5
2 s
Mean torque: 100.3 N·m
SD: 4.0 N·m
CV: 4.0%
ApEn: 0.24
DFA α: 1.43

Figure 2

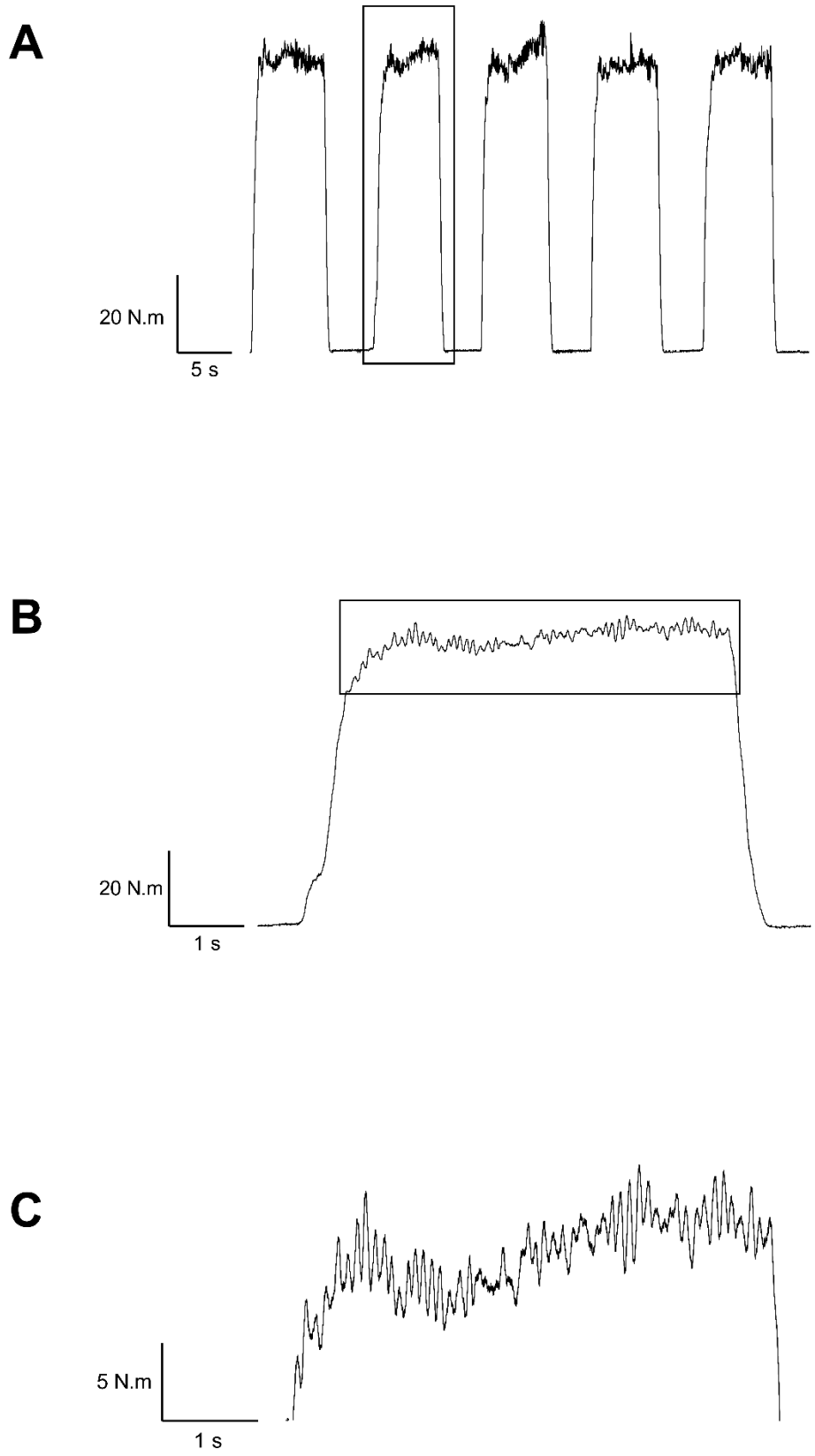
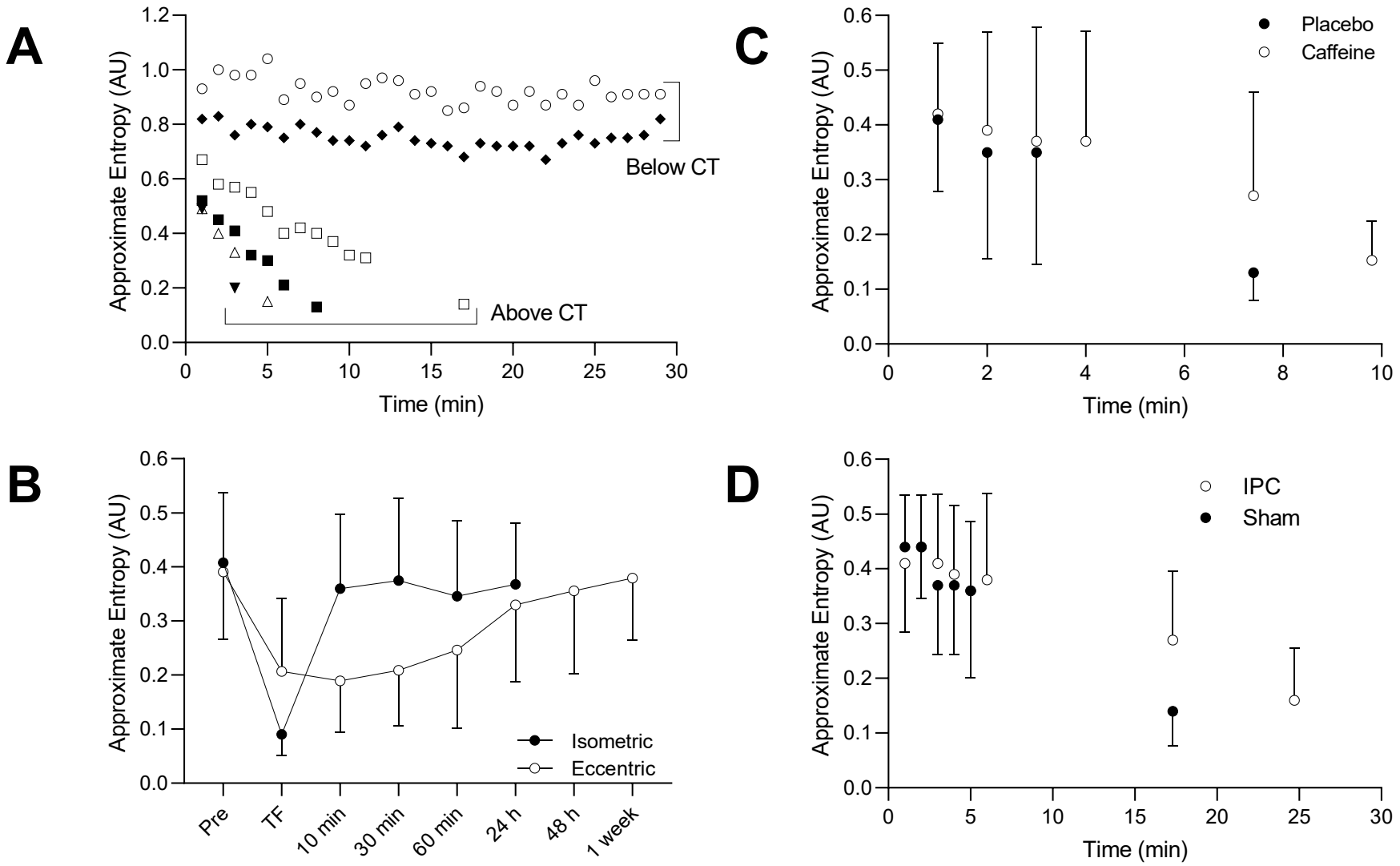


Figure 3


A
Approximate Entropy (AU)
Time (min)
Below CT
Above CT
B
Approximate Entropy (AU)
Isometric
Eccentric
Pre
TF
10 min
30 min
60 min
24 h
48 h
1 week
C
Approximate Entropy (AU)
Time (min)
Placebo
Caffeine
D
Approximate Entropy (AU)
Time (min)
IPC
Sham

Measure	What does it quantify?	Calculation requirements	Output	Interpretation	Advantages	Limitations
Standard deviation (SD)	Absolute amount of variability in a time-series	Time series of x data points	Value expressed in unit of measurement of time-series (e.g. N.m when applied to torque)	Greater values are indicative of decreased force steadiness	Easy to calculate; proven clinically useful	Fails to discriminate time-series with distinctly different dynamics
Coefficient of variation (CV)	Amount of variability in a time-series normalised to the mean	Standard deviation and mean of a time-series	Value expressed as a percentage	Greater values are indicative of decreased force steadiness	Easy to calculate; proven clinically useful	Fails to discriminate time-series with distinctly different dynamics
Approximate entropy (ApEn)	Randomness/ regularity of a time-series	**The number of data points in a time-series (*N*), the length of the template to be compared (*m*) and the tolerance for accepting matching templates (*r*), typically set to between 10 and 25% of the standard deviation**	Value expressed in arbitrary units, ranging from 0 to 2	Low values are indicative of regular/periodic time-series; high values are indicative of irregular/random time-series	Characterises temporal structure (i.e. dynamics) of time-series	Dependent on number of data points in time-series (*N*); counts self-matches; evaluates regularity on only one time scale; needs to be complemented by other measures
Sample entropy (SampEn)	Randomness/ regularity of a time-series	**The number of data points in a time-series (*N*), the length of the template to be compared (*m*) and the tolerance for accepting matching templates (*r*), typically set to between 10 and 25% of the standard deviation**	Value expressed in arbitrary units, ranging from 0 to 2	Low values are indicative of regular/periodic time-series; high values are indicative of irregular/random time-series	Characterises temporal structure (i.e. dynamics) of time-series; greater relative consistency than ApEn	Evaluates regularity on only one time scale; needs to be complemented by other measures

Multiscale entropy (MSE)	Randomness/ regularity of a time-series	The original time-series is coarse grained to derive multiple signals; the sample entropy of each coarse grained signal is then analysed	Sample entropy of each course-grained time-series plotted; area under curve is complexity index	Low values over a large range of time scales are indicative of regular/periodic outputs; high values over a large range of time scales are indicative of irregular/random time-series	Characterises temporal structure (i.e. dynamics) of time-series; evaluates regularity on multiple time scales	Limited application to force and EMG time-series
Detrended fluctuation analysis (DFA)	Long-range fractal correlations and noise colour in a time-series	The time-series is integrated then detrended; detrended series separated into boxes of equal length *n*; regression analysis at different box sizes; calculation of α exponent achieved by linear regression of all previous results (i.e. repeated over all time scales)	α scaling exponent, ranging from ~0.5 to ~1.5	α = 0.5 is indicative of white noise (values are random and independent), α = 1.0 is indicative of pink noise (statistically self-similar fluctuations, long-range correlations), α = 1.5 is indicative of Brownian noise (long-term memory)	Identifies intrinsic variation; evaluates across time scales	Requires large data sets

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