True Responders in Exercise Science: Novel Insight from Replicated Cross-over Designs

A legitimate question when reviewing research is "does this apply to *me*?". Experiments in exercise science can be limited by ostensibly small sample sizes yet often benefit from cross-over designs whereby each participant serves as their own control. This combination carries the duty and opportunity for a comprehensive illustration of all available data. The customary bar chart can overlook the distribution of individual observations (i.e. the infamous 'dynamite plunger plot'; 3), which *may* be defensible when summarising group effects in large parallel trials but is rarely justified in cross-over designs for which the consistency of individual responses should be illustrated (e.g. dot plots with paired scores coupled).

It is undoubtedly positive that more publications are now presenting individual data but an emerging trend has been to take this a step further and plot observations in series, ranked according to the direction and magnitude of differences between a single treatment-control contrast. Data presented in this way are often (erroneously) interpreted as evidence that some people respond differently than others to the same treatment and so can be categorized as positive-, negative- or non-responders. Such graphical illustrations do not necessarily infer any more than error in measurement and/or natural test-retest oscillations in response (1). However, true individual differences in response can be established by entirely repeating the treatment and control trials (i.e. a replicated cross-over design; 7), although the time-consuming and labour-intensive nature of doing so may explain why this approach has never before been exploited in the exercise sciences.

In this issue of *Medicine & Science in Sports & Exercise*, Goltz *et al* have for the first time utilized a replicated cross-over design to follow-up on previous observations of individual variation in appetite suppression following exercise (6). Specifically, the data they now report not only confirm those earlier findings but go much further by verifying the reproducibility of those responses and, most importantly, establish that true inter-individual differences do indeed exist in response to exercise (5). The fact that these were *physiological* responses is especially important considering the recent fashion for more personalized treatments and the focus on genetic testing as a means to predict the efficacy of interventions on an individual basis (2). Genotype is just one of many possible contributors to individual variability in response (4), whereas measuring phenotype in terms of the physiology underlying that response integrates multiple sources of variability and is more directly translated to the outcomes of interest (e.g. Goltz *et al* link gut hormones to hunger).

Replicated cross-over designs should therefore be considered by exercise scientists planning cross-over trials. So many methods to boost the scientific quality and future value of an experiment are limited by available equipment and/or technical expertise, whereas the replication of trial arms by definition involves no alternate resources beyond those already required for the single treatment-control contrast, plus more efficient use of those existing resources than independently replicating an equivalent study. It is therefore commendable when workload is multiplied to address fundamental issues such as reproducibility and inter-individual differences using a replicated cross-over design, rather than adding separate treatment arms or conducting another study. This commentary highlights the recognition deserved for the investment and sacrifices that enable such advancement in current understanding.

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References

1. Atkinson, G and Batterham, AM, True and false interindividual differences in the physiological response to an intervention. *Exp Physiol*, 2015; 100: 577-88.

2. Betts, JA and Gonzalez, JT, Personalised nutrition: What makes you so special? *Nutrition Bulletin*, 2016; 41: 353-359.
3. Drummond, GB and Vowler, SL, Show the data, don't conceal them. *J Physiol*, 2011; 589: 1861-3.
4. Dworkin, RH, et al., Interpreting patient treatment response in analgesic clinical trials: implications for genotyping, phenotyping, and personalized pain treatment. *Pain*, 2014; 155: 457-60.
5. Goltz, FR, et al., Interindividual Responses of Appetite to Acute Exercise: A Replicated Crossover Study. *Med Sci Sports Exerc*, 2017.
6. King, JA, et al., Individual Variation in Hunger, Energy Intake, and Ghrelin Responses to Acute Exercise. *Med Sci Sports Exerc*, 2017; 49: 1219-1228.
7. Senn, S, Rolfe, K and Julious, SA, Investigating variability in patient response to treatment--a case study from a replicate cross-over study. *Stat Methods Med Res*, 2011; 20: 657-66.