Predictors of reliable symptom change: Secondary analysis of the Preschool Autism Communication Trial

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Abstract

Background and aims: Despite recent gains in the amount and quality of early autism intervention research, identifying what works for whom remains an ongoing challenge. Exploiting data from the Preschool Autism Communication Trial (PACT), we undertook secondary analysis to explore prognostic indicators and predictors of response to one year of PACT therapy versus treatment as usual within this large and rigorously characterised cohort recruited across three UK trial sites.

Methods: In this secondary analysis of variability in child gains on the primary trial outcome measure – social-communication symptom severity – we used a pragmatic and data-driven approach to identify a subgroup of children who showed reliable improvement and a subgroup showing clear lack thereof. We then tested which among several baseline child and family factors – including measures routinely collected in research trials and clinical practice – varied as a function of child outcome status and treatment group.

Results: Greater baseline child non-verbal ability was a significant *prognostic indicator* of symptom reduction over time (i.e. irrespective of treatment group). By contrast, parent synchrony presented as marginal *predictor*, and trial recruitment site as a significant predictor, of differential outcome by treatment group. Specifically, lower parent synchrony showed some association with poorer outcomes for children from families assigned to treatment as usual (but with no such effect for those assigned to PACT). Similarly, children at one recruitment site were more likely to have poorer outcomes if assigned to treatment as usual, compared to children at the same site assigned to PACT.

*Details of the members of the PACT are given at the end of the article.

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Conclusions: The current data contribute to an evidence base indicting that early non-verbal ability is a robust indicator of generally better prognosis for young children with autism. Lower parent synchrony and a broadly more deprived socio-geographical context may inform the appropriate targeting of PACT. That is, given that the former factors predicted poorer outcome in children from families assigned to treatment as usual, the receipt of a relatively low-dose, parent-mediated and communication-focused therapy might be developmentally protective for young children with autism. Nevertheless, results from this study also highlight the paucity of meaningful predictors of outcome among routine clinical characterisation measures such as those investigated here.

Implications: Understanding the factors associated with differential treatment outcomes is critical if we are to individualise treatment decisions for children with autism. Inherently tied to this objective is a need to delineate those factors which specifically *predict* positive response (or lack of response) to one or other treatment option, versus those that indicate generally better (or poorer) prognosis, irrespective of treatment.

Autism is highly heterogeneous, with core symptoms, cognitive and adaptive skills, and associated behaviour difficulties varying widely (Jeste & Geschwind, 2014). While systematic reviews and meta-analyses demonstrate the promise of various early childhood intervention approaches (e.g. Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015; Oono, Honey, & McConachie, 2013; Smith & Iadarola, 2015), heterogeneity remains a major barrier to determining best-practice (Romanczyk, Callahan, Turner, & Cavalari, 2014; Spence & Thurm, 2010). Even where trials demonstrate overall efficacy, some children show little improvement (Magiati, Tay, & Howlin, 2012) and, conversely, some children make considerable gains in the absence of intervention (Howlin, Magiati, & Charman, 2009). To further the field, it is important that we identify those children with autism most likely to benefit from a given intervention approach and any for whom the approach may be contraindicated (Kraemer, Wilson, & Fairburn, 2002). Three key barriers to this end include (1) inconsistent use of terminology and methods, in studies reported to date, for delineating *predictors* of positive response (or lack of response) to a particular treatment option versus *prognostic indicators* of generally better (or poorer) outcome irrespective of treatment; (2) lack of guidelines for what constitutes *meaningful* improvement (or lack thereof) for young children with autism; and (3) limited numbers of adequately designed and well-powered studies to address this broad aim.

Prognostic indicators versus predictors of response

The extant literature highlights a variety of characteristics associated with more positive outcomes for young children with autism. For example, milder autism symptom severity and better cognitive, linguistic and social skills have been shown to be associated with more positive outcomes in intervention studies (see Vivanti, Prior, Williams, & Dissanayake, 2014) as have parent/family factors such as lower stress, greater motivation for and fidelity to treatment, higher socio-economic status (SES) and stronger support networks (e.g. Karst & Van Hecke, 2012; Sherer & Schreibman, 2005). Further – and particularly relevant to the context of parent-mediated interventions – child outcomes have been associated with features of the parent–child relationship (Perryman et al., 2013). What remains unclear, however, is whether and which of these represent true *predictors* of positive response to intervention, as opposed to *prognostic indicators* of greater 'natural' improvement over time.

Many studies inadequately separate *predictors* from *prognostic indicators*. Evidence of a *prognostic indicator* presents as a main effect (e.g. where children with characteristic X are observed to have better outcomes than those with characteristic Y). By contrast, evidence of a *predictive* effect presents only in a significant interaction term (e.g. where, in treatment condition A, children with characteristic X are observed to have better outcomes than those with characteristic Y, but this is not the case in treatment condition B). Hence, evaluation of *predictors* versus *prognostic indicators* must necessarily occur within the context of some comparative or controlled investigation of one treatment condition versus another. However, the lack of sufficient rigorously conducted, well-powered autism intervention studies means that we are not yet able to draw definitive and appropriate conclusions about what works for whom.

Further complicating efforts toward this end, the existing evidence concerning associations between baseline characteristics and later outcomes for children with autism is also inconsistent. While milder symptoms and better cognitive/linguistic abilities tend to correlate with

positive outcomes (e.g. Virués-Ortega, 2010), this is not true across all trials (e.g. Howlin et al., 2009) and these same variables often present as *prognostic indicators* of outcome in the absence of intervention (Magiati, Tay, & Howlin, 2014). Findings are similarly mixed regarding characteristics of parents and features of parent-child interaction behaviour (e.g. Perryman et al., 2013; Siller & Sigman, 2008; Vivanti et al., 2014). Further, other potentially relevant sources of *prognostic* or *predictive* influence – such as family ethnicity and cultural values (Kasari & Patterson, 2012) and genetic and endophenotypic factors (Parr, Gray, Wigham, McConachie, & LeCouteur, 2015) – remain virtually unexplored in the field of autism intervention.

What constitutes meaningful improvement?

An associated challenge for the field concerns the operationalisation of *positive* child *outcomes*. Rather than following best-practice guidelines to specify primary and secondary outcomes *a priori* (e.g. National Institute for Health and Care Excellence, 2013), autism intervention researchers often examine multiple outcomes, including cognitive/linguistic skills and adaptive behaviours (Magiati et al., 2012). In the context of intervention for pre-schoolers with autism, a key objective is often to achieve reduction in core symptom presentation (Bieleninik et al., 2017). Achieving this aim has proved challenging (e.g. Waddington, van der Meer, & Sigafoos, 2016), and there is also little consensus on what might constitute *meaningful* reduction in core symptoms (e.g. see McConachie et al., 2015) nor on how to determine the appropriate target difference when planning a randomised controlled trial (Cook et al., 2014). Gold-standard measures to quantify autism symptom presentation (Lord et al., 2000; Lord, Rutter, & Le Couteur, 1994) were developed to inform diagnostic decision-making, rather than to measure sensitively change over time or in response to treatment. Nevertheless, as recently synthesised by Bieleninik et al. (2017), several prospective cohort studies as well as a small number of randomised controlled trials (e.g. Dawson et al., 2010; Green et al., 2010; Solomon, Van Egeren, Mahoney, Quon Huber, & Zimmerman, 2014) have adopted gold-standard diagnostic measures as ambitious targets by which to evaluate intervention outcome.

Background to this study: The Preschool Autism Communication Trial

As already described, a third key barrier to understanding how to individualise early autism intervention concerns the lack of studies adequately designed to address predictors of response. Given the proliferation of available treatment options, it is critical to determine whether children are more or less likely to benefit from particular approaches, and this requires thorough assessment of factors associated with differential outcome (e.g. such as for students with learning disabilities (Fuchs, Fuchs, & Compton, 2012) but is rare in studies of autism). Beyond formal intention-to-treat (ITT), moderation and mediation analyses, secondary exploratory analysis of clinical trial datasets may elucidate factors informative for designing subsequent, hypothesis-driven trials (Kraemer et al., 2002).

The Preschool Autism Communication Trial (PACT; Green et al., 2010) was an efficacy randomised controlled trial (RCT) of a parent-mediated, communication-focussed therapy conducted across three UK sites. Among 152 parent–child dyads, around half were assigned to receive PACT therapy ($n = 77$) versus community treatment as usual (TAU; $n = 75$). While Green et al. reported no significant overall ITT effect on the *a priori* nominated primary outcome measure – severity of child social-communication symptoms – at 13-month treatment endpoint ($d = -.24$; 95% CI: $-.59$, $-.11$), substantial variability in outcomes was apparent. Nevertheless, pre-specified moderator analysis revealed no significant *predictive* effects (i.e. statistical interaction terms) among the following baseline measures: child age, symptom severity, non-verbal ability, receptive language, family SES or trial recruitment site.

Current aims and hypotheses

We undertook secondary analysis to explore the substantial variability in child outcomes apparent within the PACT dataset. Using a pragmatic and data-driven approach, we examined which among various measures of child and parent/family factors collected at baseline might differentiate those children who went on to make improvement and clear lack of improvement in their core social-communication symptoms across the year-long trial period. To mirror the pragmatic context of a clinician seeking to tailor treatment to characteristics of the presenting client, we focused our examination on baseline measures commonly collected both within research trials and as part of clinical service provision – initial child symptom severity and cognitive, linguistic and adaptive skills, and family socio-demographic characteristics – noting that these have also previously been examined as potential associates of outcome within past research (e.g. Vivanti et al., 2014). As this was a multi-site trial and PACT was a parent-mediated intervention, we also included recruitment site in our investigation (see Carr et al., 2015; Nunes et al., 2010) and a measure of parent interaction with the child (i.e. parent

synchrony; Aldred, Green, & Adams, 2004; Hudry et al., 2013).

Lack of consensus in the literature precluded us from drawing strong conclusions around likely specific *predictors* of response to PACT. However, following Magiati et al. (2014) and Siller and Sigman (2008), we hypothesised that child cognitive/linguistic abilities and parent synchrony might be *prognostic indicators* of symptom reduction (i.e. presenting as main effects of child outcome). Our particular interest, however, was to understand whether these or other factors might *predict* specific response to PACT versus TAU.

Methods

Participants and design

Among the 152 dyads enrolled into PACT, 146 (96%) were retained to 13-month outcome (Green et al., 2010). At trial entry, children were aged 24 to 59 months, had ≥12 months non-verbal age-equivalence (NVAE; Mullen, 1995) and met algorithm cut-offs for autism on at least two domains of the Autism Diagnostic Interview – Revised (ADI-R; Lord et al., 1994) as well as algorithm cut-off for autism on the Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000).

Outcome measure

Our primary interest was to ascertain meaningful change on the primary trial outcome measure – ADOS-G social-communication algorithm score (Lord et al., 2000) – with higher scores indicating greater symptom severity. As described above, the ADOS-G was administered at baseline as part of our procedure to confirm child diagnosis. This was re-administered at 13-month trial outcome, with slight adaptation to standard protocol, for the measure of primary outcome.

Typically, the appropriate ADOS-G module is selected according to participant age and language level and then comprises a set of relevant semi-structured tasks focusing on social interaction between the examiner and the participant. Module 1 is used with children who are minimally verbal and Module 2 with those using short phrase speech. However, as reported by Green et al. (2010), children in this trial were administered the same module at outcome assessment as had been administered at baseline, to avoid discontinuity of scores due to the change in module that would typically occur for a child who developed phrase speech. Further, slight adaptation to the conversion of raw item codes to the algorithm was applied, such that raw codes of 3 were retained as such (rather than

rescaled to 2) and raw codes of 8 were rescaled to 3 (rather than to 0), thereby ensuring more sensitive measurement of improvement over time.

Administration was by individuals trained to high standard and participating in regular coding meetings to ensure maintenance of research-level reliability. Coding of outcome ADOS-G assessments was conducted blind to treatment group. Intra-class correlation (ICC) computed from 66 ratings made across 15 tapes evidenced strong agreement among researchers for the standard social-communication algorithm score (ICC = 0.79) and when coding modifications were applied (ICC = 0.83).

Characterisation measures

Additional standardised examiner-administered and parent-report assessments were conducted at baseline assessment, alongside the collection of parent–child interaction footage. As described above, for further confirmation of child diagnosis, the Autism Diagnostic Interview-Revised (ADI-R; Lord et al, 1994) was administered, providing a second metric of autism symptom severity. The ADI-R is a structured interview conducted with parents, spanning the child's full developmental history. It comprises three principal diagnostic domains – social interaction skills and difficulties, communication skills and difficulties, and restricted and repetitive behaviours – and includes cutoff scores suggestive of autism on each of these as well as for a symptom onset domain.

Developmental and language abilities were assessed in several ways. The visual reception and fine motor scales of the examiner-administered Mullen Scales of Early Learning (MSEL; Mullen, 1995) were used to quantify non-verbal developmental abilities in the children, with a NVAE score computed as the average of these domains. The parent-report MacArthur-Bates Communicative Development Inventories, Words and Gestures form (MCDI, Fenson, Dale, & Reznick, 1993) was administered to obtain raw counts of child receptive vocabulary knowledge. An expressive vocabulary count was also available from the MCDI, and Auditory Comprehension and Expressive Language standard scores were obtained from administration of the Preschool Language Scales – 3rd Edition, UK Adaptation (Zimmerman, Steiner, & Pond, 1997). However, these were omitted from the main analysis due to observed multi-collinearity with MSEL NVAE and MCDI receptive vocabulary.

Parent–child interaction. Child pragmatic communication toward the parent, and also parent interaction behaviour toward the child, was quantified from filmed 8-minute free-play interaction samples via the Dyadic

Communication Measure for Autism coding scheme (see Aldred et al., 2004; Green et al., 2010; Hudry et al., 2013). Specifically, coding of child communication focused on classifying initiations (i.e. spontaneous communication acts directed toward the parent) and responses (i.e. acts following on from a previous parental contribution). Coding of parent behaviour focused on classifying communication acts as synchronous (i.e. supportive of the child's attentional focus and commenting on the child's play/activity) or asynchronous (i.e. directive/redirective or placing some demand on the child's attention or behaviour). For analysis, proportionate Child Initiation was computed as the proportion of all child communication acts that were initiations, and proportionate Parent Synchrony was computed as the proportion of all parent communication acts that were synchronous. Moderate to good inter-rater agreement was evident across these scales (computed from 66 ratings made across 22 tapes): Child Initiation, $ICC = .59$; Parent Synchrony, $ICC = .80$.

Family and treatment-related factors. Demographic data were collected via semi-structured parent interview and questionnaire responses, and the following were dichotomous variables were coded for analysis: family composition (dual vs. single parent status), ethnicity (both parents white vs. one/both parents non-white), household Income (less than vs. equal to or greater than £40,000 per annum) and parental educational attainment (less than vs. equal to or greater than one parent with some qualification post 16 years of age). As already described, families were recruited from three trial sites, situated in South London, Manchester and the North East of England. Among families assigned to the PACT arm, the number of treatment sessions attended by families was also recorded for a measure of PACT dose.

Analysis plan

We sought to delineate subgroups of children who improved/did not improve on their ADOS-G scores. While a 4-point reduction has been suggested to represent clinically meaningful improvement (Aldred et al., 2004), this was based on data from a relatively small sample. Hence, we adopted Jacobson and Truax's (1991) Reliable Change Index (RCI), enabling identification of children whose improvement/deterioration could be considered *psychometrically reliable* (vs. attributable to variability of scores/measurement error; see also Eldevik, Jahr, Eikeseth, Hastings, & Hughes, 2010).

Following Jacobson and Truax (1991; formula below), we computed RCI z scores for the change in ADOS-G from baseline to outcome. Our index of reliability (r) was the correlation between baseline and

outcome ADOS-G scores among children randomised to TAU ($n = 72$; test–retest $r = .735$), and our index of variance was the standard deviation (SD) of ADOS-G scores at baseline ($n = 152$; $SD = 4.135$):

$$\text{RCI } z \text{ score} = \frac{(ADOS \text{ baseline score} - ADOS \text{ outcome score})}{\sqrt{2\left(SD\sqrt{(1-r)}\right)^2}}$$

We then sought to delineate two child subgroups – reliable *Improvers* and *Non-Improvers* – where reliable improvement was defined by RCI z scores < -1.96 and reliable deterioration by RCI z scores > 1.96 (i.e. both signifying change unlikely to have occurred by chance; $p < .05$).

We then planned to conduct two-way between-subjects analyses of variance (ANOVAs) – two outcome status (Improvers and Non-Improvers) × two treatment groups (PACT and TAU) – on continuous baseline characteristics of interest or χ^2 contingency analyses in the case of categorical measures. Again, preliminary analysis indicated multi-collinearity among many measures of development and language ability/knowledge taken with child participants. Hence, key baseline characteristics retained for these analyses were:

- parent-reported child autism symptoms: sum of ADI-R algorithm items,
- assessment of child developmental level: NVAE from MSEL, with log-10 transformation was applied to address significant positive skew in the raw data,
- parent-reported receptive vocabulary count from the MCDI,
- proportionate Child Initiation and Parent Synchrony coded from parent–child interaction, with square-root transformation applied to address significant positive skew in raw data for the former,
- parent-reported demographic characteristics: family composition, ethnicity, household income and highest level of education, and
- trial recruitment site and, where relevant, dose of PACT therapy received.

From these analyses, *prognostic indicators* would be evidenced by significant main effects of outcome status, and *predictors* of treatment response would be evidenced by significant two-way (treatment group by outcome status) interaction terms. Subsequently, we planned to include significant baseline characteristics within a logistic regression to identify which singly/ together contributed predictive value for child Improver versus Non-Improver outcome status.

Results

Reliable symptom improvement (i.e. RCI $z < -1.96$) was identified for 43 children, with this threshold corresponding to a ≥ 6-point decrease in ADOS-G scores. No child showed *reliable deterioration* in autism symptoms (i.e. RCI $z > 1.96$), so we made the post hoc decision to classify as Non-Improvers those children who made *no change* or showed *any* increase in ADOS-G scores over time. Hence, Non-Improvers comprised those 41 children whose RCI $z \geq 0$, reflecting 0–5-point increase in ADOS-G scores.

Table 1 shows baseline data for the whole cohort and for Improver and Non Improver subgroups. We also show data for the remaining 62 children who showed intermediate, non-reliable change (i.e. RCI $z = -1.96$ to 0) but were then excluded from further analysis.

Full data supporting the principal analyses reported below are shown in the online Appendix A. Table 2 shows ANOVA results for the continuous baseline characterisation measures. A significant main effect of outcome status presented for baseline NVAE, such that this was greater among children who were Improvers ($M = 29.5$, $SD = 10.6$) versus Non-Improvers

($M = 25.5$, $SD = 10.8$), with moderate effect size ($d = .46$). The two-way interaction term approached significance for parent synchrony, such that this was somewhat lower among parents from families assigned to TAU where children were Non-Improvers ($M = 23.9$, $SD = 9.2$), compared to both those families assigned to TAU where children were Improvers ($M = 30.5$, $SD = 10.2$) *and* to those assigned to PACT, irrespective of child outcome status (Improvers $M = 28.3$, $SD = 11.4$; Non-Improvers $M = 31.3$, $SD = 16.4$).

Table 3 shows χ^2 contingency test results for the categorical baseline characterisation measures. A significant association presented for trial recruitment site such that, among children from South London, there were more Non-Improvers than Improvers. Children recruited from Manchester and North-East England, however, were more often Improvers than Non-Improvers. Follow-up analysis indicated this association to apply only within the TAU trial arm such that, among families assigned to TAU, there were more Non-Improvers than Improvers at the South London site (vs. similar proportion of Improvers/Non-Improvers in TAU at the other two sites). Finally, among families assigned to PACT, therapy

Table 1. Baseline characteristics of total cohort and subgroups of reliable Improvers, Non-Improvers and children making intermediate gains.

	Cohort (N = 146)	Improvers (N = 43)	Intermediate (N = 62)	Non-Improvers (N = 41)
Child characteristics				
Age (months)	44.7 (7.9)	45.0 (7.7)	44.7 (8.0)	44.7 (8.2)
ADI-R algorithm score	34.3 (6.7)	34.0 (6.9)	34.8 (6.6)	33.8 (6.8)
MSEL non-verbal age-equivalence[a]	26.3 (10.0)	*29.5 (10.6)*	*24.6 (8.5)*	25.5 (10.8)
MCDI receptive vocabulary[b]	162 (120)	178 (110)	144 (125)	172 (122)
Parent–child interaction measures				
DCMA Child Initiation	13.7 (9.8)	14.9 (8.7)	12.2 (9.8)	14.8 (10.6)
DCMA Parent Synchrony	28.4 (11.9)	29.2 (10.9)	28.6 (11.7)	27.3 (13.4)
Family measures				
Single (vs. dual) parent family	23%	16%	21%	32%
Both parents white (vs. other)	58%	67%	55%	54%
Income <£40K (vs. ≥£40K)	65%	65%	63%	68%
Parental education (≥1 post 16 years)	73%	74%	71%	76%
Site[a]: South London	N = 50	N = 9	N = 21	N = 20
Manchester	N = 50	N = 18	N = 21	N = 11
North East England	N = 46	N = 16	N = 20	N = 10

Note. Data are mean (standard deviation) unless otherwise indicated. Descriptive statistics based on scores prior to log-10/square-root transformation. ADI-R: Autism Diagnostic Interview – Revised (Lord et al., 1994); MSEL: Mullen Scales of Early Learning (Mullen, 1995); MCDI: MacArthur Bates Communicative Development Inventories (Fenson et al., 1993); DCMA: Dyadic Communication Measure for Autism (Aldred et al., 2004; Hudry et al., 2013).
[a]Italicised values indicate significant between-group differences.
[b]Data missing on five cases.

Table 2. Results of ANOVAs comparing continuous baseline characteristics across Improver and Non-Improver subgroups randomised to PACT and TAU.

| | Main effects | | |
	Outcome status	Treatment group	Two-way interaction
Chronological age	$F(1,80) = .08$, $p = .783$, $d = .04$	$F(1,80) = .13$, $p = .723$, $d = .07$	$F(1,80) = .48$, $p = .492$, $\eta^2 = .01$
ADI-R autism symptoms	$F(1,80) = .17$, $p = .685$, $d = .04$	$F(1,80) = 1.54$, $p = .218$, $d = .27$	$F(1,80) = 1.05$, $p = .310$, $\eta^2 = .01$
MSEL non-verbal ability	$F(1,80) = 4.08$, $p = .047$, $d = .46$	$F(1,80) = .06$, $p = .806$, $d = .11$	$F(1,80) = .10$, $p = .757$, $\eta^2 = .00$
MCDI receptive vocabulary	$F(1,78) = .08$, $p = .774$, $d = .05$	$F(1,78) = .55$, $p = .462$, $d = .16$	$F(1,78) = .19$, $p = .667$, $\eta^2 = .00$
DCMA Child Initiation	$F(1,79) = .29$, $p = .591$, $d = .13$	$F(1,79) = .87$, $p = .353$, $d = .22$	$F(1,79) = 2.07$, $p = .154$, $\eta^2 = .03$
DCMA Parent Synchrony	$F(1,79) = .45$, $p = .506$, $d = .15$	$F(1,79) = .93$, $p = .337$, $d = .23$	$F(1,79) = 3.28$, $p = .074$, $\eta^2 = .04$

Note. ADI-R: Autism Diagnostic Interview – Revised (Lord et al., 1994); MCDI: MacArthur Bates Communicative Development Inventories (Fenson et al., 1993); DCMA: Dyadic Communication Measure for Autism (Aldred et al., 2004; Hudry et al., 2013); MSEL: Mullen Scales of Early Learning (Mullen, 1995); PACT: Preschool Autism Communication Trial; TAU: treatment as usual; ANOVA: analysis of variance.

Table 3. Results of chi-square contingency analyses comparing categorical baseline characteristics across improver and non-improver subgroups randomised to PACT and TAU.

	Overall contingency	Within PACT group	Within TAU group
Family composition: single versus dual parent	$\chi^2(1) = 2.75$, $p = .097$	$\chi^2(1) = .82$, $p = .365$	$\chi^2(1) = 1.66$, $p = .198$
Ethnicity: both parents white versus other	$\chi^2(1) = 1.67$, $p = .196$	$\chi^2(1) = 1.46$, $p = .227$	$\chi^2(1) = .55$, $p = .458$
Household income: <£40K (vs. ≥£40K)	$\chi^2(1) = .10$, $p = .758$	$\chi^2(1) = .89$, $p = .345$	$\chi^2(1) = 1.46$, $p = .226$
Parental education: <1 ≥ parent post 16 years	$\chi^2(1) = .02$, $p = .900$	$\chi^2(1) = .63$, $p = .426$	$\chi^2(1) = .01$, $p = .945$
Recruitment site	$\chi^2(1) = 7.20$, $p = .027$	$\chi^2(1) = 1.84$, $p = .398$	$\chi^2(1) = 8.57$, $p = .014$

Note. PACT: Preschool Autism Communication Trial; TAU: treatment as usual.

dose did not differentiate Improvers from Non-Improvers, $z = .45$ $p = .650$.

We included child NVAE and interaction terms of treatment group by each of recruitment site and parent synchrony within a logistic regression on Improver versus Non-Improver outcome status. The overall model was statistically significant – $\chi^2(3) = 13.63$, $p = .009$; *Cox & Snell* $R^2 = .151$; *Nagelkerke* $R^2 = .202$ – increasing correct classification from 50.6% (no predictors entered) to 66.3%. However, only the treatment group × recruitment site interaction (i.e. South London vs. others) carried unique predictive value (*Wald* = 5.28, $p = .022$), with non-significant unique effects for NVAE (*Wald* = 2.64, $p = .104$) and treatment group × parent synchrony (*Wald* = 0.19, $p = .663$).

Given the unique association of recruitment from the South London site with poorer child outcomes – particularly for families *not* assigned to the PACT trial arm – we conducted further post hoc exploration of cross-site differences in attempt to identify possible explanations for this effect at this particular site. As shown in Table 4 and consistent with the ANOVA results described above, families recruited from this site had parents with lower synchrony and children with lower verbal and non-verbal abilities and greater autism symptom severity. Families from this site were also more often single-parent and in the lower household income band than those at both other sites and had somewhat lower educational attainment than families from North-East England.

Furthermore, examination of data on families' access to TAU services revealed that families recruited from South London versus from Manchester and North East England had additional contacts with health, social and other therapeutic supports across the trial period. These included, on average, two more contacts with health service providers (including outpatient hospital visits or inpatient/emergency admissions, appointments with general practitioners, nurses, health visitors, paediatricians, dentists, ophthalmologists, audiologists and dieticians/nutritionists), five more contacts with providers of therapy services (including portage workers, educational/clinical psychologists, occupational therapists, physiotherapists and speech language therapists), and three more contacts with social care services (including social workers, family support workers, community autism specialists, home care workers, play workers or visits to walk-in centres). As shown in Table 5, however, none of these between-group differences was statistically significant

Table 4. Baseline characterisation differences between families recruited into TAU trial arm at three sites.

	South London (N = 26)	Manchester (N = 24)	North East England (N = 22)	Difference between South London and other two sites
Child characteristics				
Age (months)	42.8 (8.2)	45.4 (8.5)	47.4 (7.4)	t(70) = 1.83, p = .072; d = .40
ADI-R algorithm score	35.9 (7.0)	35.0 (7.6)	33.4 (5.4)	t(70) = .97, p = .336; d = .21
MSEL non-verbal age-equivalence (months)	*22.2 (7.6)*	*25.6 (8.3)*	*29.1 (12.1)*	*t(70) = 2.20, p = .022; d = .59*
MCDI receptive vocabulary	136 (122)	162 (110)	199 (141)	t(67) = 1.41, p = .163; d = .35
Parent–child interaction measures				
DCMA Child Initiation	11.3 (8.5)	15.4 (10.0)	15.2 (11.3)	t(70) = 1.37, p = .176; d = .30
DCMA Parent Synchrony	*23.9 (11.3)*	*28.3 (11.7)*	*30.7 (10.1)*	*t(70) = 2.06, p = .044; d = .49*
Family measures				
Single (vs. dual) parent family	*39%*	*21%*	*14%*	*$\chi^2(1) = 3.93, p = .047$*
Both parents white (vs. other)	*15%*	*75%*	*82%*	*$\chi^2(1) = 26.60, p < .001$*
Household income <£40K (vs. ≥£40K)	85%	75%	64%	$\chi^2(1) = 2.01, p = .157$
Parental education (≥1 post 16 years)	54%	54%	77%	$\chi^2(1) = .90, p = .342$

Note. Data are mean (standard deviation) unless otherwise indicated. Italicised values indicate significant between-group differences.
ADI-R: Autism Diagnostic Interview – Revised (Lord et al., 1994); MSEL: Mullen Scales of Early Learning (Mullen, 1995); MCDI: MacArthur Bates Communicative Development Inventories (Fenson et al., 1993); DCMA: Dyadic Communication Measure for Autism (Aldred et al., 2004; Hudry et al., 2013); PACT: Preschool Autism Communication Trial; TAU: treatment as usual.

Table 5. Numbers of contacts with services by families assigned to the TAU arm at the South London versus two other trial recruitment sites.

	South London	Manchester/ North East England	Coefficient	95% CI	p
N	26	43			
Health contacts	7.31 (5.56)	9.26 (6.65)	−1.95	(−5.05 to 1.16)	0.215
Therapy contacts	13.78 (13.43)	19.39 (18.26)	−5.61	(−14.31 to 3.09)	0.202
Social care contacts	6.69 (15.60)	3.21 (8.39)	3.48	(−2.28 to 9.24)	0.232

Note. PACT: Preschool Autism Communication Trial; TAU: treatment as usual; CI: confidence interval.

and so differential access to TAU services is unlikely to explain the observed site-specific effects on child outcome.

Discussion

Recent reviews highlight the need for treatment to be better adapted to individual children with autism, particularly in light of limited resources (e.g. Romanczyk et al., 2014). However, identifying factors associated with differential outcomes presents a significant challenge, and existing studies have often failed to differentiate true *predictors* of treatment response from indicators of generally better *prognosis*. Exploiting the large PACT dataset (Green et al., 2010) and retaining focus on the a priori nominated primary outcome measure of change in core symptom severity – for which substantial variability was observed – we adopted a

pragmatic and data-driven approach to try to identify for whom this particular parent-mediated, communication-focussed treatment might have been most appropriate. We identified subgroups of children who were reliable improvers and non-improvers in autism symptom severity and then examined whether commonly available baseline characteristics varied between these subgroups, seeking to mirror the process that might be adopted by community professionals to guide individualised treatment decision-making for pre-schoolers with autism.

Non-verbal developmental level as a prognostic indicator

Among the large cohort, followed over around one year, ~30% of children showed decreases in their social-communication symptoms of autism to an

extent that was highly unlikely to have occurred by chance (and corresponding to a ≥6-point reduction on the ADOS-G modified algorithm total score). Similarly, a subgroup of ~28% of children showed a clear lack of improvement or some worsening in their symptoms across the same period. Nevertheless, among the various baseline factors available for our analysis – child age, initial autism symptom severity, receptive language knowledge, social initiations and parent/family socio-demographic factors – we found a striking lack of differences between our Improver and Non-Improver subgroups.

One clear exception to this pattern of results was for child non-verbal ability, which presented as a significant *prognostic* indicator of outcome for children in this trial. This replicates findings from other studies (see Magiati et al., 2014) such that children who made reliable improvement in their autism symptoms had shown greater initial non-verbal ability than those whose symptoms did not improve. That this effect was *prognostic* – applicable to children who received the PACT intervention or community TAU – rather than predictive of response within one particular condition or other, was identifiable within this dataset given sound experimental design with random assignment of children to intervention arms. Conversely, many studies of early autism intervention are prospective cohort studies, rather than intervention trials (see Bieleninik et al., 2017) within which it is not possible to disentangle prognostic indicators – such as non-verbal ability – from *true predictors* of treatment response.

The significance of parental communicative synchrony

Alongside our clear prognostic effect of NVAE, we also observed a trend toward significant *predictive* effect for parent communicative synchrony. That is, a marginal interaction of outcome status by treatment group presented, such that baseline parent synchrony was somewhat lower specifically among TAU families with children who were *non-improvers*, compared to both TAU families with children who were improvers *and* also to families assigned to PACT therapy irrespective of child outcome. This effect should be interpreted with caution, pending future replication work. However, we have recently demonstrated the mechanistic importance of parent synchrony, through mediation analysis on the PACT dataset, for (1) proximal gains in child initiation skills and (2) more distal reduction in child symptoms. That is, to the extent that participation in PACT had an overall (small, non-significant) effect on child symptoms (Green et al., 2010), this was achieved through a large

proximal treatment effect on parent synchrony which brought moderate downstream improvements in child communicative initiations, and (attenuated) reductions in core symptom presentation (Pickles et al., 2015). The current result – a marginally significant *predictive* effect of reduced parent synchrony for poorer child outcomes, in the context of one year of receipt of community TAU – provides further support for the importance of parent interaction behaviour in the context of early childhood autism. In the absence of participation in a therapy that focuses on supporting parent sensitive interaction with their child, greater 'natural' parent synchrony may be a protective factor against (and lower 'natural' synchrony a risk factor for) poorer child outcome during the preschool period. That is, for parents with more limited communicative synchrony, participation in PACT therapy may mitigate the odds of the child maintaining or increasing their core social-communication symptoms.

The significance of trial recruitment site

Finally, we observed a significant *predictive* effect of trial recruitment site, such that children recruited from South London showed poor outcomes if assigned to TAU, but more balanced odds of core symptom improvement if assigned to receive PACT therapy. We had included trial site within our analysis, because of its potential impact on factors such as treatment session attendance and adherence to therapy processes (e.g. see Carr et al., 2015).

When entered into the logistic regression on child outcome status, recruitment site carried unique predictive value in this dataset, with no further variance explained by child non-verbal ability or parent synchrony. Exploratory post hoc analysis of community services accessed by families across the three trial sites provided no evidence that this effect might be underpinned by the amount or type of TAU available to families in South London versus Manchester and North East England. However, this former cohort differed from those at the latter two sites in having higher representation of (a) children with greater baseline autism symptoms, (b) poorer verbal and non-verbal skills, (c) parents with lower communicative synchrony and (d) more single-parent and culturally/ethnically diverse households. As noted by Kasari and Patterson (2012) research with under-represented populations is very limited in the field of autism, with few trials involving ethnically or culturally diverse samples. The current findings suggest that the provision of routine TAU may be inadequate, particularly for more disadvantaged families, even within relatively high resource countries.

Considerations and future directions

Within the PACT cohort, we were able to identify a subgroup of children who showed clear improvement in their autism symptoms, using Jacobson and Truax's (1991) RCI. We did not, however, identify any children who experienced reliable symptom *deterioration*. While this is clinically encouraging, evidence from adult mental health studies indicates that the predictors of positive outcomes may differ from those associated with negative treatment response (Starcevic & Brakoulias, 2008). Thus, further work is required to understand not only for whom particular interventions may be helpful but also whether there are any children for whom an approach may be contraindicated.

This field also lacks good, functional indicators of outcome for young children with autism. Nevertheless, evaluation of the natural developmental growth suggests the possibility of divergent trajectories for core symptom presentation versus adaptive behaviour, thereby justifying ongoing focus on differential types of intervention outcome (Szatmari et al., 2015). Here, retaining the a priori aim of the PACT trial (Green et al., 2010; Pickles et al., 2015), our analysis focus was on changes in child core autism symptoms. However, other constructs may be equally important indicators of outcome and other measures may be more sensitive to change over time (e.g. social-communication skills, adaptive behaviour, quality of life; McConachie et al., 2015). Future consideration is therefore warranted regarding the predictors of change in secondary outcome measures within this RCT dataset, including *parent synchrony* as the direct proximal target of PACT therapy sessions and *child initiation* as the proximal target outcome for children.

Statistical power for the current analysis may have been limited. However, we adopted this pragmatic alternative to formal moderation analysis to explore the predictors of *clearly* (i.e. reliably) positive child outcome or *clear lack* thereof. Moreover, we verified that our observed associations of symptom change with NVAE, parent synchrony and site also held when more conventional analysis was undertaken retaining both the full participant sample and symptom change as a continuous metric. Furthermore, our failure to identify additional prognostic or predictive associations is unlikely to be due to limited statistical power as the effect sizes observed here for non-significant between-group comparisons were small. Rather, it seems likely that broad characterisation measures – such as age, core symptom severity and developmental/cognitive ability – are insufficiently sensitive to serve as predictors of treatment response in young children with autism. Indeed, other groups have begun to explore more specific indicators of early skills – such as the exploration

and functional use of objects, joint attention, imitation, and social motivation and response to social reward – as potential predictors of treatment response (see Vivanti et al., 2014).

Summary and conclusion

In summary, this study contributes to a growing empirical evidence base for the prognostic value of child non-verbal ability – contextualising this clearly as a *prognostic* indicator of child outcome irrespective of therapy group assignment. Further, these data provide some further indication of the potential importance of parent synchrony as a *protective factor* in autism (see also Pickles et al., 2015). Finally, these results highlight the importance of considering trial *recruitment site* and what comprises *TAU* when interpreting outcomes from intervention trials. These findings require replication in the context of other evaluations of autism treatment *efficacy* – including other parent-mediated approaches and therapist-delivered interventions alike. Our approach should equally be applied within community-based evaluations of treatment *effectiveness*.

Tasked with identifying and providing treatment approaches best suited to particular children and families, clinicians face the potential misuse of costly or limited resources, and possible exacerbation of child behaviour problems and parent stress from wasted time and effort (March, 2009; Winburn et al., 2014). Hence, it is critical to expand our understanding of what works for whom to develop an evidence base around individualising treatment plans for young children and their parents.

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