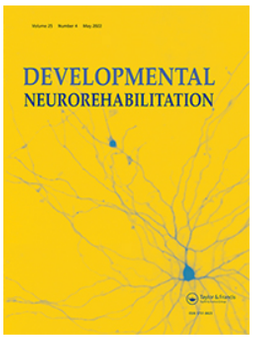

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Demonstration of functional rehabilitation treatment effects in children and young people after severe acquired brain injury

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ABSTRACT

Purpose: To examine relationships between functional outcomes after pediatric acquired brain injury (ABI) and measures of rehabilitation dose.

Methods: An observational study of children receiving residential neurorehabilitation after severe ABI.

Results: Basic total rehabilitation dose shows a paradoxical *inverse* relationship to global outcome. This is due to confounding by both initial injury severity and length of stay, and variation in treatment content for a given total rehabilitation dose. Content-aware rehabilitation dose measures show robust *positive* correlations between fractions of rehabilitation treatment received and plausibly related aspects of outcome: specifically, between rates of recovery of gross motor function and the fraction of rehabilitation effort directed to active practice and motor learning. This relationship was robust to adjustment for therapists' expectations of recovery.

Conclusion: Content-aware measures of rehabilitation dose are robustly causally related to pertinent aspects of outcome. These findings are step toward a goal of comparative effectiveness research in pediatric neurorehabilitation.

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Rehabilitation content; dose-response effects; causal inference; pediatric neurorehabilitation

Introduction

Acquired brain injury (ABI) is an umbrella term for brain injury acquired (often suddenly) after a period of normal development, in contrast to cerebral palsy arising from brain problems originating before, during or shortly after birth. Numbers of children with ABI are increasing as improvements in emergency and intensive care reduce the mortality of severe illness. Annually approximately 350 children in the UK sustain an ABI severe enough to require a period of inpatient rehabilitation.[1]

Rehabilitation remains the mainstay of the clinical response to ABI in the post-acute period. Rehabilitation refers to the multiple approaches health professionals take to promoting recovery after ABI through guided practice and re-learning, compensating for changes in ability, and helping child and family adapt to change and return to as normal a life as possible. Understandably, the potential for recovery of intrinsic function is of considerable importance to families.[2] Animal models suggest that better recoveries should be possible than are typically seen in clinical practice.[3]

Understanding the difference that rehabilitation can make to an individual's outcome is complex, comprising at least three distinct challenges. First, it is necessary to develop models of severity-adjusted outcome following ABI, to identify individuals achieving better – or worse – than expected outcomes. The residuals from these models (the variation in outcome not explained by initial severity) are where possible rehabilitation treatment effects may lie. Second, differences in outcome need to be related to the rehabilitation received, which in turn requires methods for the quantification of rehabilitation treatment: i.e. of "ingredients" and "dose" delivered to individuals. We have recently described a novel approach to this challenge, the Pediatric Rehabilitation Ingredients Measure (PRISM).[4] PRISM invites the rehabilitation multidisciplinary team (MDT) to estimate the proportions of the whole team's "rehabilitation effort" allocated across a range of possible treatment contents and targets. The third challenge is to acknowledge that therapists alter rehabilitation treatments in response to the recovery they are seeing (i.e. they may change approach if something is seen to be "not working" but emphasize approaches that are associated with improvement); hence there may be a reciprocal relationship between recovery-to-date and ongoing treatment that needs to be accommodated within the analysis approach adopted.

Part of the motivation for development of PRISM was a concern that basic measures of rehabilitation dose (e.g. therapist-hours) are meaningless if the aims and content of that rehabilitation (and thus what might plausibly be expected

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ABBREVIATIONSABI Acquired Brain Injury, ADLs Activities of Daily Living, DOC Disorder of Consciousness, UKFIM+FAM UK Functional Independence and Functional Assessment Measure (part of UKROC outcomes battery - see text), GMFM Gross Motor Function Measure, LOS Length of Stay, MDT Multidisciplinary Team, PRISM Pediatric Rehabilitation Ingredients Measure (see text), RCS Rehabilitation Complexity Scale (part of UKROC battery - see text), TCT The Children's Trust (a residential children's neurorehabilitation center), UKROC UK Rehabilitation Outcomes Collaborative (see text)

to change as a result of that intervention) are undefined. "Total rehabilitation dose received" is a problematic *composite variable*: a proportion of the total rehabilitation effort would not, *a priori*, be expected to result in functional gains. For example, although the total rehabilitation dose for a child with a severe Disorder of Consciousness (DOC)[5–7] will be very high, PRISM will typically confirm that the proportion of that effort directed to active practice and relearning of movement and skill is low.[4] The team's focus is typically elsewhere: for example, on prevention of deformity, ensuring comfort and tolerance of care procedures, and enabling participation through environmental adaptation and family support. Therefore progress should be expected in domains such as family competence and emotional health as opposed to active skill development. However, even with improved methods for defining rehabilitation content there remains an important question of causal inference: are therapists' actions *responsible* for functional gains, or are they (at least in part) *responding* to recovery they are observing?

The challenges and pitfalls of causal inference in observational data have received greater methodological attention in recent years.[8] Interpretation of data without an *a priori* model of the data generating processes and associated causal relationships can result in paradoxical situations where the derived associations between two variables can appear, disappear, or even reverse sign (switch from a positive association to a negative association, or *vice versa*). An important tool in causal inference methods approaches to observational research is the Directed Acyclic Graph (DAG)[9] which makes explicit the assumed underlying data generating process and thus causal relationships between model covariates, thus formally identifying confounders and variables that may mediate the focal causal relationship (refer to Supplemental Material for more details).

The first objective of this paper is to demonstrate the superior ability of a content-aware measure of rehabilitation dose (PRISM) over a basic "total rehabilitation dose" measure, to demonstrate correlations between plausibly related aspects of delivered rehabilitation and recovery observed. Specifically here PRISM is used to demonstrate relationships between rehabilitation effort allocated to active practice, and recovery of gross motor recovery after pediatric ABI. The second objective of the paper is to examine these correlations within a rigorous DAG causal inference framework.

Methods

The Children's Trust, Tadworth, Surrey (TCT), is the UK's largest provider of residential rehabilitation for children after ABI and uses the UK Rehabilitation Outcomes Collaborative (UKROC) toolbox of instruments for estimation of injury severity, rehabilitation delivered, and outcomes observed after ABI. Although the UKROC instruments were developed for adults, TCT staff have been collecting developmentally-adapted UKROC data in children receiving inpatient rehabilitation for the last 9 years. Results presented here use the following items from TCT's routine UKROC data return:

- The Rehabilitation Complexity Scale[10] provides a patient-level measure of complexity of needs. It is a 22-point summed measure of subscales covering: Basic care needs or Risk, Special nursing needs, Medical environment, Therapy disciplines (TD), Therapy intensity (TI) and Equipment (see Table 1). Its use as a quantifier of rehabilitation delivered is established in UK adult neurorehabilitation practice.[11,12] Although the RCS combines medical, nursing and therapy needs, children with high levels of acute medical or nursing dependency cannot be accommodated at TCT: it is their complex therapy needs that dictate admission and dominate their RCS scores. A basic rehabilitation dose statistic was calculated for each admission by performing a linear regression through repeated RCS measurements and calculating the "area under the trapezoid" of this best fit RCS line between admission and discharge to give a total basic dose in "RCS-days" (Figure 1(i))

- The UK Functional Independence Measure and Functional Assessment Measure (UKFIM+FAM) is a 30-item scale capturing functional independence, i.e. lack of need for assistance in Activities of Daily Living (ADLs). Summed total scores can range between 30 and 210 (high scores are good) with motor and cognitive subdomains recognized.[13] By convention full independence in the ADLs captured by the UKFIM+FAM is expected by age 8 in typically developing children. Its use for children above this age with ABI has been validated[14]: TCT use other measures[15] in younger children but they were excluded from this analysis.
- The Neurological Impairment Score (NIS) provides a summary of a patient's intrinsic impairments due to ABI across 13 domains[16] in a summed score between zero (no impairment) and 50.

The UKROC data collection schedule requires providers to collect the RCS on admission and fortnightly until discharge, with NIS and UKFIM+FAM on admission and discharge only. Additionally, TCT routinely collect monthly Gross

Table 1. The rehabilitation complexity scale extended version 13[10].

Score	Care (C)	Risk (R)	Nursing (N)	Medical (M)	Therapy disciplines (TD)	Therapy Intensity (TI)	Equipment (E)
0	Independent	None	No skilled nursing need	None	None	None	None
1	Help of 1	Low	General nursing	Community-providable	1	< daily	Basic
2	Help of 2	Medium	Trained rehab nursing	District hospital-providable	2–3	Daily, one provider	Highly specialist
3	Help of ≥3	High	Specialist (e.g. tracheostomy)	Potentially unstable	4–5	Therapist + assistant, ~25-30 hours per week	n/a
4	1:1	Very High	High dependency	Acutely unwell	≥6	≥2 therapists, ≥30 hours/week	

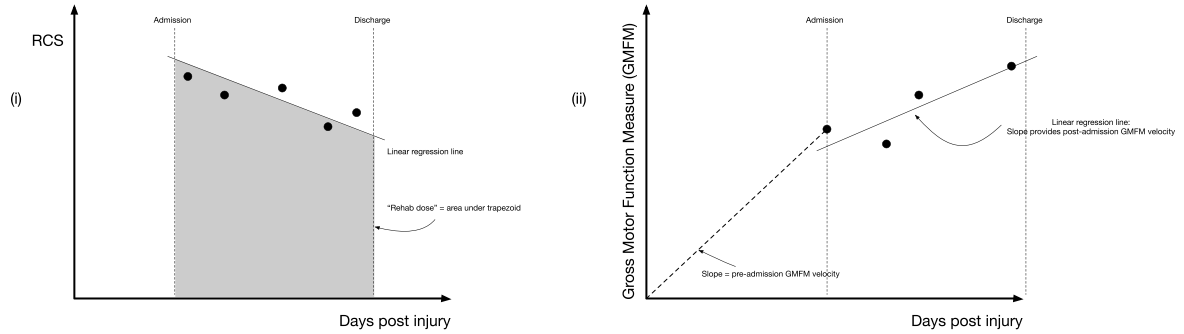

Figure 1. (i) Approach to calculating basic rehabilitation "dose." (ii) Approach to calculating pre-admission and post-admission Gross Motor Function Measure (GMFM) velocities.

Motor Function Measure (GMFM) data. The GMFM-66 is a Rasch-propertied unidimensional, interval measure of gross motor function initially developed for children with cerebral palsy.[17] We have previously demonstrated the validity of the GMFM in the severe ABI population.[18] Pre-admission and post-admission GMFM *velocities*, i.e. the rates of change (GMFM units/day) for the period between injury and admission, and during admission, were calculated as illustrated in Figure 1(ii). Note that this assumes a GMFM of zero on the day of injury.

For a subset of n = 16 consecutive admissions PRISM data were also recorded. PRISM is described in more detail elsewhere.[4] It is used to describe the areas of focus of the combined efforts of the rehabilitation MDT, expressed as proportions across a range of items selected as required from a pre-defined "menu" of 11 options. In this study specifically, we examined relationships between recovery of gross motor function (sitting, standing, walking) as captured by the GMFM, and the PRISM-derived proportion of rehabilitation effort that could be expected to directly influence this, namely "Active practice and relearning of skills" (abbreviated henceforth in this paper to "active practice fraction") one of the 11 areas of focus amongst which total rehabilitation effort can be allocated using the PRISM approach. PRISM estimations come with an internal consistency statistic.

Statistical Methods

We considered possible determinants of the average active practice fraction, and particularly the possibility that therapists might emphasize active practice in children explicitly or implicitly assessed as having greater "recovery potential" on the basis of rate of gross motor recovery demonstrated prior to admission, injury type, age and/or gender. A directed acyclic graph (DAG) was developed to capture the hypothesized underlying data-generating processes. This is shown in Figure 2 (ii). With the exception of assumed independence between age and gender it is saturated (i.e. every possible forward causal transmission is deemed possible). Thus the DAG accommodates the possibility that injury type (coded as "hypoxic," "traumatic" or "other ABI") may be influenced by age and gender; that pre-admission GMFM velocity may be influenced by age, gender and injury type; that PRISM active practice fraction may be influenced by age, gender, injury type and pre-admission GMFM velocity; and that post-admission GMFM velocity may be influenced by age, gender, injury type, pre-admission GMFM velocity and PRISM active practice fraction. GMFM velocities and average active practice fraction throughout the admission were used as summary features in preference to absolute GMFM gain during admission and total rehabilitation dose received as the latter would introduce spurious associations due to shared dependency on length of

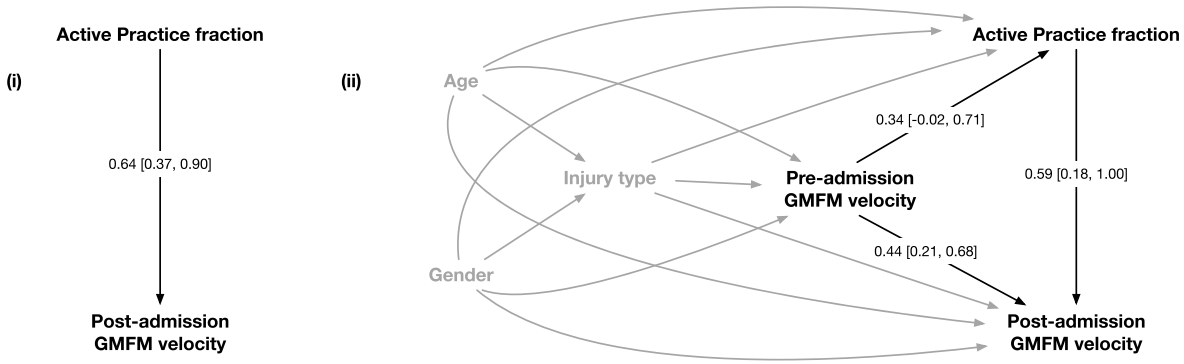

Figure 2. DAGs illustrate hypothesized relationships between recovery potential, rehabilitation received and outcome, with corresponding path standardized coefficients derived from the appropriately informed regression analyses. (i) A restricted DAG indicating the simple bivariate correlation between fraction of active practice rehabilitation effort and GMFM rate of gain following admission. (ii) A more realistic DAG (though potentially still omitting some unknown confounding) informing various regression models where it is acknowledged that therapists may adjust rehabilitation content in light of (perhaps implicit) appraisals of recovery potential based on pre-admission GMFM velocity and information on injury type, age and gender. The coefficients [and 95% Confidence Intervals] on DAG edges are the standardized path coefficients (≤±1), permitting comparison of causal influence.

admission, and because causal assessment cannot be evaluated robustly using change-scores.[19]

The DAG was evaluated against observed data and specific conditional relationships were examined by linear regression using the *lm* and *lm.beta* packages in R v3.6.2 (R Foundation for Statistical Computing, Vienna, Austria, 2018). Standardized path coefficients (with 95% confidence intervals) reflect the strength of causal relationship estimated (with values $\leq \pm 1$), facilitating comparison of effect sizes.

As an observational study that used routinely collected clinical data, with no consequences for or effects on patient care, this study was deemed service evaluation by standard criteria (www.hra-decision tools.org.uk) and research ethics review was therefore not sought. The study was endorsed by the TCT Research Committee (TCT049 May 2017).

Results

In total UKROC data were available for 330 consecutive residential rehabilitation episodes in 280 children and young people between December 2010 and February 2018. This paper reports analyses on the first admissions only (ignoring readmissions) of children over 8 years on admission for whom UKFIM+FAM data was available (see Methods): a total of 158 individual admissions. A small majority (58%) were male. Age at injury (median, range; IQR) was 13.1 (7.1–17.9; 10.9–14.3) years; length of stay (LOS) 114 (21–630; 85–181) days and interval from injury to admission 119 (14–3943; 82–188) days.

UKFIM+FAM results are shown in Figure 3. UKFIM+FAM scores tend to increase (i.e. children become more independent in ADLs) during admission (Figure 3(i)). There is an inverse relationship between admission Neurological Impairment Score (NIS) and UKFIM+FAM score at discharge (Figure 3(ii)) suggesting that rehabilitation does not fully reverse the effects of severe primary injury (at least by the time of discharge), although there is a cluster of cases in the top right of Figure 3(ii) of children making reasonably good recoveries despite initially severe injury. In Figure 3(iii) the relationship between discharge UKFIM+FAM and a basic total rehabilitation dose measure (total RCS-days, calculated by the method illustrated in Figure 1(i)) is shown. There is an inverse relationship with the highest rehabilitation doses being received by the children with the poorest discharge UKFIM+FAM scores. However, the color-coding of Figure 3(iii) demonstrates important relationships with initial injury severity. Points are color-coded by NIS quintile: i.e. children are divided into five equally sized groups ordered by NIS. There is clear clustering with the children with the lowest NIS scores (least severely injured) in the top left achieving the best outcomes and receiving the smallest basic rehabilitation doses, and those with higher NIS scores (turquoise and purple) toward the bottom right of the plot.

The group of $n = 16$ consecutive admissions with additional PRISM and GMFM data comprised 4 traumatic, 4 hypoxic and 8 other-mechanism ABIs. Ages ranged from 0.7–17.4 years (median 9.6; IQR 4.8–11.4 years). 11 were male. Pre-admission GMFM velocity (i.e. GMFM on admission divided by days since injury) ranged from 0 to 1.5 units/day (median 0.3; IQR 0.08–0.81). Median GMFM on admission was 32.8 (range 0–99.4; IQR 11.9–88.8) with a median post-admission GMFM velocity (units gained/day) of 0.05 (IQR 0–0.19).

Average active practice fraction varied from 2% to 69%. When evaluated directly, in contrast to the *inverse* relationship between basic total rehabilitation dose and outcome shown in Figure 3 (iii), there is a *positive*, large standardized path coefficient (0.64, 95% CI 0.37–0.90) between the average fraction of rehabilitation effort addressing gross motor function gain through practice, and the speed of that gain after admission (Figure 2(i)). The edges in the DAG (Figure 2(ii)) are labeled with the standardized path coefficients for the regressions of active practice fraction influencing pre-admission GMFM velocity, post-admission GMFM velocity influencing pre-admission GMFM velocity and post-admission GMFM velocity influencing active practice fraction, each with adjustment for all the confounders indicated in the DAG. The strong positive influence of active practice fraction on post-admission GMFM velocity is robust to the necessary statistical

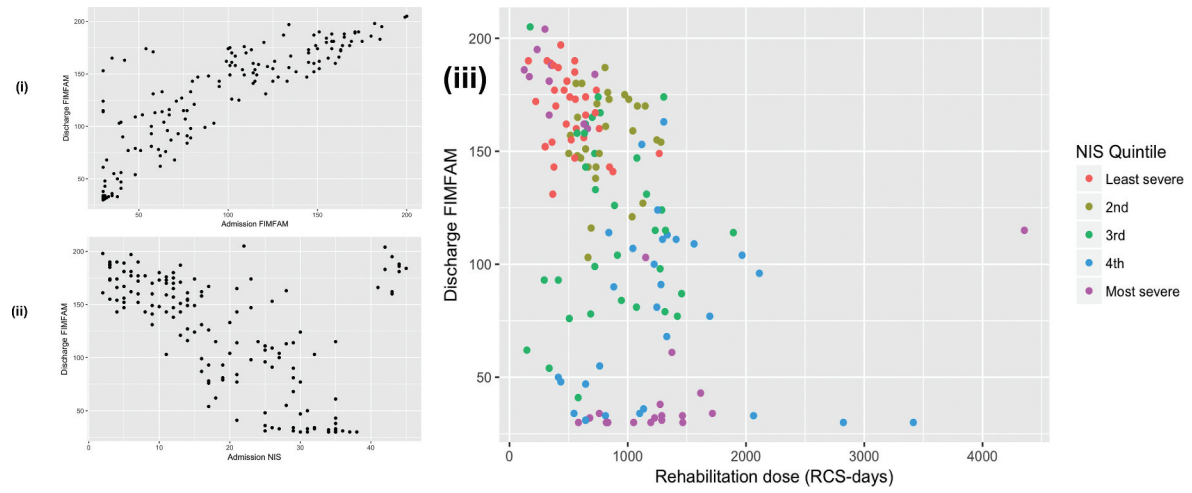

Figure 3. UKFIM+FAM results tend to increase between admission and discharge as shown by the distribution of points in (i) above and to the left of the y = x line. There are inverse relationships between Discharge UKFIM+FAM and the Neurological Impairment Score (NIS) on admission (ii), and between Discharge UKFIM+FAM and total basic rehabilitation dose in RCS-days (iii) but this is in part due to a confounding effect of injury severity (color coding, see text).

adjustment (0.59; 95% CI 0.18–1.00). (Qualitatively very similar results, not shown for brevity, are obtained with a rehabilitation dose measure combining TI from the RCS-E (Table 1) and the PRISM active practice fraction).

Discussion

In the Introduction we highlighted three challenges in examining possible rehabilitation treatment effects: the need to interpret observed recovery in light of severity-related expectations; the fact that "rehabilitation dose" is a composite variable that needs unpacking; and the challenge of causal inference in situations where therapists' treatment may change over time in ways that may in part be a response to observed recovery.[20–23]

The findings of Figure 3(iii), where the highest basic rehabilitation doses are received by those with the greatest levels of persisting disability at discharge, highlight the challenges of causal inference in this population. This is a specific example of a general phenomenon known as the reversal paradox, where statistical relationships within subgroups (here, NIS quintiles) disappear or reverse when these groups are combined. The RCS-days measure illustrated here is vulnerable to this confounding in part because of the "days" multiplier. Others have confirmed that greater Length of Stay (LOS) is associated with poorer outcome at discharge.[24,25] "Rehabilitation efficiency" measures (functional gain per day) have been suggested as a solution to the LOS issue[26] however the primary aim of this paper is to draw attention to a less-emphasized limitation of basic "input" measures such as the RCS (even without the days multiplier), namely that it and similar measures are insensitive to variation in rehabilitation treatment *content.*

As discussed in the Introduction without knowledge of treatment content and thus what aspect(s) of outcome might plausibly be expected to be changing it is not possible to interpret rehabilitation effectiveness. We confirm that the content of a given total dose of rehabilitation varies widely, with average active practice fractions of 2% to 69%. Higher rates of stroke and motor vehicle accidents contribute to ABI rates in adults much greater than those seen in children; and rehabilitation services for adults are also more established and standardized. However, even in adult practice, attempts to demonstrate dose-response effects in neurorehabilitation have been challenging and often unsuccessful[27–30] (reviewed in Forsyth *et al.*[4]). These difficulties may relate in part from insufficient attention to the content of the delivered rehabilitation and/or the occurrence of reversal paradoxes.

We confirm that, in contrast to Figure 3(iii), where basic rehabilitation dose and outcome are inversely related, post-admission gross motor recovery speed (GMFM gain/day) is strongly *positively* associated with average active practice fraction (Figure 2(i)). Our previous work[31] confirmed that therapists set goals that they consider realistic in a given clinical context and tailor the content of rehabilitation accordingly. We hypothesized that therapists may have implicit expectations of prospects for further gross motor recovery that are influenced by perceived "recovery potential" and that may affect rehabilitation content decisions. For instance, if therapists see a child was already recovering rapidly prior to admission they may "ride that wave" by emphasizing further active practice. We tested this hypothesis by incorporating pre-admission GMFM velocity into a causal model. We show, at least in this sample, that the strong positive bivariate correlation between active practice fraction and post-admission GMFM velocity persists and is robust to the appropriate confounder adjustments indicated by Figure 2(ii). (It should be emphasized that active practice incorporates practice of much more than gross motor skills).

The third challenge highlighted in the Introduction, the possibility (if not likelihood) that treatment content will change over time in ways that reflect recovery to date has only been partially addressed here and is the subject of ongoing research. It can be argued that such responsiveness to change and modification of treatment content is a hallmark of good therapy.[32] Figure 4 shows a potential approach to the analysis of this phenomenon. Cycles of reassessment of progress to date and possible revision of rehabilitation content are likely to have a period of a few weeks. However a trend to shorter rehabilitation admissions at TCT and resource constraints preventing GMFM and PRISM estimations more than monthly precluded testing of a Figure 4 model in this data. Further examination of these issues would require repeated measurement with greater temporal resolution, and the application of advanced methods of statistical analysis for robust causal inference – such as g-methods.[33] The availability of only ~3 GMFM measurements per child meant that although we have previously shown that over the longer term GMFM trajectories have an asymptotic form[18] we had to assume linearity in the observed section of the recovery trajectory. This means that whilst we have shown relationships between rehabilitation dose and *rate* of recovery, we have not been able to examine effects on final (asymptotic)

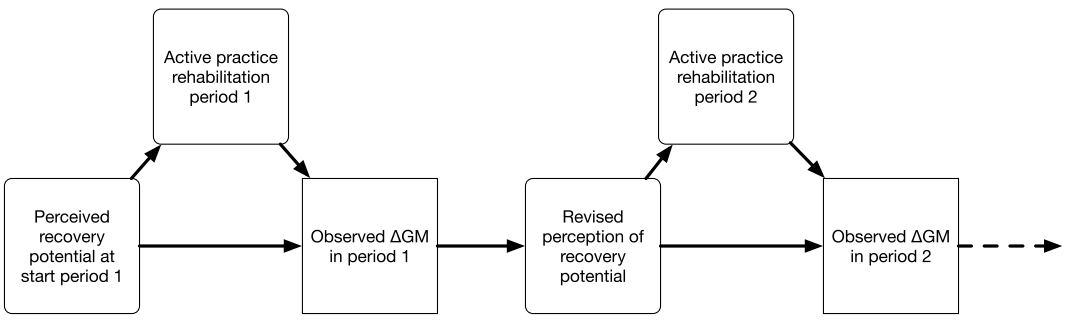

Figure 4. Schematic illustration of how change in rehab content over time could be analyzed.

outcome: i.e. it is possible that active practice rehabilitation is enabling faster, but not necessarily ultimately better, recoveries.[34]

Reversal paradoxes can also arise from a less intuitive problem known as "conditioning on a collider" or "collider bias,"[35,36] which is discussed in the Supplemental Material. This remains the main limitation of this study: if we have information that a TCT patient has achieved a good outcome we can infer they received a large rehabilitation dose, because the fact that the child was a TCT patient is informative: patients admitted to TCT are a selected population with generally poorer outcomes (i.e. we are conditioning on outcome). This work therefore needs to be replicated in larger, unselected populations (that might include children with initially apparently-severe injuries who made good recoveries "despite" only receiving small rehabilitation doses). Other limitations with this pilot study included the necessary assumption of a GMFM of zero on the day of injury, and the small sample, with the potential for both imprecise estimates due to patient heterogeneity and under-adjustment due to omitted confounders. All models also assumed appropriate variable distributions, with only linear relationships explored and no interactions considered (again, due to the small sample size).

Notwithstanding the limitations discussed above this study demonstrates that with attention to rehabilitation treatment content and challenges of causal inference, strong and robust effects of treatment, at least on rate of recovery after pediatric ABI, are evident. This provides an important foundation for further studies of the comparative effectiveness of different rehabilitation treatment regimes.

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