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1	Recovery after stroke: not so proportional after all?				
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23 ABSTRACT

The proportional recovery rule asserts that most stroke survivors recover a fixed proportion of lost
function. To the extent that this is true, recovery from stroke can be predicted accurately from
baseline measures of acute post-stroke impairment alone. Reports that baseline scores explain more

- 27 than 80%, and sometimes more than 90%, of the variance in the patients' recoveries, are rapidly
- 28 accumulating. Here, we show that these headline effect sizes are likely inflated.

29 The key effects in this literature are typically expressed as, or reducible to, correlation 30 coefficients between baseline scores and recovery (outcome scores minus baseline scores). Using 31 formal analyses and simulations, we show that these correlations will be extreme when outcomes 32 are less variable than baselines, which they often will be in practice regardless of the real relationship between outcomes and baselines. We show that these effect sizes are likely to be over-33 34 optimistic in every empirical study that we found, which reported enough information for us to 35 make the judgement, and argue that the same is likely to be true in other studies as well. The 36 implication is that recovery after stroke may not be as proportional as recent studies suggest.

38 1. INTRODUCTION

39 Clinicians and researchers have long known stroke patients' initial symptom severity is related to 40 their longer term outcomes (Jongbloed, 1986). Recent studies have suggested that this relationship 41 is stronger than previously thought: that most patients recover a fixed proportion of lost function. 42 Studies supporting this 'proportional recovery rule' are rapidly accumulating (Stinear, 2017): in five 43 studies since 2015 (Byblow et al., 2015; Feng et al., 2015; Winters et al., 2015; Buch et al., 2016; 44 Stinear et al., 2017b), researchers used the Fugl-Meyer scale to assess patients' upper limb motor 45 impairment within two weeks of stroke onset ('baselines'), and then again either three or six months 46 post-stroke ('outcomes'). The results were consistent with earlier observations (Prabhakaran et al., 47 2007; Zarahn et al., 2011) that most patients recovered ~70% of lost function. Taken together, these 48 studies report highly consistent recovery in over 500 patients, across different countries with 49 different approaches to rehabilitation, regardless of the patients' ages at stroke onset, stroke type, 50 sex, or therapy dose (Stinear, 2017). And there is increasing evidence that the rule also captures 51 recovery from post-stroke impairments of lower limb function (Smith et al., 2017), attention (Marchi 52 et al., 2017; Winters et al., 2017), and language (Lazar et al., 2010; Marchi et al., 2017), and may 53 even apply generally across cognitive domains (Ramsey et al., 2017). Even rats appear to recover 54 proportionally after stroke (Jeffers et al., 2018).

55 Strikingly, many of these studies report that the baseline scores predict 80%-90%, or more, 56 of the variance in empirical recovery. When predicting behavioural responses in humans, these 57 effect sizes are unprecedented. Recently, Winters and colleagues (2015) reported that recovery 58 predicted from baseline scores explained 94% of the variance in the empirical recovery of 146 stroke 59 patients. Like many related reports (Stinear, 2017), this study also reported a group of (65) 'non-60 fitters', who did not make the predicted recovery. But if non-fitters can be distinguished at the acute 61 stage, as this and other studies suggest (Stinear, 2017), the implication is that we can predict most 62 patients' recovery near-perfectly, given baseline scores alone. Stroke researchers are used to 63 thinking of recovery as a complex, multi-factorial process (Nelson et al., 2016). If the proportional 64 recovery rule is as powerful as it seems, post-stroke recovery is simpler and more consistent than 65 previously thought.

In what follows, we argue that the empirical support for proportional recovery is weaker
than it seems. These results are typically expressed as, or reducible to, correlations between
baselines and recovery (outcomes minus baselines). These analyses pose well-known challenges,
which have been discussed by statisticians for decades (Lord, 1956; Oldham, 1962; Cronbach and
Furby, 1970; Hayes, 1988; Tu *et al.*, 2005). Much of this discussion is focused on problems induced

by measurement noise, and measurement noise is also the focus of the only prior application of that discussion to the proportional recovery rule (Krakauer and Marshall, 2015). Here, we argue that empirical studies of proportional recovery after stroke are likely confounded entirely regardless of measurement noise.

Our argument is that: (a) correlations between baselines and recovery are spurious when they are stronger than correlations between baselines and outcomes; (b) this is likely when outcomes are less variable than baselines; which (c) will often happen in practice, whether or not recovery is proportional. This argument follows from a formal analysis of correlations between baselines and recovery, which we introduce in section 2 and illustrate with examples. We then employ that analysis to re-examining the empirical support for the proportional recovery rule in section 3.

82

83 2. THE RELATIONSHIPS BETWEEN BASELINES, OUTCOMES, AND RECOVERY

For the sake of brevity, we define 'baselines' = X, 'outcomes' = Y, and 'change' (recovery) = Δ : i.e. Y minus X. The 'correlation between baselines and outcomes' is r(X,Y), and the 'correlation between baselines and change' is r(X, Δ). Finally, we define the 'variability ratio' as the ratio of the standard deviation (σ) of Y to the standard deviation of X: σ_Y/σ_X .

88 X and Y are construed as lists of scores, with each entry being the performance of a single 89 patient at the specified time point. We assume that higher scores imply better performance, so 90 $r(X,\Delta)$ will be negative if recovery is proportional (to lost function). One can equally substitute 'lost 91 function' (e.g. maximum score minus actual score), for 'baseline score', but while this makes $r(X,\Delta)$ 92 positive if recovery is proportional, it is otherwise equivalent.

93

94 2.1. Strong correlations imply the potential for accurate predictions

Strong correlations between any two variables typically imply that we can use either variable to predict the other. Out-of-sample predictions should tend toward the least-squares line defined by the original (in-sample) correlation. Some empirical studies employ this logic to derive 'predicted recovery' ($p\Delta$) from the least-squares line for r(X, Δ), reporting r($p\Delta$, Δ) instead of r(X, Δ) (Winters *et al.*, 2015; Marchi *et al.*, 2017). Since the magnitudes of r(X, Δ) and r($p\Delta$, Δ) are the same by definition (see proposition 8, Appendix A, and Figure 1), the preference for either expression over the other is arguably cosmetic. Nevertheless, the correlation between predicted and empirical data is a common measure
 of predictive accuracy: the stronger the correlation, the better the predictions. Very strong
 correlations are unusual when predicting behavioural performance in humans – both because
 behaviour itself is complex, and because of measurement noise in behavioural assessment. Once

- 106 $r(p\Delta, \Delta) > \sim 0.95$, for example (Winters *et al.*, 2015), this prognostic problem has seemingly been
- 107 'solved' more accurately than many might have thought possible.
- 108

109 2.2. $r(X,\Delta)$ is spurious when stronger than r(X,Y)

- 110 Recovery is precisely the difference between baselines and outcomes. When $r(X,\Delta)$ is strong,
- 111 implying that we can predict recovery accurately given baselines, it is tempting to assume that we
- 112 can also predict outcomes equally accurately, by simply adding predicted recovery to baselines.
- 113 More formally, the assumption is that $r(X+p\Delta,Y) \approx r(p\Delta,\Delta)$. This assumption is wrong.
- 114 In fact, $r(X+p\Delta,Y) \approx r(X,Y)$ (see appendix A, proposition 8, and Figure 1). When recovery is 115 predicted from baselines, the correlation between 'baselines plus predicted recovery' and outcomes, 116 is never stronger than the correlation between baselines and outcomes. When $r(X,\Delta)$ is stronger 117 than r(X,Y), $r(X,\Delta)$ is *spurious*, because it encourages an over-optimistic impression of how
- 118 predictable outcomes are, given baselines.
- 119

120 2.3. The canonical example of spurious $r(X,\Delta)$

121 The canonical example of spurious $r(X,\Delta)$ is when X and Y are independent random variables with the 122 same variance: $\sigma_Y/\sigma_X \approx 1$ and $r(X,Y) \approx 0$, but $r(X,\Delta) \approx -0.71$ (Oldham, 1962). This $r(X,\Delta)$ suggests that 123 we can predict recovery relatively well, but we cannot use 'predicted recovery' to predict outcomes 124 equally well (see Figure 1).

- 125
- 126

--Figure 1--

127

128 Krakauer and Marshall (2015) recently argued that this scenario has little relevance to (most) 129 empirical studies of recovery after stroke. This is because: (a) spurious $r(X,\Delta)$ only emerge here when 130 r(X,Y) is weak; and (b) empirical r(X,Y) are usually strong, because X and Y are dependent, repeated 131 measurements from the same patients. If spurious $r(X,\Delta)$ only or mainly emerged when $\sigma_Y/\sigma_X \approx 1$ and 132 $r(X,Y) \approx 0$, they might indeed be irrelevant in practice. Unfortunately, spurious $r(X,\Delta)$ also emerge in 133 another scenario, which is very common in studies of recovery after stroke.

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135 2.4. Spurious $r(X,\Delta)$ are likely when σ_Y/σ_X is small

136 For any X and Y, it can be shown that:

137

$$r(X,\Delta) = \frac{\sigma_Y \cdot r(X,Y) - \sigma_X}{\sqrt{\sigma_Y^2 + \sigma_X^2 - 2 \cdot \sigma_X \cdot \sigma_Y \cdot r(X,Y)}} \quad (\text{Equation 1})$$

138 A formal proof of Equation 1 is provided in Appendix A (proposition 4 and theorem 1; also 139 see (Oldham, 1962)); its consequence is that $r(X,\Delta)$ is a function of r(X,Y) and σ_Y/σ_X . To illustrate that 140 function, we performed a series of simulations (see Appendix B) in which r(X,Y) and σ_Y/σ_X were 141 varied independently. Figure 1 illustrates the results: a surface relating $r(X,\Delta)$ to r(X,Y) and σ_Y/σ_X . 142 Figure 2 illustrates example recovery data at six points of interest on that surface.

143

145

Point A corresponds to the canonical example of spurious $r(X,\Delta)$, introduced in the last section: i.e., $\sigma_Y/\sigma_X \approx 1$ and $r(X,Y) \approx 0$, but $r(X,\Delta) \approx -0.71$ (see Figure 3a). At point B, $\sigma_Y/\sigma_X \approx 1$ and r(X,Y)is strong, so recovery is approximately constant (Figure 3b) and $r(X,\Delta) \approx 0$, consistent with the view that strong r(X,Y) curtail spurious $r(X,\Delta)$ (Krakauer and Marshall, 2015). However the situation is more complex when σ_Y/σ_X is more skewed.

When σ_Y/σ_X is large, Y contributes more variance to Δ , and $r(X, \Delta) \approx r(X,Y)$; this is Regime 1. 151 152 Points C and D illustrate the convergence (Figure 3c-d). Data like this might suggest recovery 153 proportional to *spared* function. By contrast, when σ_Y/σ_X is small, X contributes more variance to Y-X, 154 and $r(X,\Delta) \approx r(X,-X)$: i.e. -1 (see appendix A, theorem 2); this is Regime 2, where the confound 155 emerges. Point E corresponds to data predicted by the proportional recovery rule: all patients 156 recover exactly 70% of lost function (Figure 2e). Here, $\sigma_{\rm Y}/\sigma_{\rm X}$ is already small enough (0.3) to be 157 dangerous: after randomly shuffling Y, $r(X,Y) \approx 0$, but $r(X,\Delta)$ is almost unaffected (Point F, and Figure 158 3f). Even if patients do recover proportionally, in other words, empirical data may enter territory, on 159 the surface in Figure 2, where spurious $r(X,\Delta)$ are likely.

161 2.5. σ_{Y}/σ_{X} will often be small, whether or not recovery is proportional

162 Proportional recovery implies small $\sigma_{\rm Y}/\sigma_{\rm X}$, but small $\sigma_{\rm Y}/\sigma_{\rm X}$ does not imply proportional recovery; for 163 example, constant recovery with ceiling effects will produce the same effect. To illustrate this, we 164 ran 1,000 simulations in which: (i) 1,000 baseline scores are drawn randomly with uniform probability from the range 0-65 (i.e. impaired on the 66-point Fugl-Meyer upper-extremity scale); (ii) 165 166 outcome scores were calculated as the baseline scores plus half the scale's range (33); and (iii) 167 outcome scores greater than 66 were set to 66 (i.e. a hard ceiling). Mean r(X,Y) and $r(X,\Delta)$ were 168 calculated both before and after shuffling the outcomes data for each simulation. After shuffling, $r(X,Y) \approx 0$ and $r(X,\Delta) = -0.88$: ceiling effects make σ_Y/σ_X small enough to encourage spurious $r(X,\Delta)$. 169 170 And just as importantly, before shuffling, r(X,Y) = 0.89 and $r(X,\Delta) = -0.90$: even when $r(X,\Delta)$ is not 171 spurious (because r(X,Y) is similarly strong), we cannot conclude that recovery is really proportional.

172

173 3. RE-EXAMINING THE EMPIRICAL LITERATURE ON PROPORTIONAL RECOVERY

174 The relationships between r(X,Y), r(X, Δ) and σ_{Y}/σ_{X} , merit a re-examination of the empirical support 175 for the proportional recovery rule. In the only study we found, which reports individuals' behavioural 176 data, Zarahn and colleagues (2011) consider 30 patients' recoveries from hemiparesis after stroke. 177 Across the whole sample, r(X,Y) = 0.80 and $r(X,\Delta) = -0.49$; after removing 7 non-fitters: r(X,Y) = 0.75178 and $r(X,\Delta) = -0.95$. Removing the non-fitters increases the apparent predictability of recovery but 179 reduces the predictability of outcomes (and reduces σ_{Y}/σ_{X} from 0.88 to 0.36). Notably, the residuals 180 for both correlations are identical (see Figure 4), and in fact this is always true (see Appendix A, 181 proposition 10). $r(X,\Delta)$ has the same errors as r(X,Y), but a larger effect size: $r(X,\Delta)$ is over-optimistic. 182

183

--Insert Figure 3--

184

We can also use Equation 1 to reinterpret studies that do not report individual patient data. One example is the first study to report proportional recovery from aphasia after stroke (Lazar *et al.*, 2010). Here, $r(X,\Delta) \approx -0.9$ and $\sigma_Y/\sigma_X \approx 0.48$; Equation 1 implies that r(X,Y) was either ~0.78 or zero. Similarly, in the recent study of proportional recovery in rats (Jeffers *et al.*, 2018), $\sigma_Y/\sigma_X \approx 0.8$, and $r(X,\Delta) \approx -0.71$; Equation 1 implies that r(X,Y) was either much stronger (>0.95) or considerably weaker (~0.29) than $r(X,\Delta)$. In both cases, $r(X,\Delta)$ tells us less than expected about how predictable outcomes really were, given baseline scores.

- 192 Many recent studies report inter-quartile ranges (IQRs), rather than standard deviations, for 193 the baselines and outcomes of patients deemed to recover proportionally. Accepting some room for 194 error, we can also estimate $\sigma_{\rm Y}/\sigma_{\rm X}$ from those IQRs. In one case (Winters *et al.*, 2015), r(X, Δ) = -0.97 195 and $\sigma_{\rm Y}/\sigma_{\rm X}$ = 0.158, while in another (Veerbeek *et al.*, 2018), $\sigma_{\rm Y}/\sigma_{\rm X}$ = 0.438 and r(X, Δ) \approx -0.88. In both 196 cases, Equation 1 implies that r(X, Δ) would be at least that strong as that reported, regardless of 197 r(X,Y): here again, the headline effect sizes do not tell us how predictable outcomes actually are, 198 given baseline scores.
- 199 Many studies in this literature only relate baselines to recovery through multivariable 200 models (Buch et al., 2016; Marchi et al., 2017; Winters et al., 2017); in these studies, we cannot 201 demonstrate confounds directly with Equation 1. Nevertheless, these studies are also probably 202 confounded, because any inflation in one variable's effect size will inflate the multivariable model's 203 effect size as well. As discussed in section 2.5, empirical studies of recovery after stroke should tend 204 to encourage small $\sigma_{\rm Y}/\sigma_{\rm X}$, whether or not recovery is really proportional. Consequently, the null 205 hypothesis will rarely be that $r(X,\Delta) \approx 0$. For example, in the only multivariable modelling study, 206 which reports IQRs for its fitter-patients' baselines and outcomes (Stinear *et al.*, 2017c), $\sigma_Y/\sigma_X \approx 0.48$, 207 which implies that the weakest $r(X,\Delta)$ was -0.88, for any positive value of r(X,Y).
- Finally, while $r(X,\Delta)$ can be misleading if it is extreme relative to r(X,Y), the reverse is also true. One study in this literature which employs outcomes as the dependent variable, rather than recovery (Feng *et al.*, 2015), reports that $r(X,Y) \approx 0.8$ and $\sigma_Y/\sigma_X = 1.2$ in their 'combined' group of 76 patients. By Equation 1, $r(X,\Delta) = -0.05$: i.e. recovery was uncorrelated with baseline scores. These authors only report proportional recovery in a sub-sample of their patients (but not the information we need to re-examine that claim), but their full sample seems better described by constant recovery (as in Figure 3b).
- 215

216 4. Discussion

The proportional recovery rule is striking because it implies that recovery is simple and consistent across patients (non-fitters notwithstanding), and because that implication appears to be justified by strong empirical results (Stinear, 2017). We contend that the empirical support for the rule is weaker than it seems.

221 In summary, our argument is that $r(X,\Delta)$ is spurious when stronger than r(X,Y), and that the 222 conditions which encourage spurious $r(X,\Delta)$ will be common in empirical studies of recovery after 223 stroke, whether or not recovery is really proportional. Many empirical $r(X, \Delta)$ in this literature appear to be spurious in this sense. And in any case, strong $r(X,\Delta)$ are insufficient evidence for proportional recovery if they are *not* spurious (because they are accompanied by similarly strong r(X,Y)).

226 The only previous discussion of the risk of spurious $r(X,\Delta)$, in analyses of recovery after stroke, 227 (Krakauer and Marshall, 2015), concluded that this risk is small provided the tools used to measure 228 post-stroke impairment are reliable: i.e. so long as measurement noise is minimal. Crucially, our 229 analysis applies entirely regardless of measurement noise. We contend that the risk of spurious $r(X,\Delta)$ 230 is significant, if there are ceiling effects on the scale used to measure post-stroke impairment, and if 231 most patients improve between baseline and subsequent assessments. The criteria will usually be met 232 in practice, because every practical measurement of post-stroke impairment employs a finite scale, 233 and because non-fitters, who do not make the predicted recovery, are removed prior to calculating 234 r(X,∆).

235 We are not suggesting that there is anything wrong with the practice of distinguishing fitters 236 from non-fitters. Indeed, our results prove that this work may be valid regardless of our other 237 concerns. Non-fitters do not recover as predicted; by definition, they contribute the largest, negative 238 residuals to $r(X,\Delta)$. In Figure 4 and appendix A (proposition 9), we show that the residuals for r(X,Y)239 and $r(X,\Delta)$ are exactly the same, so the same patients will be placed in the same sub-groups regardless 240 of which correlation is used, and biomarkers which distinguish those sub-groups at the acute stage (Stinear, 2017), will be equally accurate regardless of which correlation is used. Nevertheless, extreme 241 242 $r(X,\Delta)$ for patients classified as fitters, will naturally encourage the assumption that those fitters' 243 outcomes are largely determined by initial symptom severity. If this assumption is true, therapeutic 244 interventions must be largely ineffective (or at least redundant) for these patients. Our analysis 245 suggests that this assumption is wrong.

Nevertheless, we are not claiming that the proportional recovery rule is wrong. Our analysis suggests that empirical studies to date do not demonstrate that the rule holds, or how well, but we could only confirm that $r(X,\Delta)$ was actually over-optimistic in one study, which reported individual patient data. And while we have also shown that extreme $r(X,\Delta)$ and r(X,Y) can result from nonproportional (constant) recovery, this is simply a plausible alternative hypothesis about how patients really recover.

252 Quite how to interpret empirical recovery with confidence in this domain, remains an open 253 question: we have articulated a problem here, hoping that recognition of the problem will motivate 254 work to solve it. Nevertheless, we can make some recommendations for future studies in the field.

First, these studies should report $r(X,\Delta)$, r(X,Y), and σ_Y/σ_X , for those patients deemed to recover proportionally. Despite our concerns about $r(X,\Delta)$, we do learn something when r(X,Y) is strong, but $r(X,\Delta)$ is weak, as in Feng and colleagues' (2015) results in section 3, which appeared to be better explained by constant recovery than by proportional recovery.

Second, future studies should consider explicitly testing the hypothesis that recovery depends on baseline scores (Oldham, 1962; Hayes, 1988; Tu *et al.*, 2005; Tu and Gilthorpe, 2007; Chiolero *et al.*, 2013). These tests sensibly acknowledge that the null hypothesis is rarely $r(X,\Delta) \approx 0$ in these analyses. However, they do not address the proper measurement and interpretation of effect sizes, which is our primary concern here; somewhat paradoxically, this means that they may be less useful in larger samples than in smaller samples (Friston, 2012; Lorca-Puls *et al.*, 2018).

265 These hypothesis tests will also all be confounded by ceiling effects. We recommend that future studies should measure the impact of such effects, perhaps by reporting the shapes of the 266 267 distributions of X and Y (greater asymmetry implying more prominent ceiling effects). Future studies 268 should also attempt to minimise ceiling effects. One approach might be to remove patients whose 269 outcomes are at ceiling: though certainly inefficient, this does at least remove the spurious $r(X,\Delta)$ in 270 our simulations of constant recovery (section 2.5). However, it may be difficult to determine which 271 patients to remove in practice; the Fugl-Meyer scale, for example, imposes item-level ceiling effects, which could distort σ_{y}/σ_{x} well below the maximum score. A better, though also more complex 272 273 alternative, may be to employ assessment tools expressly designed to minimise ceiling effects, or to 274 add such tools to those currently in use.

275 More generally, we may need to replace correlations with alternative methods, which can 276 provide less ambiguous evidence for the proportional recovery rule. One principled alternative might 277 employ Bayesian model comparison to adjudicate between different forward or generative models of 278 the data at hand: i.e. using the empirical data to quantify evidence for or against competing 279 hypotheses about the nature of recovery, which may or may not be conserved across patients. We 280 hope that our analysis here will encourage work to develop such methods, delivering better evidence 281 for (or against) the proportional recovery rule.

282

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- 288
- 289

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- 357

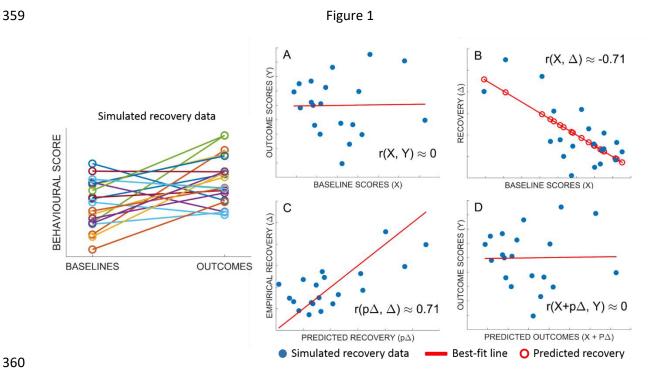
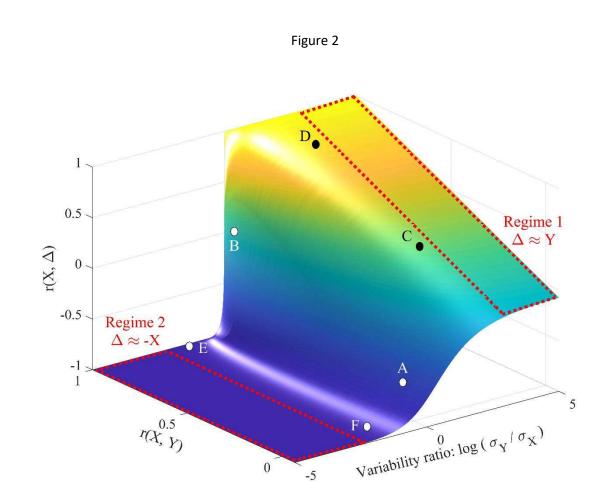


Figure 1: A canonical example of spurious r(X, Δ). Baselines scores are uncorrelated with outcomes

(A), but baseline scores appear to be strongly correlated with recovery (B). That correlation can be

used to derive predicted recovery, which is strongly correlated with empirical recovery (C) – but predicted outcomes, derived from that predicted recovery, are still uncorrelated with empirical

outcomes (D).



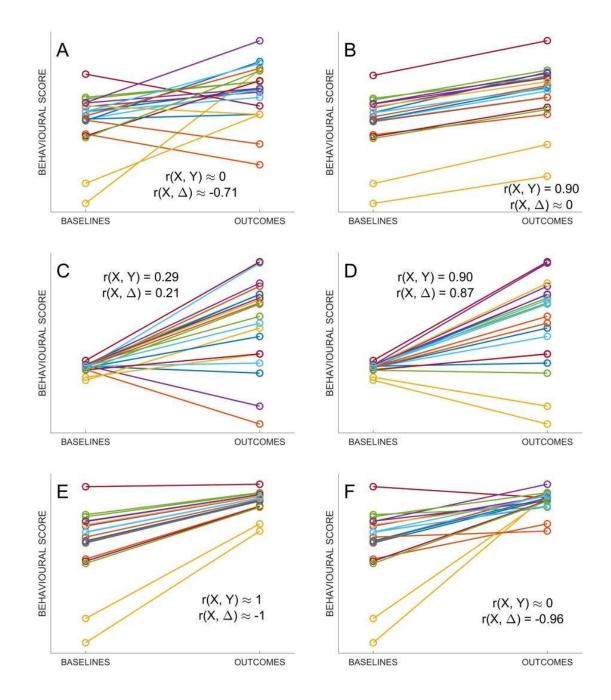


368

370 Figure 2: The relationship between r(X,Y), $r(X,\Delta)$ and σ_Y/σ_X . Note that the x-axis is log-transformed to ensure symmetry around 1; when X and Y are equally variable, $log(\sigma_Y/\sigma_X) = 0$. Proposition 7 in Appendix 371 372 A provides a justification for unambiguously using a ratio of standard deviations in this figure, rather 373 than $\sigma_{\rm Y}$ and $\sigma_{\rm X}$ as separate axes. The two major regimes of Equation 1 are also marked in red. In Regime 374 1, Y is more variable than X, so contributes more variance to Δ , and $r(X,\Delta) \approx r(X,Y)$. In Regime 2, X is more variable than Y, so X contributes more variance to Δ , and $r(X,\Delta) \approx r(X,-X)$ (i.e. -1). The transition 375 376 between the two regimes, when the variability ratio is not dramatically skewed either way, also allows for spurious $r(X,\Delta)$. For the purposes of illustration, the figure also highlights 6 points of interest on 377 378 the surface, marked A-F; examples of simulated recovery data corresponding to these points are 379 provided in Figure 3.

380

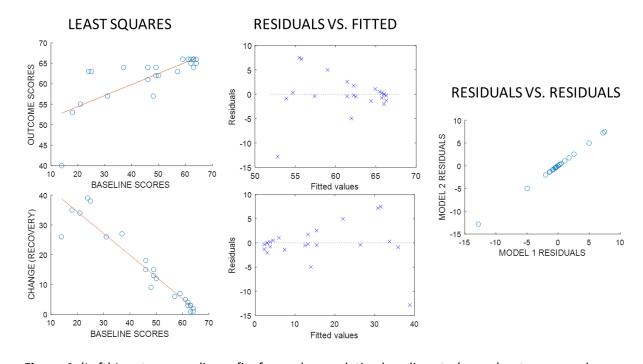
381



383

Figure 3: Exemplar points on the surface in Figure 2. Simulated recovery data, corresponding to the 384 385 points A-F marked on the surface in Figure 1. (A) Baselines and outcomes are entirely independent 386 (r(X,Y)=0), yet $r(X, \Delta)$ is relatively strong; this is the canonical example of mathematical coupling, first 387 introduced by Oldham (1962); (B) Recovery is constant with minimal noise, so baselines and outcomes are equally variable $(\sigma_Y/\sigma_X \approx 1)$ and recovery is unrelated to baseline scores $(r(X, \Delta) \approx 0)$; 388 389 (C-D) Outcomes are more variable than baselines ($\sigma_Y/\sigma_X \approx 5$), and r(X, Δ) converges to r(X, Y); (E) 390 Recovery is 70% of lost function, so outcomes are less variable than baselines ($\sigma_v/\sigma_x \approx 0.3$); even 391 with shuffled outcomes data (F) baselines and recovery still appear to be strongly correlated.

Figure 4



393

Figure 4: (Left) Least squares linear fits for analyses relating baselines to (upper) outcomes and
(lower) recovery, using the fitters' data reported by Zarahn and colleagues (Zarahn *et al.*, 2011).
(Middle) Plots of residuals relative to each least squares line, against the fitted values in each case.
(Right) A scatter plot of the residuals from the model relating baselines to change, against the

residuals from the model relating baselines to outcomes: the two sets of residuals are the same.

Table 1

REGIME	VARIABILITY OF Y (σ_{Y})	VARIABILITY OF X (σ_X)	Δ [= Y-X]	r(X,∆) [=r(X,Y-X)]
1	Smaller	Larger	Y-X ≈ -X	$r(X,Y-X) \approx r(X,-X) = -1$
2	Larger	Smaller	Y-X ≈ Y	r(X,Y-X) ≈ r(X,Y)

402 Supplementary Appendix A: formal relationships between the correlations

- 403 We present a simple, general and self-contained formulation of the proportional recovery concept.
- 404 We have derived all of the key results from first principles, while acknowledging previous
- 405 presentations of these results when they can be found in the literature.

406 We assume two variables X' and Y' corresponding to performance at initial test (X') and at second 407 test (Y'). These will be represented as column vectors, with each entry being the performance of a single patient and vector lengths being $N \in \mathbb{N}$. Performance improves as numbers get bigger, up to a 408 409 maximum, denoted Max, which corresponds to no discernible deficit. Severity is measured as 410 difference from maximum, i.e. Max - X'.

- 411 The two variables (X' and Y') could be specialised to more detailed formulations: e.g., true score
- 412 theory or with an explicit modelling of measurement or state error. However, this would not impact
- 413 any of the derivations or inferences that follow. Indeed, the results that we present would hold even
- 414 in the complete absence of measurement noise, which has been considered the main concern for
- 415 the validity of quantifications of proportional recovery.
- 416

417 Demeaning

418 Without loss of generality, we work with demeaned variables. That is, where over-lining denotes 419 mean, we define new variables as,

$$420 X = X' - \overline{X'}$$

$$421 Y = Y' - \overline{Y'}$$

422 This also means that recovery, i.e. Y - X, will be demeaned, since, using proposition 1, the following 423 holds.

424
$$Y - X = (Y' - \overline{Y'}) - (X' - \overline{X'}) = (Y' - X') - (\overline{Y'} - \overline{X'}) = (Y' - X') - \overline{(Y' - X')}$$

Proposition 1 425

426 Let V and W be vectors of the same length, denoted N. Then, the following holds,

427
$$\overline{V} + \overline{W} = \overline{(V+W)}$$

with $\overline{V} - \overline{W} = \overline{(V - W)}$ as a trivial consequence. 428

- 429 Proof
- 430 By distributivity of multiplication through addition and associativity of addition, the following holds.

431
$$\bar{V} + \bar{W} = \left(\frac{1}{N}\sum_{i=1}^{N}V_i\right) + \left(\frac{1}{N}\sum_{i=1}^{N}W_i\right) = \frac{1}{N}\left(\sum_{i=1}^{N}V_i + \sum_{i=1}^{N}W_i\right) = \frac{1}{N}\left(\sum_{i=1}^{N}(V_i + W_i)\right) = \overline{(V + W)}$$
432 QED

432

433 Correlations

- 434 There are two basic correlations we are interested in, (1) the correlation between initial
- performance and performance at second test, i.e. r(X, Y), and (2) the correlation between initial 435
- 436 performance and recovery, i.e. $r(X, Y - X) = r(X, \Delta)$. The latter of these is the key relationship, and

- 437 we would expect this to be a negative correlation; that is, as initial performance is smaller (i.e.
- 438 further from Max), the larger is recovery. (One could also formulate the correlation as r((Max Max))
- 439 *X*), Y X), which would flip the correlation to positive, but the two approaches are equivalent).
- 440 Our main correlations are defined as follows,

441
$$r(X,Y) = \frac{\sum_{i=1}^{N} X_i \cdot Y_i}{(N-1) \cdot \sigma_X \cdot \sigma_Y}$$

442
$$r(X, (Y - X)) = \frac{\sum_{i=1}^{N} (X_i \cdot (Y_i - X_i))}{(N - 1) \cdot \sigma_X \cdot \sigma_{(Y - X)}}$$

443 Standard Deviation of a Difference

444 We need a straightforward result on the standard deviation of a difference.

445 **Proposition 2**

$$\sigma_{(A-B)} = \sqrt{\sigma_A^2 + \sigma_B^2 - 2 \cdot cov(A,B)}$$

447 **Proof**

The result is a direct consequence of the following standard result from probability theory, e.g. see
Ross, S. M. (2014). *Introduction to probability and statistics for engineers and scientists*. Academic
Press.,

451
$$\sigma_{(A-B)}^2 = \sigma_A^2 + \sigma_B^2 - 2 \cdot cov(A,B)$$

452

453 Key Results

454 The following proposition enables us to express the key correlation, r(X, (Y - X)), in terms of 455 covariance of its constituent variables.

456 Proposition 3

457
$$r(X, (Y - X)) = \frac{cov(X, Y) - cov(X, X)}{\sigma_X \cdot \sqrt{\sigma_Y^2 + \sigma_X^2 - 2 \cdot cov(X, Y)}}$$

458 **Proof**

Using distributivity of multiplication through addition, associativity of addition, the definition ofcovariance and proposition 2, we can reason as follows.

461
$$r(X,(Y-X)) = \frac{\sum_{i=1}^{N} (X_i \cdot (Y_i - X_i))}{(N-1) \cdot \sigma_X \cdot \sigma_{(Y-X)}} = \frac{\sum_{i=1}^{N} (X_i Y_i - X_i X_i)}{(N-1) \cdot \sigma_X \cdot \sigma_{(Y-X)}} = \frac{\sum_{i=1}^{N} (X_i Y_i) - \sum_{i=1}^{N} (X_i X_i)}{(N-1) \cdot \sigma_X \cdot \sigma_{(Y-X)}}$$

462
$$= \frac{cov(X,Y) - cov(X,X)}{\sigma_X \cdot \sigma_{(Y-X)}} = \frac{cov(X,Y) - cov(X,X)}{\sigma_X \cdot \sqrt{\sigma_Y^2 + \sigma_X^2 - 2 \cdot cov(X,Y)}}$$

463 QED

464 It is straightforward to adapt proposition 3 to be fully in terms of correlations.

465 Proposition 4

466

$$r(X, (Y - X)) = \frac{\sigma_Y \cdot r(X, Y) - \sigma_X \cdot r(X, X)}{\sqrt{\sigma_Y^2 + \sigma_X^2 - 2 \cdot \sigma_X \cdot \sigma_Y \cdot r(X, Y)}}$$

467 **Proof**

468 Straightforward from proposition 3 and definition of correlations, which gives the relationship 469 $cov(A, B) = \sigma_A \cdot \sigma_B \cdot r(A, B)$. QED

470 Scale Invariance

- 471 The next set of propositions justifies working with a standardised *X* variable.
- 472 Lemma 1

473 $\forall c \in \mathbb{R} \, \cdot |c|. \, \sigma_A = \sigma_{(c.A)}$

474 **Proof**

475 Using distributivity of a multiplicative constant through averaging, $\sqrt{d^2} = |d|$ and distributivity of 476 square root through multiplication, we can reason as follows.

477
$$\sigma_{(c,A)} = \sqrt{\frac{\sum_{i=1}^{N} (c,A_i - \overline{c,A})^2}{N-1}} = \sqrt{\frac{\sum_{i=1}^{N} (c,A_i - c,\overline{A})^2}{N-1}} = |c| \cdot \sqrt{\frac{\sum_{i=1}^{N} (A_i - \overline{A})^2}{N-1}} = |c| \cdot \sigma_A$$

478 QED

479 **Proposition 5 (Invariance to scaling)**

480 The absolute magnitude of a correlation is not changed by scaling either variable by a constant, i.e.

481
$$\forall c \in \mathbb{R} \cdot r(A, B) = sign(c).r(c, A, B) = sign(c).r(A, c, B)$$

482 where sign(d) = if (d < 0) then -1 else +1.

483 **Proof**

For any $c \in \mathbb{R}$, using distributivity of multiplication through mean and addition, and lemma 1, the following holds,

486
$$r(c.A,B) = \frac{\sum_{i=1}^{N} (c.A_i - \overline{c.A})(B_i - \overline{B})}{(N-1) \cdot \sigma_{(c.A)} \sigma_B} = \frac{\sum_{i=1}^{N} (c.A_i - c.\overline{A})(B_i - \overline{B})}{(N-1) \cdot \sigma_{(c.A)} \sigma_B}$$

$$=\frac{c \cdot \sum_{i=1}^{N} (A_i - \bar{A})(B_i - \bar{B})}{(N-1) \cdot |c| \cdot \sigma_A \cdot \sigma_B} = \frac{sign(c) \cdot \sum_{i=1}^{N} (A_i - \bar{A})(B_i - \bar{B})}{(N-1) \cdot \sigma_A \cdot \sigma_B} = sign(c) \cdot r(A, B)$$

- 488 Then, one can multiply both sides by sign(c) to obtain $r(A, B) = sign(c) \cdot r(c, A, B)$. Additionally, 489 as correlations are symmetric, $sign(c) \cdot r(c, B, A) = sign(c) \cdot r(A, c, B)$, and the full result follows.
- 490 QED
- 491 Corollary 1

492
$$\forall c \in \mathbb{R} \cdot r(A, B) = r(c, A, c, B)$$

493 **Proof**

Follows from twice applying proposition 5, and that $sign(c)^2 = +1$. 494 QED

495 **Proposition 6**

496

$$\forall c \in \mathbb{R} \cdot r(X, (Y - X)) = r(c.X, (c.Y - c.X))$$

497 Proof

498 We can use distributivity of multiplication through subtraction and corollary 1 to give us the 499 following.

500
$$r(c.X, (c.Y - c.X)) = r(c.X, c.(Y - X)) = r(X, (Y - X))$$

501 QED

502 It follows from proposition 6 that we can work with a standardised X variable, since,

 $r(X/\sigma_X, (Y/\sigma_X - X/\sigma_X)) = r(X, (Y - X))$

504 Proposition 7 (Sufficiency of variability ratio)

505 Assume two pairs of variables: X_1 , Y_1 and X_2 , Y_2 , such that, $r(X_1, Y_1) = r(X_2, Y_2)$, then,

506
$$\frac{\sigma_{Y_1}}{\sigma_{X_1}} = \frac{\sigma_{Y_2}}{\sigma_{X_2}} \implies r(X_1, (Y_1 - X_1)) = r(X_2, (Y_2 - X_2))$$

507 Proof

508 The proof has two parts.

509 1) We consider the implications of equality of ratio of standard deviations. Firstly, we note that,

510
$$\frac{\sigma_{Y_1}}{\sigma_{X_1}} = \frac{\sigma_{Y_2}}{\sigma_{X_2}} \iff \frac{\sigma_{X_2}}{\sigma_{X_1}} = \frac{\sigma_{Y_2}}{\sigma_{Y_1}} \quad (eqn \ ratios)$$

511 Secondly, using eqn ratios, we can argue as follows,

512
$$\frac{\sigma_{Y_1}}{\sigma_{X_1}} = \frac{\sigma_{Y_2}}{\sigma_{X_2}} \iff \left(\sigma_{Y_2} = \frac{\sigma_{X_2}}{\sigma_{X_1}} \sigma_{Y_1} \land \sigma_{X_2} = \frac{\sigma_{Y_2}}{\sigma_{Y_1}} \sigma_{X_1}\right) \iff \left(\sigma_{Y_2} = \frac{\sigma_{X_2}}{\sigma_{X_1}} \sigma_{Y_1} \land \sigma_{X_2} = \frac{\sigma_{X_2}}{\sigma_{X_1}} \sigma_{X_1}\right)$$

513
$$\Rightarrow (\exists d \in \mathbb{R} \cdot \sigma_{Y_2} = d. \sigma_{Y_1} \wedge \sigma_{X_2} = d. \sigma_{X_1})$$

2) Using 4, the fact that $r(X_1, Y_1) = r(X_2, Y_2)$, the property just derived in part 1), with $d = \frac{\sigma_{X_2}}{\sigma_{X_1}}$ and 514 515 rules of square roots, we can reason as follows,

516
$$r(X_{2}, (Y_{2} - X_{2})) = \frac{\sigma_{Y_{2}} \cdot r(X_{2}, Y_{2}) - \sigma_{X_{2}} \cdot r(X_{2}, X_{2})}{\sqrt{\sigma_{Y_{2}}^{2} + \sigma_{X_{2}}^{2} - 2 \cdot \sigma_{X_{2}} \cdot \sigma_{Y_{2}} \cdot r(X_{2}, Y_{2})}} = \frac{\sigma_{Y_{2}} \cdot r(X_{1}, Y_{1}) - \sigma_{X_{2}} \cdot r(X_{1}, X_{1})}{\sqrt{\sigma_{Y_{2}}^{2} + \sigma_{X_{2}}^{2} - 2 \cdot \sigma_{X_{2}} \cdot \sigma_{Y_{2}} \cdot r(X_{1}, Y_{1})}}$$

517
$$= \frac{d \cdot \sigma_{Y_1} \cdot r(X_1, Y_1) - d \cdot \sigma_{X_1} \cdot r(X_1, X_1)}{\sqrt{d^2 \cdot \sigma_{Y_1}^2 + d^2 \cdot \sigma_{X_1}^2 - 2 \cdot d \cdot \sigma_{X_1} \cdot d \cdot \sigma_{Y_1} \cdot r(X_1, Y_1)}} = \frac{d \cdot (\sigma_{Y_1} \cdot r(X_1, Y_1) - \sigma_{X_1} \cdot r(X_1, X_1))}{d \cdot \sqrt{\sigma_{Y_1}^2 + \sigma_{X_1}^2 - 2 \cdot \sigma_{X_1} \cdot \sigma_{Y_1} \cdot r(X_1, Y_1)}}$$
518
$$= r(X_1, (Y_1 - X_1)).$$

518

519 QED

520 **Proposition 8**

521 If $\Delta = Y - X$ and $p\Delta = X$. β , where $\beta \in \mathbb{R}$, then,

522 1) $r(p\Delta, \Delta) = sign(\beta). r(X, \Delta)$; and

523 2) $r(X + p\Delta, Y) = sign(1 + \beta).r(X, Y).$

524 **Proof**

525 Both results are easy consequences of proposition 5.

526 1)
$$r(p\Delta, \Delta) = r(X, \beta, \Delta) = sign(\beta). r(X, \Delta)$$

527 2)
$$r(X + p\Delta, Y) = r((X + (X, \beta)), Y) = r((X, (1 + \beta)), Y) = sign(1 + \beta).r(X, Y) = r(X, Y).$$

- 528 QED
- 529 Main Findings

530 Theorem 1:

531 Since *X* will be standardised, we can adapt the finding in proposition 4, to give us the key

532 relationship we need,

533
$$r(X,(Y-X)) = \frac{\sigma_Y \cdot r(X,Y) - \sigma_X}{\sqrt{\sigma_Y^2 + 1 - 2 \cdot \sigma_Y \cdot r(X,Y)}} \quad (\text{eqn Imprint})$$

- 534 Note, this equation can be found in (Oldham, 1962), and also in (Tu *et al.*, 2005).
- 535 Proof

536 Immediate from proposition 4. QED

537 Theorem 1 shows clearly that r(X, (Y - X)) is fully defined by the correlations r(X, Y) and r(X, X),

along with the variability of Y. The correlation of X with itself, i.e. r(X, X), is a prominent aspect of

this equation, which drives its oddities. r(X, X) reflects the coupling in the equation that arises

because X appears in both the terms being correlated in r(X, (Y - X)). r(X, X) is of course a

541 constant, i.e. 1 for any X, so in fact, σ_Y and r(X, Y), are the only variables; accordingly, their size

- determines the extent to which the imprint of X in Y X drives r(X, (Y X)).
- 543 This leads to the key observation that, as σ_Y gets smaller, r(X, (Y X)) tends towards -r(X, X),
- 544 which equals -1. In other words, as the variability of Y decreases, the imprint of X becomes

545 increasingly prominent. This is shown in the next theorem.

546 Theorem 2

 $r(X, (Y - X)) \rightarrow -r(X, X) = -1, \text{ as } \sigma_Y \rightarrow 0$

548 Proof

549 The right hand side of equation *Imprint*, has five constituent terms, two in the numerator and three

- in the denominator. Of these five, three are products with the standard deviation of *Y*, i.e. σ_Y .
- Assuming all else is constant, as σ_Y reduces, the absolute value of each of these three terms reduces
- towards zero. The rate of reduction is different amongst the three, but they will all decrease.
- Accordingly, as σ_Y decreases, r(X, (Y X)) becomes increasingly determined by the two terms not

- involving σ_Y , and thus, it tends towards $-\frac{r(X,X)}{\sqrt{+1}} = -r(X,X) = -1$.
- 555 QED
- 556

557 Equality of Residuals

- 558 An important finding of section 5 of the main text, is that the residuals resulting from regressing Y
- 559 onto X are the same as regressing Y-X onto X. We show in this section, that this equality of residuals 560 is necessarily the case.
- 561 We focus on the following two equations,
- 562 Eqn 1) $Y = \tilde{X} \cdot \beta_1 + \varepsilon_1$
- 563 Eqn 2) $Y X = \tilde{X} \cdot \beta_2 + \varepsilon_2$

564 where \tilde{X} is the $N \times 2$ matrix, with first column being X and second being the $N \times 1$ vector of ones 565 (which provides the intercept term); β_1 and β_2 are 2×1 vectors of parameters and Y, X, ε_1 and ε_2 566 are $N \times 1$ vectors. As in the rest of this document, Y and X are our (demeaned) initial and outcome 567 variables, while ε_1 and ε_2 are our residual error terms.

568 Proposition 9

569 If we assume that β_1 and β_2 are fit with ordinary least squares, with ε_1 and ε_2 the associated 570 residuals, then, $\varepsilon_1 = \varepsilon_2$.

571 **Proof**

- 572 Under ordinary least squares, the parameters are set as follows.
- 573 $\beta_1 = (\tilde{X}^T \tilde{X})^{-1} \tilde{X}^T Y \quad (\text{Eqn 3})$
- 574

575 We start with the second of these, and using left distributivity of matrices, and then substituting Eqn 576 3, we obtain the following.

 $\beta_2 = (\tilde{X}^T \tilde{X})^{-1} \tilde{X}^T (Y - X) \quad (\text{Eqn 4})$

577
$$\beta_2 = (\tilde{X}^T \tilde{X})^{-1} \tilde{X}^T (Y - X) = (\tilde{X}^T \tilde{X})^{-1} \tilde{X}^T Y - (\tilde{X}^T \tilde{X})^{-1} \tilde{X}^T X = \beta_1 - (\tilde{X}^T \tilde{X})^{-1} \tilde{X}^T X$$

578 Using the fact that the variable *X* is demeaned, we can now evaluate the main term here as follows,

579
$$\beta_2 = \beta_1 - (\tilde{X}^T \tilde{X})^{-1} \tilde{X}^T X = \beta_1 - \begin{pmatrix} X^2 & \Sigma X \\ \Sigma X & N \end{pmatrix}^{-1} \begin{pmatrix} X^2 \\ \Sigma X \end{pmatrix} = \beta_1 - \frac{1}{A} \begin{pmatrix} N & -\Sigma X \\ -\Sigma X & X^2 \end{pmatrix} \begin{pmatrix} X^2 \\ \Sigma X \end{pmatrix}$$

580 where X^2 is the dot product of X with itself, ΣX is the sum of the vector X, and $A = NX^2 - \Sigma X \Sigma X$ is 581 the determinant of the matrix being inverted. From here we can derive the following,

582
$$\beta_2 = \beta_1 - \frac{1}{A} \begin{pmatrix} NX^2 - \Sigma X \Sigma X \\ -\Sigma X \cdot X^2 + X^2 \cdot \Sigma X \end{pmatrix} = \beta_1 - \frac{1}{A} \begin{pmatrix} A \\ 0 \end{pmatrix} = \beta_1 - \begin{pmatrix} 1 \\ 0 \end{pmatrix}$$

583 We can then substitute this equality for β_2 in eqn 2 and re-arrange to obtain,

584
$$Y - X = \tilde{X}\beta_2 + \varepsilon_2 = \tilde{X}\left(\beta_1 - \binom{1}{0}\right) + \varepsilon_2 = \tilde{X}\beta_1 - X + \varepsilon_2$$

585 It follows straightforwardly from here that,

$$Y - \tilde{X}\beta_1 = \varepsilon_2$$

QED

587 i.e. $\varepsilon_1 = \varepsilon_2$, as required.

588 Proposition 9 shows that the residuals resulting from fitting equations 1 and 2 will be the same. A

consequence of this is that the error variability will be the same. As a result of this, the factor that

590 determines whether more variance is explained when regressing Y onto X or when regressing Y - X

- 591 onto *X*, is the variance available to explain. That is, the relative variance of *Y* and Y X drive the R^2
- values of these two regressions. This then implicates the variance of Y and X and in fact their covariance (which impacts the variance of Y - X).
- 555 covariance (which impacts the variance of 1 2
- 594 More precisely, we can state the following.

595 1) If $\sigma_{(Y-X)}^2$ is big relative to σ_Y^2 , then regressing Y - X onto X will explain more variability than 596 regressing Y onto X.

- 597 2) If $\sigma_{(Y-X)}^2$ is small relative to σ_Y^2 , then regressing Y X onto X will explain less variability than 598 regressing Y onto X.
- 599

600

```
602 Supplementary Appendix B: illustrating the relationship between the correlations
```

```
604
      % This function illustrates the relationship
      function [r XY,std Y,r2,r3] = CheckEqn1()
605
606
607
      noise = [0.01:0.01:1,2:100]; % controls r(X,Y)
      scale = [0.01:0.01:1,2:100]; % controls sigma Y/sigma X
608
609
      X = single(randn(1000, 1));
610
      for j=1:length(noise)
611
          Y = X + single(randn(1000,1).*noise(j)); %Y is X plus noise
612
          Y = zscore(Y); % then scale to X so the actual scaling is consistent
613
          for k=1:length(scale)
614
              Y1 = Y.*scale(k); % rescale to control the variability ratio
615
              r XY(j,k) = corr(X,Y); % calculate the correlation with outcomes
616
617
              r2(j,k) = corr(X,YI-X); % calculate the correlation with change
618
              std Y(j,k) = std(Yl)./std(X); % record the variability ratio
619
              r3(j,k) = eqn r X XminusY(r XY(j),std Y(j,k)); % check Equation 1
620
          end
621
      end
622
623
      % display the resulting surface (Figure 1)
624
      figure,surf(log(std Y),r XY,r3,'edgecolor','none')
625
      lighting flat
626
      l = light('Position', [50 100 100]);
627
      l = light('Position', [50 100 -50]);
628
      l = light('Position', [50 -100 -50]);
629
      l = light('Position', [-50 -15 29]);
      l = light('Position',[-50 -15 -29]);
630
631
      l = light('Position', [-50 15 -29]);
632
      l = light('Position', [50 15 -29]);
633
     l = light('Position', [50 15 -50]);
634
     shading interp
635
     xlabel('log ( sigmaY / sigmaX )')
636
     ylabel('r(X,Y)')
637
      zlabel('r(X,Y-X)')
638
639
      % confirm that equation 1 does actually match 'empirical' r(X,Y-X)
640
      figure, scatter(r2(:), r3(:))
641
      xlabel('Empirical coefficients')
642
      ylabel('Derived coefficients')
643
644
      end
645
646
      % This function implements Equation 1
647
      function res = eqn r X XminusY(r XY, std Y)
648
649
      res = (((r XY.*std Y) - 1) ./ sqrt(1 + (std Y).^2 - (2*(r XY.*std Y))));
650
651
      end
652
653
```