

# Moderators of response to child-based and parent-based child anxiety treatment: a machine learning-based analysis

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**Background:** Identifying moderators of response to treatment for childhood anxiety can inform clinical decision-making and improve overall treatment efficacy. We examined moderators of response to child-based cognitive-behavioral therapy (CBT) and parent-based SPACE (Supportive Parenting for Anxious Childhood Emotions) in a recent randomized clinical trial. **Methods:** We applied a machine learning approach to identify moderators of treatment response to CBT versus SPACE, in a clinical trial of 124 children with primary anxiety disorders. We tested the clinical benefit of prescribing treatment based on the identified moderators by comparing outcomes for children randomly assigned to their optimal and nonoptimal treatment conditions. We further applied machine learning to explore relations between moderators and shed light on how they interact to predict outcomes. Potential moderators included demographic, socioemotional, parenting, and biological variables. We examined moderation separately for child-reported, parent-reported, and independent-evaluator-reported outcomes. **Results:** Parent-reported outcomes were moderated by parent negativity and child oxytocin levels. Child-reported outcomes were moderated by baseline anxiety, parent negativity, and parent oxytocin levels. Independent-evaluator-reported outcomes were moderated by baseline anxiety. Children assigned to their optimal treatment condition had significantly greater reduction in anxiety symptoms, compared with children assigned to their nonoptimal treatment. Significant interactions emerged between the identified moderators. **Conclusions:** Our findings represent an important step toward optimizing treatment selection and increasing treatment efficacy. **Keywords:** Anxiety; parent training; behavior therapy; machine learning.

## Introduction

Well-established treatments for childhood anxiety disorders, including cognitive-behavioral therapy (CBT) and medication, are insufficiently efficacious in up to 50% of cases (Wang et al., 2017). Parent-based treatment provides an alternative to current frontline therapies, and a recent randomized controlled trial (RCT) was the first to compare the efficacy of an entirely parent-based treatment with that of CBT (Lebowitz, Marin, Martino, Shimshoni, & Silverman, 2020). SPACE (Supportive Parenting for Anxious Childhood Emotions), the parent-based treatment, was efficacious and noninferior to CBT. These findings represent an important development for the field and underscore the potential of parent-based treatment for childhood anxiety.

The availability of an efficacious parent-based alternative to CBT raises important questions however, and among them the question of personalizing treatment prescription. In the absence of empirical data to inform treatment assignment, clinicians rely on subjective factors such as patient or therapist preference (Chu, Merson, Zandberg, & Areizaga, 2012). Given the overall similar efficacy of SPACE and CBT, it is theoretically possible that treatment

selection is of little importance. However, given the distinct modalities, and hypothesized mechanisms and active ingredients of SPACE and CBT, it is also possible that despite overall similar response rates, individual response to each treatment could be meaningfully different.

Apart from the differences inherent in treating a child directly versus treating the child's disorder exclusively through parents, SPACE and CBT focus on different aspects of child anxiety and target different behaviors for change. CBT focuses on children's cognitive and behavioral symptoms (Gosch, Flannery-Schroeder, Mauro, & Compton, 2006). SPACE focuses on family accommodation of childhood anxiety (Lebowitz & Omer, 2013). Parents in SPACE are guided in identifying and systematically reducing family accommodation and are taught to increase supportive responses by conveying acceptance of the child's distress along with confidence in the child's ability to tolerate anxiety. The interpersonal/affiliative aspects of child anxiety targeted in SPACE and the individual-level symptoms targeted in CBT also involve different neurobiological systems that may differentially impact treatment outcomes.

Identifying moderators of treatment outcomes is a critical step toward more precise clinical decision-making, as emphasized by NIMH's Strategic

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Research Priorities (National Institute of Mental Health, 2019). Traditional approaches to examining outcome moderators focus on single variables and have yielded important, albeit inconsistent, results (Norris & Kendall, 2020). For example, most studies examining child age and sex as potential moderators of anxiety treatment outcome reported nonsignificant findings, while others reported significant effects (Bodden et al., 2008; Cobham, Dadds, Spence, & McDermott, 2010; Legerstee et al., 2008; Nilsen, Eisemann, & Kvernmo, 2013). Likewise, examining psychosocial factors such as specific anxiety disorders or comorbid diagnoses and symptoms has yielded both significant and nonsignificant findings (Berman, Weems, Silverman, & Kurtines, 2000; Compton et al., 2014; Liber et al., 2008; Manassis et al., 2002; Puleo & Kendall, 2011; Shortt, Barrett, & Fox, 2001; Taylor et al., 2018; Walkup et al., 2003), as has examining parental psychopathology and family functioning (Bodden et al., 2008; Cobham, Dadds, & Spence, 1998; Taylor et al., 2018; Victor, Bernat, Bernstein, & Layne, 2007).

The inconsistent pattern of results highlights limitations inherent to searching for a single factor to explain variability in treatment response, while it is more plausible to hypothesize that no single factor is as important as a set of interrelated factors in predicting who benefits the most from each treatment. Treating each moderator as a separate hypothesis also leads to multiple comparisons and potentially inflated type I errors, model misspecification, and multicollinearity, reducing replicability across studies. Although technically possible, examining multiple moderators concurrently using traditional moderation analyses is usually not feasible given the sample sizes in childhood anxiety studies.

Machine learning approaches offer an alternative to traditional moderation analysis and address these challenges by examining moderation effects within a set of interrelated variables, allowing for the integration of multiple units of analysis from various domains. Machine learning has been instrumental in identifying moderators where few consistent findings could previously be reached (e.g., Cohen & DeRubeis, 2018; Zilcha-Mano, Roose, Brown, & Rutherford, 2018).

Our goal was to apply a machine learning method capable of evaluating multiple moderators and their interactions, to the search for moderators of treatment response to SPACE versus CBT. We examined a range of potential moderators, building on and expanding previous research, and reflecting important differences between SPACE and CBT. Thus, we included demographic (age and sex), socioemotional (anxiety diagnosis and severity, family accommodation, comorbid diagnoses/symptoms, social skills), parenting (acceptance, control, involvement, negativity), and parent-level socioemotional (anxiety, depression, marital satisfaction) variables.

We further extended prior research by also including biological variables, child and parent salivary oxytocin levels. Identifying biological moderators is particularly important as these are objectively measured (and not prone to subjective biases) and can provide new insights into underlying mechanisms targeted by different treatments. We focused on the oxytocinergic system because previous research implicates it in interpersonal/affiliative behavior and anxiety regulation, as well as in parental responses to child anxiety: a crossroads of interpersonal behavior and anxiety regulation (MacDonald & Feifel, 2014; Milrod et al., 2014; Neumann & Slatery, 2016). In particular, oxytocin levels have been significantly linked to family accommodation (Lebowitz et al., 2016) and reducing accommodation is a central focus of SPACE.

Using machine learning, we examined the effects of the proposed moderators on child anxiety outcomes, as reported by children, parents, and independent-evaluators. Intra-informant agreement is typically low in childhood anxiety research (Mash & Hunsley, 2005), making it important to compare and contrast results across informants. Each of the three outcomes/informants was examined in separate models to create a multidimensional assessment that can underscore their distinct pros and cons likely to be instrumental to future clinical decision-making, and to ensure that the psychometric properties of each instrument are retained. Correlations between the three measures are provided in the Supplement (Tables S1-S3).

To test the clinical benefit of prescribing treatment based on identified moderators, we compared symptom reduction for patients randomly assigned to their optimal and nonoptimal treatment conditions. We hypothesized that children randomly assigned to their optimal treatment condition would show significantly more anxiety reduction, compared with children randomly assigned to their nonoptimal treatment.

Finally, to explore relations between moderators and shed light on how they interact to predict outcomes, we used regression tree analysis conducted separately for child-reported and parent-reported outcomes, focusing on those variables with the strongest moderating effects in the random forest analyses. The random forest analysis is aimed at identifying the strongest moderators whereas the regression tree analysis is aimed at exploring how the variables interact to predict outcomes.

## Methods

The methods and sample characteristics for the RCT are detailed elsewhere (Lebowitz et al., 2020). In brief, 124 children (ages 7–14 years) were randomly assigned to either 12 sessions of parent-based SPACE with no direct child-therapist contact, or to 12 sessions of child-based CBT. All children had primary anxiety disorders, were either medication free or on a stable dose of antidepressant or stimulant and agreed to refrain from

changes or additional treatments during the study. Therapists were doctoral and postdoctoral level psychology students and received extensive training in SPACE and CBT. The study was approved by the Institutional Review Board; parental informed permission and consent, and child assent, were obtained.

## Measures

All potential moderators were assessed prior to treatment assignment and the same variables were included in analyses focusing on child-reported, parent-reported and independent-evaluator-reported outcomes. Of note: the machine learning approach used can effectively handle highly intercorrelated variables. The following variables were included as potential moderators:

### Demographic variables: Child sex and age

**Child-rated variables.** Anxiety symptoms (child rated Screen for Child Anxiety Related Emotional Disorders; SCARED-C; Muris, Merckelbach, Van Brakel, & Mayer, 1999) depression symptoms (Child Depression Inventory; CDI; Kovacs, 1985) family accommodation (Family Accommodation Scale – Anxiety, Child-Report; FASA-CR; Lebowitz, Scharfstein, & Jones, 2015) maternal acceptance, maternal psychological control and maternal firm control (Child Report of Parental Behaviors Inventory; CRPBI; Schaefer, 1965) social skills (child-rated Social Skills Rating System; SSRS-C; Gresham & Elliott, 1990).

**Parent-rated variables.** Child anxiety symptoms (parent rated Screen for Child Anxiety Related Emotional Disorders; SCARED-P; Muris et al., 1999) child depression symptoms (parent-rated Mood and Feelings Questionnaire; MFQ; Angold & Costello, 1987) family accommodation (parent-rated Family Accommodation Scale – Anxiety; FASA; Lebowitz et al., 2013) child externalizing symptoms (Externalizing Problems on the Child Behavior Checklist; CBCL-EXT; Achenbach, 1994) maternal acceptance, psychological control and firm control (Parent Report of Parental Behaviors Inventory; PRPBI; Schaefer, 1965) child social skills (parent-rated Social Skills Rating System; SSRS-P; Gresham & Elliott, 1990) parent anxiety symptoms (Beck Anxiety Inventory; BAI; Beck, Epstein, Brown, & Steer, 1988) parent depression symptoms (Beck Depression Inventory; BDI; Beck, Steer, & Brown, 1996) marital satisfaction (Couples Satisfaction Index; CSI; Funk & Rogge, 2007).

**Independent-evaluator-assessed variables.** Child diagnoses (Anxiety Disorders Interview Schedule: Child and Parent Versions; ADIS C/P; Albano & Silverman, 2020) child anxiety symptoms (Pediatric Anxiety Rating Scale; PARS; RUPP Anxiety Study Group, 2002).

**Behavioral observations.** Maternal behavior was coded based on a brief parent-child interaction involving a series of challenging tangram-block puzzles. Interactions were coded by two independent-evaluators trained to reliability (Hudson & Rapee, 2001). Two variables were coded: parental negativity during the interaction (Parent Negativity) and parental involvement during the interaction (Parent Involvement).

**Biological variables.** Salivary oxytocin levels were measured in children and parents. Samples were collected using salivettes (Sarstedt, Rommelsdorf, Germany), between 4PM and 5PM, after a 2-hour fast and stored at  $-20^{\circ}\text{C}$  until centrifuged twice, 2 days apart, at  $40^{\circ}\text{C}$  at 1,500 g for 20 min. Liquid samples were lyophilized and stored at  $-80^{\circ}\text{C}$ . Samples were reconstituted in water and concentrated  $\times 4$  before immunoassay with an Enzo<sup>®</sup> (NY, USA) ELISA kit. Measurements were

performed in duplicate. Concentrations were calculated using Matlab-7 according to relevant standard curves.

Two samples were collected from each child and mother, before and after the parent-child interaction, and were included in analyses both separately (Child OT [Before]; Child OT [After]; Parent OT [Before]; Parent OT [After]), and as the mean of both measurements (Child OT; Parent OT). As noted, the machine learning approach effectively handles high collinearity.

## Statistical analyses

**Overview.** A four-step process was followed. First, the 39 a priori selected potential moderators were introduced to a random forest machine learning algorithm to identify the strongest moderators. Second, the importance of the moderators was calculated, they were ranked by order of importance, and the most important ones were identified and used in the next step. Third, to explore the utility of the identified variables, we estimated the Personalized Advantage Index (PAI). Fourth, to explore the directions of the effects and drive potential post hoc explanations, we applied regression tree analyses, which enable the detection of complex interactions between variables.

**Identifying the strongest moderators.** To identify the strongest moderators of the association between treatment condition and outcome, we used bootstrap aggregation of model-based recursive partitioning by the random forest algorithm, implemented in the R package ‘*mobForest*’ (version 1.2; Garge, Bobashev, & Eggleston, 2013). In this method, 1,000 model-based trees (pathways determining which variables best moderate outcomes) were constructed based on bootstrapped samples from the primary dataset. For each tree, the model-based recursive partitioning searched for binary splits in the sample that result in model parameters on one side of the split being most different from those on the other side. We used a random sample of partitioning variables for splitting at each node (potential split-point). In each leaf (i.e., split) of the tree, we estimated outcomes for SPACE versus CBT. Final model predictions were obtained by aggregation across trees. The minimum alpha level for splits was set to 0.05, and the minimum leaf size was set to 30 children. To impute missing observations in the predictors, we used a Markov Chain Monte Carlo-based method, with 500 repetitions.

**Estimating the importance of potential moderators.** To identify the strength of potential moderator splits, we calculated a variable-importance statistic using the conditional permutation scheme (Strobl, Boulesteix, Kneib, Augustin, & Zeileis, 2008). The importance statistic reflects the contribution of each variable to predicting the target variable. It is measured by the amount of worsening in prediction of ‘held out’ cases in a bootstrapped sample, when using a random permutation of each original variable separately. Although the bootstrapped scheme is exploratory, using it to select variables can result in stable predictors, often less sensitive to unique features of a given dataset. We repeated this process for each of the three informants.

**Exploring the utility of the potential identified moderators.** To examine the utility of the models for improving treatment efficacy through treatment assignment, we compared the difference in symptom reduction between participants randomly assigned to their predicted optimal treatment versus those assigned to their nonoptimal treatment (DeRubeis et al., 2014). The optimal treatment for each patient was determined within a Cross-Validation procedure. We removed each patient in turn from the dataset and fitted a regression with the main effects and interactions with treatment arm of the moderators identified by the random forest

using the data from the rest of the patients. This fit was used to estimate the potential predicted outcome of the patient removed, had that patient been assigned to each arm. The treatment with the highest predicted symptom reduction was considered optimal if the difference was at least 0.1 times the standard deviation of the symptom index (equivalent to a small effect size). Individuals with below-threshold difference did not enter the PAI calculation. The difference in average outcome for patients assigned to their optimal versus nonoptimal treatment is the average Personalized Advantage Index (PAI; DeRubeis et al., 2014).

*Exploring interactions between identified moderators in predicting outcomes.* To explore how identified moderators interact with treatment condition in predicting outcomes, we used the most robust predictors identified in mobForest. These were introduced in regression tree analysis applying the 'mob' function of the R 'party' package (Zeileis, Hothorn, & Hornik, 2008). The criterion for adding splits to the tree was a level of significance of 0.1 for the split. Regression tree analyses were conducted only when mobForest resulted in  $\geq 2$  moderators, so that interactions between moderators could be explored.

## Results

### Identified moderators

The random forest analyses identified a set of variables as important moderators of treatment outcome for each of the three informants. Figure 1 shows the resulting variable-importance plots. For the analysis based on parent-reported child anxiety outcomes (SCARED-P), two variables were selected by the algorithm: Child OT (After) and Parent Negativity. For the analysis based on child-reported outcomes (SCARED-C), three variables were selected: baseline SCARED-C, Oxytocin Parent (Before), and Parent Negativity. For the analysis based on independent-evaluator-rated outcomes (PARS) only baseline PARS level was selected.

### Utility of identified moderators

For parent-rated outcomes (SCARED-P), 55 patients were randomly assigned to their optimal treatment and 49 to their counter-optimum treatment. The mean decrease in the former was 12.98 versus 8.52 in the latter, a significant difference ( $t(86.7) = -2.18$ ,  $p = .031$ ,  $d = 0.47$ ). Thus, patients gained 4.46 points reduction on average through random assignment to their optimal treatment.

For SCARED-C as the outcome, 50 patients were randomly assigned to their optimal treatment and 44 to their counter-optimum treatment. The mean decrease in the former was 11.97 versus 11 in the latter, a nonsignificant difference ( $t(73.9) = -0.31$ ,  $p = .75$ ,  $d = 0.07$ ).

### Interactions between moderators

Two regression tree analyses were conducted, for the two outcome variables for which random forest

identified  $\geq 2$  variables (SCARED-P; SCARED-C; Figure 2). For SCARED-P, for participants with higher Parent Negativity ( $>2.5$ ) and higher Child Oxytocin (After) ( $>18.28$ ), SPACE led to greater symptom reduction than CBT (true for  $n = 38$  participants). For those with higher Parent Negativity ( $>2.5$ ) but lower Child Oxytocin (After) ( $\leq 18.28$ ), no meaningful differences were apparent between the treatments (true for  $n = 21$  participants). For those with lower Parent Negativity ( $\leq 2.5$ ), CBT led to more symptom reduction than SPACE (true for  $n = 45$  participants).

For SCARED-C, for those with higher baseline SCARED-C ( $>28$ ), CBT led to more symptom reduction than did SPACE. For those with baseline SCARED-C  $\leq 28$ , no meaningful differences were apparent between the treatments (Figure 3).

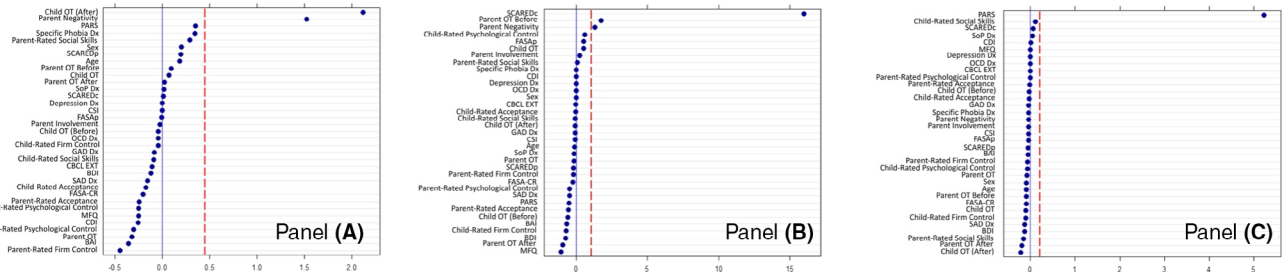
## Discussion

We applied machine learning to evaluate moderators of treatment response to child-based CBT versus parent-based SPACE for childhood anxiety. Potential moderators included demographic, clinical, behavioral, and biological variables relating to both the parent and the child, and we examined moderation of outcomes rated by children, parents, and independent-evaluators.

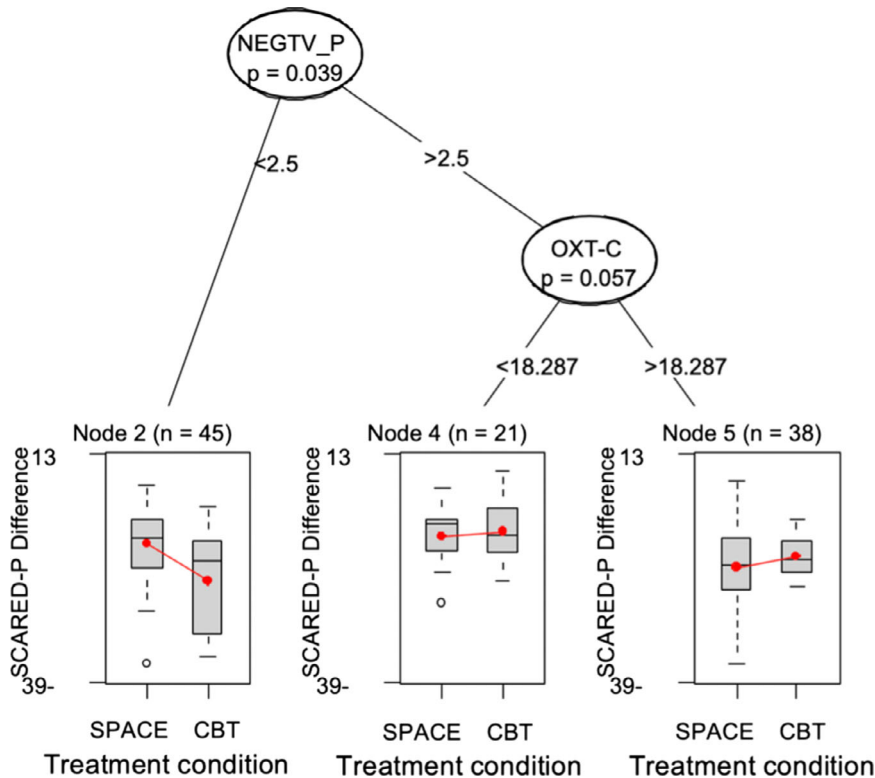
For each of these outcomes, meaningful moderators emerged. The models based on child-rated and parent-rated outcomes both pointed to parental negativity and to oxytocinergic functioning as important moderators. The model based on child reports also identified child self-reported anxiety severity as an important moderator. The model based on independent-evaluator assessments was different and pointed only to baseline anxiety severity, also as assessed by the independent-evaluator.

The concordance between the separate models, based on child-rated and parent-rated outcomes, strengthens confidence in the importance of identified moderators. Both underscore the importance of parental negativity and oxytocinergic functioning in treatment response. Parental negativity, especially in relation to child anxiety, may be an important aspect of the clinical presentation that is addressed more through parent-based treatment than through CBT. Changing parental responses may be particularly important for when negativity is high. This is strengthened by the exploration of interactions between moderators, showing higher parental negativity, in conjunction with higher child oxytocin levels, predicted greater improvement in SPACE, whereas low negativity predicted greater response to CBT.

Both models also highlighted oxytocinergic functioning as an important moderator. Oxytocin is implicated in anxiety regulation and in the modulation of social/affiliative behavior (Lebowitz et al., 2016; MacDonald & Feifel, 2014; Neumann & Slatery, 2016). As such, it may be particularly important for comparing child-based treatment with

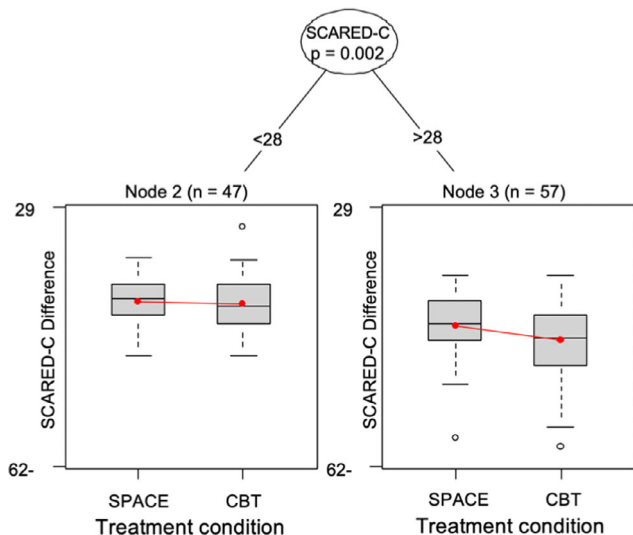


**Figure 1** Variance-importance plot for model-based recursive partitioning trees based on parent-reported (Panel A), Child-Reported (Panel B), and Independent-Evaluator-Reported (Panel C) Child Anxiety Outcomes. The horizontal axis represents the average increase in classification accuracy gained by using the specific variable in the ‘real’ data, compared with using the specific variable in permuted data. Positive values indicate that a variable predicts child-specific treatment outcome and performs better than random noise. Variables to the right of the red line are selected for later modeling. Note: PARS – Pediatric Anxiety Rating Scale; Child-Rated Social Skills – Social Skills Rating System, child-report; SCAREDc – Screen for Childhood Anxiety Related Disorders, child report; SoP Dx – Diagnosis of Social Phobia; CDI – Child Depression Inventory, child report; MFQ – Mood and Feelings Questionnaire, parent-report; Depression Dx – Diagnosis of Major or Persistent Depression; OCD Dx – Diagnosis of OCD; CBCL EXT – Child Behavior Checklist (Externalizing Problems); Parent-Rated Psychological Control; Parent Report of Parental Behavior (Psychological Control); Parent-Rated Acceptance – Parent Report of Parental Behavior (Acceptance); Child OT (Before) – Child Salivary; Oxytocin Level (pg/ml) Before Parent-Child Interaction; Child-Rated Acceptance – Child Report of Parental Behavior (Acceptance); GAD Dx – Diagnosis of Generalized Anxiety Disorder; Specific Phobia Dx – Diagnosis of Specific Phobia; Parent Negativity – Parent Negativity during Parent-Child Interaction; Parent Involvement-Parent Involvement during Parent-Child Interaction; CSI – Couple’s Satisfaction Index; FASAp – Family Accommodation Scale – Anxiety, parent-report; SCAREDP – Screen for Childhood Anxiety Related Disorders, parent-report; BAI – Beck Anxiety Inventory; Parent-Rated Firm Control – Parent Report of Parental Behavior (Firm Control); Child-Rated Psychological Control – Child Report of Parental Behavior (Psychological Control); Parent OT – Parent Salivary Oxytocin Level (pg/ml), mean of before and after interaction; Sex – N/A; Age – N/A; Parent OT Before – Parent Salivary Oxytocin Level (pg/ml) Before Parent-Child Interaction; FASA-CR – Family Accommodation Scale –Anxiety, Child-Report; Child OT – Child Salivary Oxytocin Level (pg/ml), mean of before and after interaction; Child-Rated Firm Control – Child Report of Parental Behavior (Firm Control); SAD Dx – Diagnosis of Separation Anxiety Disorder; BDI – Beck Depression Inventory; Parent-Rated Social Skills – Social Skills Rating System, parent-report; Parent OT After – Parent Salivary Oxytocin Level (pg/ml) After Parent-Child Interaction; Child OT (After) – Child Salivary Oxytocin Level (pg/ml) After Parent-Child Interaction



**Figure 2** Regression tree for identifying moderators of treatment response based on parent-reported child anxiety outcomes. The red dots are the means of the outcome variables (calculated as the difference from post- to pretreatment) for the specific subgroup. The red line connects the two means. The three middle black lines (the box) of the box-plots are as follows: the middle is the median, and the two other lines are the first and third quartiles. The two extreme lines (the whiskers) extend to the most extreme data point, which is no more than 1.5 times the length of the box





**Figure 3** Regression tree for identifying moderators of treatment response based on child-reported child anxiety outcomes. The red dots are the means of the outcome variables (calculated as the difference from post- to pretreatment) for the specific subgroup. The red line connects the two means. The three middle black lines (the box) of the box-plots are as follows: the middle is the median, and the two other lines are the first and third quartiles. The two extreme lines (the whiskers) extend to the most extreme data point, which is no more than 1.5 times the length of the box. Note: SCARED-C: Screen for Childhood Anxiety Related Emotional Disorders – Child Report

parent-based treatment focused on changing parent-child interactions. Furthermore, higher oxytocin levels in anxious children have been shown to increase the impact of negative interpersonal interactions. For example, negative peer interactions predicted more suicidality in anxious children with high oxytocin levels, but not with low oxytocin levels (Lebowitz, Blumberg, & Silverman, 2019). This may explain the finding that parental negativity only moderated outcomes for children with high oxytocin levels, leading to more improvement in SPACE.

For the model based on independent-evaluator-rated outcomes, the algorithm selected only baseline anxiety severity as an important moderator. It may be that the difference in measures used by independent-evaluators and by parents and children impacted findings. Whereas parents and children completed the SCARED, a measure with numerous items covering multiple domains of anxiety, independent-evaluators used the PARS. On PARS, scores are derived from only a few items that rate overall severity across domains. The format and psychometric structure of PARS may have reduced sensitivity to moderator variables.

Overall, the current study provides novel, potentially important information that can advance more prescriptive treatment assignment. Finding that children randomly assigned to their optimal treatment experienced greater improvement than children assigned to their counter-optimal treatment supports the utility of the identified moderators in optimizing treatment

selection. If research continues to support these moderators, future cases could be evaluated on these variables and treatment selection could be algorithmically determined. Findings also support the overall utility of the machine learning approach to moderator analysis and of accounting for the effects and interactions of numerous variables simultaneously.

The study is not without limitations. Sample size was substantial for a clinical trial of child anxiety, but a larger dataset would provide more power and ability to identify moderators and their interactions. The sample was determined by the original RCT and was somewhat homogenous in race and socioeconomic status. Homogeneity hampers moderator identification and research with more heterogeneous samples may better identify treatment response moderators. The machine learning algorithm was chosen given its strength in ensuring that main effects are accounted for when considering potential interactions, but has limitations (Strobl, Boulesteix, Zeileis, & Hothorn, 2007). Especially notable is that the PAI is calculated using linear regression, whereas some of the algorithm's advantages are in detecting more complex interactions. Other limitations are inherent to peripheral oxytocin research. Despite substantial research supporting its usefulness in psychiatric research, questions remain about the degree of coordination between central and peripheral oxytocin, and about optimal methods for oxytocin quantification (McCullough, Churchland, & Mendez, 2013; Young & Anderson, 2010). Finally, to fully understand the clinical applications of any treatment selection approach, it should be applied prospectively.

Despite these limitations, the study is an important step toward identifying moderators of treatment response and toward better decision-making tools for treating childhood anxiety.

### Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

**Table S1.** Linear regressions.

**Table S2.** Correlations (baseline) between the three child anxiety outcomes.

**Table S3.** Correlations of changes (pre-to-post) between the three child anxiety outcomes.

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## Key points

- A recent randomized controlled trial demonstrated that SPACE, a parent-based treatment, is an efficacious alternative to child-based cognitive-behavioral therapy for childhood anxiety disorders.
- Despite similar efficacy for SPACE and CBT, identifying moderators of treatment response to SPACE and CBT could increase overall efficacy.
- Maternal negativity, peripheral (salivary) oxytocin levels, and baseline anxiety severity moderated treatment response to SPACE and CBT, using a machine learning-based approach to moderator analysis.
- Children who were randomly assigned to their optimal treatment condition in the clinical trial, based on the moderators identified in the current study, had significantly more reduction in parent-rated child anxiety, than did children randomly assigned to their nonoptimal treatment condition.
- Clinical practice, and child anxiety outcomes, could be improved through prescriptive treatment selection based on empirically established moderators of treatment response.

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