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ORIGINAL ARTICLE

Prediction of outcome in internet-delivered cognitive behaviour therapy for paediatric obsessive-compulsive disorder: A machine learning approach

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Abstract

Background: There are no consistent predictors of treatment outcome in paediatric obsessive–compulsive disorder (OCD). One reason for this might be the use of suboptimal statistical methodology. Machine learning is an approach to efficiently analyse complex data. Machine learning has been widely used within other fields, but has rarely been tested in the prediction of paediatric mental health treatment outcomes.

Objective: To test four different machine learning methods in the prediction of treatment response in a sample of paediatric OCD patients who had received Internet-delivered cognitive behaviour therapy (ICBT).

Methods: Participants were 61 adolescents (12–17 years) who enrolled in a randomized controlled trial and received ICBT. All clinical baseline variables were used to predict strictly defined treatment response status three months after ICBT. Four machine learning algorithms were implemented. For comparison, we also employed a traditional logistic regression approach.

Results: Multivariate logistic regression could not detect any significant predictors. In contrast, all four machine learning algorithms performed well in the prediction of treatment response, with 75 to 83% accuracy.

Conclusions: The results suggest that machine learning algorithms can successfully be applied to predict paediatric OCD treatment outcome. Validation studies and studies in other disorders are warranted.

KEYWORDS

cognitive behaviour therapy, internet, machine-learning, obsessive–compulsive disorder, prediction

1 | INTRODUCTION

Obsessive–compulsive disorder (OCD) is characterized by recurrent, anxiety provoking thoughts and compulsive behaviours, often aimed to prevent a dreaded event or feeling of distress (American Psychiatric Association, 2013). OCD affects one to two children out of 100 (Angst et al., 2004; Valleni-Basile et al., 1994) and is commonly associated with severe impairments in academic, social and family functioning (Piacentini, Bergman, Keller, & McCracken, 2003).

Cognitive behaviour therapy (CBT) is currently the recommended first-line treatment for paediatric OCD [Geller & March, 2012; National Institute for Health and Care Excellence (NICE), 2005; Socialstyrelsen, 2009]. Unfortunately, only a fraction of OCD sufferers get access to CBT due to treatment barriers such as geographical distances and limited resources including shortage of trained therapists (Goodwin, Koenen, Hellman, Guardino, & Struening, 2002; Wahl et al., 2010). Internet-delivered cognitive behaviour therapy (ICBT) has been proposed as a solution to this problem. In ICBT the patient works with the same content and treatment components as in traditional face-to-face CBT, the only difference being that the intervention is presented via an online portal, thus making treatment available independent of geographical distances, office hours or limited clinician resources. Clinician contact is usually given via asynchronous online messages. ICBT has been shown to be effective for various mental

health disorders in adults in over 100 randomized controlled trials (RCTs) with depression, anxiety and pain disorders being the most frequent targeted conditions (Hedman, Ljótsson, & Lindefors, 2012). Critically, research on ICBT for the paediatric population has been lagging behind significantly and a recent review found only 19 RCTs of ICBT for children and adolescents (Vigerland et al., 2016). In the field of paediatric OCD, two open trials (Lenhard et al., 2014; Rees, Anderson, Kane, & Finlay-Jones, 2016) and a recent RCT (Lenhard et al., 2017) have demonstrated promising effects of ICBT with significant symptom reductions in clinical relevant samples.

ICBT is not expected to substitute traditional face-to-face CBT. Rather, it may be implemented as a first-line, low-cost intervention in a stepped care model, freeing resources for more complex cases that require individualized face-to-face CBT or additional treatments (Mataix-Cols & Marks, 2006). The earlier mentioned paediatric OCD trials have indicated responder rates of about 30 to 70% at the three-month follow-up (Lenhard et al., 2014, 2017), possibly somewhat lower than in face-to-face CBT, where on average 68% of patients respond to treatment (McGuire et al., 2015). Consequently, all patients are not expected to benefit from ICBT, and some might need or prefer face-to-face CBT.

Predictors of face-to-face CBT for OCD have been extensively studied but, as shown in Table 1, results are inconclusive. In fact, no clinical or demographic variable can currently be considered a reliable predictor of treatment outcome. One explanation for these inconsistencies could be the use of suboptimal statistical methodology. As Table 1 shows, a broad range of different statistical models has been applied, ranging from correlations and *t*-tests, classical regression analyses to hierarchical regression modelling. One could hypothesize that the use of different statistical models across studies in itself creates a bias and has, in part, contributed to the difficulties in finding reliable predictors. Another aspect of the mixed results is that the standard assumptions of the usually applied classical parametric methods – linearity of associations, normally distributed data, and equal variances – most likely do not apply to the complex nature of data found in medical and psychiatric research (Malley, Malley, & Pajevic, 2011), and therefore lead to suboptimal reliability and generalizability.

To overcome these methodological limitations and gain new insights in the complexity of predicting treatment outcome it has been suggested to apply machine learning methodology (Monuteaux & Stamoulis, 2016). Machine learning is an umbrella term for a set of statistical methods that make use of the available data in an iterative process, and thus "learn" how to best fit the data. Machine learning algorithms are already widely used in everyday information technology applications, such as search engines, anti-spam email filters and tailored advertisements in social media. In neuroscience and psychiatry machine learning has been applied predominantly in the brain imaging field due to its ability to handle large amounts of data and complex interactions (Lemm, Blankertz, Dickhaus, & Müller, 2011), and has in fact been applied to predict ICBT outcome from brain imaging data in adult social anxiety disorder with an accuracy of over 90% (Månsson et al., 2015).

There are several advantages with machine learning as compared to parametric tests: machine learning comprises not only classical probability based approaches, but also so-called "algorithmic" methods which do not rely on the assumption of normally distributed data (Breiman, 2001). Machine learning algorithms can be flexible and build on both linear and non-linear (quadratic, cubic, etc.) functions, and may thus discover hidden patterns that are not discernible by classical linear models (Monuteaux & Stamoulis, 2016). A machine learning model is usually fitted and optimized several times to the data in a repetitive manner in order to find the model that best represents the data. Finally, the resulting model can directly be validated by dividing the original sample into a "training" sub-sample, in which to establish the predictive algorithm, and a "test" sub-sample, in which to test whether the algorithm performs well in new subjects.

One recent example of machine learning from the adult OCD field is the study by Askland et al. (2015), in which a machine learning approach was used to predict remission in a large longitudinal sample of $N = 296$ individuals. The resulting model was able to predict time spent in remission accurately in 75.4% of cases, using a subset of 24 baseline variables. Amongst the variables that were selected for the final model were baseline clinician-ratings of OCD severity and OCD dimension scores as well as a number of self-rated items. Another rare example from the child and adolescent mental health field is the study of Kim, Sharma, and Ryan (2015), who aimed to predict methylphenidate response in $N = 83$ youth with attention deficit hyperactivity disorder (ADHD) from a broad range of demographic, psychometric, environmental, neuropsychological, neuroimaging, and genetic variables. The machine learning model could accurately predict 84.6% of cases, with age, weight, adrenergic receptor gene polymorphisms, blood lead levels, Stroop colour word test performance, and oppositional symptoms as the most important subset of predictors.

To summarize, novel machine learning methods could potentially expand our possibilities to make more reliable predictions of treatment outcome in paediatric OCD, but have until now been tested only very sparsely in children and adolescents. The aim of this study was to investigate predictors of treatment response in ICBT for paediatric OCD. We used outcome data from a recent RCT (Lenhard et al., 2017) and applied several machine learning approaches, as well as a traditional linear regression approach, for comparison purposes.

2 | METHODS

2.1 | Participants

Sixty-seven adolescents with OCD (12–17 years) participated in a RCT (Lenhard et al., 2017) and had received either immediate or delayed (12 weeks) ICBT. Six participants in the delayed ICBT group dropped out before commencing treatment. In order to maximize power, we pooled the results from both groups rendering a total sample of 61 participants. The treatment, assessment points and procedures were identical in the two groups and they did also not differ significantly in terms of baseline characteristics or treatment outcome. See Figure 1 for details on the participant flow throughout the trial and Table 2 for a summary of baseline characteristics and ICBT outcome at the three-month follow-up.

TABLE 1 Overview of previous studies' significant and non-significant predictors for cognitive behaviour therapy (CBT) outcome in paediatric obsessive–compulsive disorder (OCD)

Study	Bolton, Luckie, Steinberc, & Psycil, 1995	Benazon, Ager, & Rosenberg, 2002	Piacentini, Bergman, Jacobs, McCracken, & Kretchman, 2002	Himle, Fischer, Van Etten, Janeck, & Hanna, 2003	Barrett, Healy-Farrell, & March, 2004	Barrett, Farrell, Dadds, & Boulter, 2005	Storch et al., 2008	Garcia et al., 2010	Micali et al., 2010	Peris et al., 2012	Mancebo et al., 2014	Rudy, Lewin, Geffken, Murphy, & Storch, 2014	Torp et al., 2014
Study sample size	*N* = 14	*N* = 16	*N* = 42	*N* = 19	*N* = 77	*N* = 48	*N* = 92	*N* = 112	*N* = 142	*N* = 49	*N* = 60	*N* = 78	*N* = 269
Prediction method (variance explained by model)	Fisher's exact test (n.a.)	*t*-tests (n.a.)	Correlations & multiple regression (42%)	*t*-test, repeated measures analysis (n.a.)	Repeated measures mixed factorial analysis of variance (ANOVA) (n.a.)	Multiple regression (59–69%)	Stepwise logistic and linear regression (n.a.)	General linear model (n.a.)	Logistic regression (n.a.)	Logistic regression (n.a.)	Stepwise cox proportional hazard regression (n.a.)	Hierarchical linear and logistic multiple regression analyses (10–21%)	Stepwise multi-variate regression (10%)
Demographic variables													
Sex		n.s.	n.s.					n.s.	n.s.		n.s.	s.	n.s.
Age			n.s.		n.s.			n.s.	n.s.		n.s.	n.s.	s.
Household income/ SES								n.s.					n.s.
OCD related variables													
OCD severity	n.s.		s.			s.		s.	n.s.		n.s.	s.	n.s.
OCD functional impairment			s.					s.			s.	n.s.	n.s.
Social adjustment	n.s.												
Onset of OCD	n.s.		n.s.								n.s.		
Duration of OCD			n.s.						s.		s.		n.s.
Insight								s.					
OCD dimensions							n.s.						
Comorbidity													
Externalizing comorbidity			n.s.					s.				n.s.	n.s.
Comorbid anxiety		n.s.	n.s.			n.s.		n.s.				n.s.	n.s.
Comorbid depression			n.s.			n.s.		n.s.				n.s.	n.s.
Comorbid tics			n.s.	n.s.					s.				n.s.
Family variables													
Family accommodation								s.				s.	n.s.
Family dysfunction						s.		n.s.		s.			
Family history of OCD								n.s.	n.s.				n.s.
Parental psychopathology	n.s.							n.s.					n.s.
Other													

(Continues)

TABLE 1 (Continued)

Study	Bolton, Luckie, Steinberc, & Psycil, 1995	Benazon, Ager, & Rosenberg, 2002	Piacentini, Bergman, Jacobs, McCracken, & Kretchman, 2002	Himle, Fischer, Van Etten, Janeck, & Hanna, 2003	Barrett, Healy-Farrell, & March, 2004	Barrett, Farrell, Dadds, & Boulter, 2005	Storch et al., 2008	Garcia et al., 2010	Micali et al., 2010	Peris et al., 2012	Mancebo et al., 2014	Rudy, Lewin, Geffken, Murphy, & Storch, 2014	Torp et al., 2014
Study sample size	*N* = 14	*N* = 16	*N* = 42	*N* = 19	*N* = 77	*N* = 48	*N* = 92	*N* = 112	*N* = 142	*N* = 49	*N* = 60	*N* = 78	*N* = 269
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Medication			n.s.	n.s.	n.s.								
Therapist experience			n.s.										
Therapy adherence			n.s.										

Note: n.s., tested and non-significant; s, tested and significant; n.a., not available; SES, socio-economic status.

2.2 | Intervention

The ICBT intervention, "BiP OCD", is a 12 week, web-based, parent-supported and therapist-guided CBT protocol. The feasibility and efficacy of BiP OCD has previously been established in an open trial, a RCT and a qualitative interview study (Lenhard et al., 2014, 2016, 2017). BiP OCD is delivered via an online portal that patients access via a personal username and password. The content of the intervention is similar to that of traditional face-to-face CBT interventions for OCD with the main focus on exposure with response prevention, the only difference being the format of delivery. Via the online portal patients get access to psychoeducational texts, videos, animations and exercises to do on their own and together with the parents. Patients have contact with a clinician several times a week through asynchronous messages (similar to emails) and occasional telephone calls. Parents log in to a separate track of the treatment to get access to specific content covering psychoeducation, parental coping strategies and how to support their child in adhering to the treatment. For a more detailed description of BiP OCD please see Lenhard et al. (2017).

2.3 | Measures

Children's Yale Brown Obsessive Compulsive Scale, CY-BOCS (Scahill et al., 1997) is a semi-structured clinician administered interview and considered the gold standard in assessment of obsessive compulsive symptom severity in children and adolescents. It also includes a symptom checklist with more than 60 examples of typical obsessions and compulsions, which can be meaningfully grouped into four major symptom dimensions (Mataix-Cols, Nakatani, Micali, & Heyman, 2008). The Clinical Global Impression – Improvement scale, CGI-I (Berk et al., 2008) is a brief clinician rating of the patients' symptom severity change relative to the basement assessment. The Children's Obsessional Compulsive Inventory Revised, CHOCI-R (Shafran et al., 2003) is a self- and parent-report measure of paediatric OCD symptom severity. Education, Work and Social Adjustment Scale – Child and Parent version, EWSAS-C/P (Mataix-Cols, 2005) is a 5-item self- and parent-rating scale of impaired functioning in psychiatric patients. Spence Child Anxiety Scale – Short version – Child and Parent version, SCAS-S-C/P (Spence, 1998) is a child and parent self-report measure of anxiety related psychopathology. In this study a short 12-item version of the SCAS was used. Child Depression Inventory – Short version, CDI-S (Ahlen & Ghaderi, 2016; Kovacs, 1985) was used to assess severity of depressive symptoms. Family Accommodation Scale, Parent-Report, FAS-PR (Flessner et al., 2009) consists of 12 items focusing on accommodation behaviours of parents with a child with OCD.

2.4 | Predictors

Given the inconclusive literature on predictors in paediatric OCD, our strategy for including potential predictors in the analysis was exploratory, i.e. we included 46 demographic and clinical baseline variables (all baseline characteristics presented in Table 2). For comparability of the classical regression analysis with the machine learning analyses, we restricted the available psychometric information to total scale scores, instead of also using single item information in the machine learning analyses.

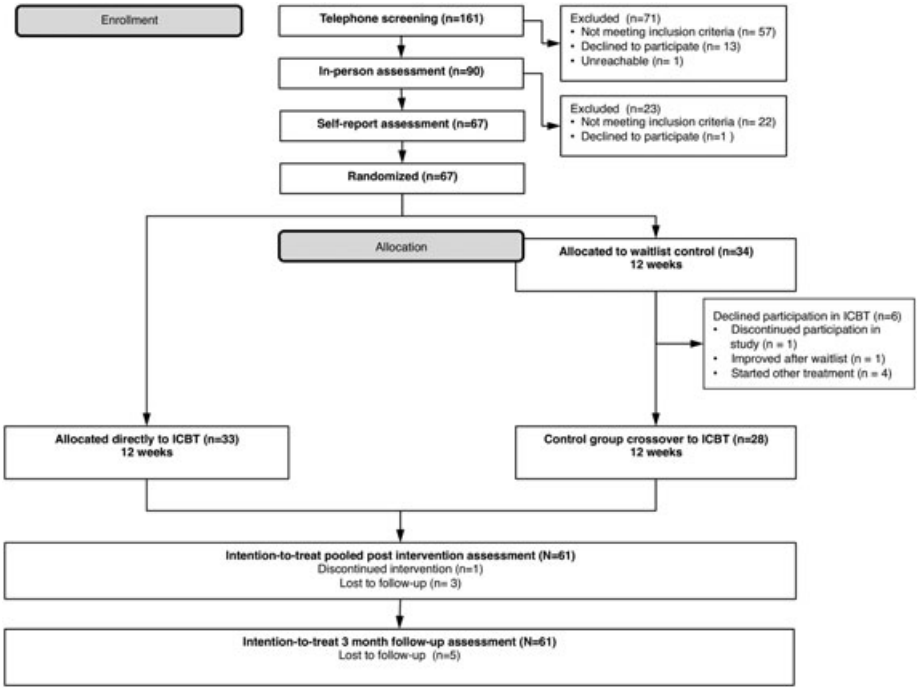

FIGURE 1 Study flow chart

2.5 | Outcome

Following strict expert consensus (Mataix-Cols et al., 2016), the relevant clinical outcome that was chosen for this study was treatment response defined as a 35% reduction of symptoms on the clinician rated CY-BOCS (Scahill et al., 1997) and a CGI-I of 1 "very much improved" or 2 "much improved". As there was an additional and clinical relevant improvement in treatment outcome from post-treatment to the three-month follow-up (see Table 2) we used the three-month time point as the outcome of interest. Approximately 41% of patients were classified as treatment responders at the three-month follow-up assessment.

2.6 | Statistical analyses

2.6.1 | Data preparation

Nominal variables with sparsely populated values ($n < 4$ per category) were excluded from the analyses. All self-rated baseline variables and most clinician-rated variables had no missing values, and apart from two clinician-rated baseline variables, all missingness was <10%. Missing values were handled with multiple imputations using the R package "mice" with parameters at default values (Van Buuren & Groothuis-Oudshoorn, 2011). Supplementary analyses as well as the R code for all analyses are available online: https://osf.io/n28vx/.

2.6.2 | Main analyses

Prediction analyses were carried out using two separate statistical approaches:

1. *Classical regression approach:* Data were first analysed using univariate logistic analyses holding baseline CY-BOCS total score as a covariate in the model. Predictors that were significant in univariate analyses ($p < 0.05$) were then carried over to a multivariate logistic regression model.
2. *Machine learning approach:* We used four different machine learning variants: a linear model with best subset predictor selection and three flexible models, L1 Elastic Net (Lasso), Random Forests and Support Vector Machines. The four chosen models have different statistical characteristics which best can be described as a trade-off between flexibility and interpretability. The Linear Model with best subset predictor selection and Elastic Net rely on linear functions (i.e. operate similar to traditional linear multivariate regression analysis). Due to underlying linear functions these models allow for better interpretability of the predictor–outcome relationship in the sense that the predictor estimates indicate that higher or lower values on a certain predictor are associated with higher or lower values in the outcome (similar to β-values in a regression analysis). Random Forest and Support Vector Machines apply non-linear functions (thus are more flexible to model non-linear distribution of the data) (James, Witten, Hastie, & Tibishirani, 2013). However, increased flexibility causes a loss of interpretability, as the algorithms may combine several non-linear associations of sometimes large numbers of variables, and can therefore be difficult to comprehend. Random Forests operate with random sub-samples of decision trees (therefore the term "Random Forest") of predictors, selecting the decision tree solution that most optimally identifies the outcome variable. The number of predictors and predictor combinations in such decision trees can be numerous; however, the advantage being that this is a non-parametric method that does not rely on the assumption of normally distributed data. Support vector machines can best be explained as a clustering algorithm, trying to find data points that lie close to each other in a dimensional space. Similar

TABLE 2 Baseline characteristics and internet-delivered cognitive behaviour therapy (ICBT) outcome at post-treatment and three-month follow-up

Variable	Mean/%	Standard deviation
Sex (% females)	43%	
Age	14.44	1.68
Country of birth		
Sweden	92%	
Other European	5%	
Asian	3%	
Parental education level		
Other	15%	
College	5%	
High school	23%	
Primary	2%	
Doctoral degree	2%	
University	51%	
Vocational	3%	
Referral to study		
Self-referral	92%	
CAMHS referral	8%	
Distance to research unit (km)	57.7	103.5
Medication		
None	75%	
SSRI	18%	
Central stimulants	3%	
SSRI & central stimulants	2%	
Tricyclic antidepressants	2%	
Any medication (yes/no)	25%	
Previous treatment experience		
None	52%	
CAMHS counselling	39%	
CAMHS CBT	5%	
CAMHS dynamic therapy	3%	
Previous CBT for OCD	23%	
Comorbidity		
Depression	8%	
Dysthymia	3%	
Panic disorder	8%	
Social anxiety disorder	8%	
Specific phobias	11%	
PTSD	2%	
Tourette syndrome	7%	
ADHD	10%	
GAD	13%	
Number of comorbid diagnoses		
One	57%	
Two	28%	
Three	5%	
Four	2%	
Baseline OCD symptoms		
CY-BOCS obsessions score	10.95	2.40
CY-BOCS compulsions score	11.64	2.22
CY-BOCS total score	22.59	4.21
Insight	1.69	0.79
Avoidance	1.60	0.95
OCD onset (age)	10.52	2.72
OCD duration (years)	4.06	2.90
OCD symptom dimensions		
Checking & obsessive hoarding	34%	
Aggressive, sexual or religious obsessions	48%	
Contamination, somatic or cleaning symptoms	64%	
Symmetry, repeating, counting & ordering symptoms	67%	
CGI-I		
Mildly ill	4%	
Moderately ill	56%	
Markedly ill	30%	
Severely ill	11%	
Self-rated baseline measures		
CHOCI-R-C symptoms	13.25	6.74
CHOCI-R-C impairment	24.39	6.99
EWSAS-C	14.75	9.42
SCAS-S-C	12.57	6.26
CDI-S	4.34	3.36
Parent-rated baseline measures		
CHOCI-R-P symptoms	11.89	5.36
CHOCI-R-P impairment	25.23	7.80
FAS-PR	16.51	11.39
EWSAS-P	15.48	8.97
SCAS-S-P	11.08	5.93
Outcome at post treatment		
Treatment responders	34.5%	
Cy-BOCS	16.12	6.37
Outcomes at three-month follow-up		
Treatment responders	41.1%	
Cy-BOCS	13.48	6.32
Effect size (Cohen's *d*) pre ICBT to three-month follow-up	1.71	

Note: CAMHS, Child and Adolescent Mental Health Service; SSRI, selective serotonin reuptake inhibitor; PTSD, post-traumatic stress disorder; ADHD, attention deficit hyperactivity disorder; GAD, generalized anxiety disorder.

data points are close, different data points are divided by gaps. Associations of up to three dimensions (e.g. two predictors and one outcome) can be drawn graphically, whereas larger dimensions tend to become rather abstract to imagine. Due to its capability to model high-dimensional non-linear associations, support vector machines can be applied to highly complex data. To address the risk of overfitting, we split the sample in an 80% training sub-sample, and a 20% test sub-sample. As for model fit we report model accuracy in the test sample, which is the number of correct predictions (true positive + true negative) divided by the total number of predictions expressed in percent, i.e. an accuracy of 100% equals no false predictions. To increase the

robustness of accuracy estimates in the relatively small sample, a 10-fold cross-validation with five repeats was performed, meaning that multiple rounds of cross-validation between the training and test sub-samples were performed using different partitions of the sample, resulting in an average accuracy estimate. All statistical analyses were carried out with R (R Core Team, 2015).

3 | RESULTS

3.1 | Logistic regression

In the univariate logistic regression analyses, two baseline variables were significantly associated with responder status at three-months follow-up (age of OCD onset, p = 0.004, and duration of OCD, p = 0.004) and were therefore carried over to the multivariate model. In the multivariate model none of the predictors remained significant (age of OCD onset: odds ratio (OR) = 0.83, p = 0.30; duration of OCD: OR = 1.40; p = 0.12).

3.2 | Machine learning approach

1. *Linear model with best subset predictor selection.* In this linear model the preselection of possible predictors was done by iteratively computing all possible subsets. More precisely, a predetermined maximum number of predictors was selected (nmax) according to an optimality criterion that is computed from the set of all possible models. The model with the best fit (based on C-p) included nmax = 10 predictors. The two variables with most importance in the model were the CY-BOCS avoidance item and age of OCD onset. Accuracy of the resulting model in the test sample was 83% [95% confidence interval (CI) (52–98%)].
2. *L1 Elastic Net (Lasso).* Next we computed an Elastic Net to see whether a flexible model would be able to detect patterns more clearly. The model identified two different predictors: CGI-I and age of OCD onset. Accuracy in the test sample was 75% [95% CI (43–95%)].
3. *Random Forest*. A Random Forest model consisting of 1000 trees, and four variables per split, was computed. A subset of five variables was identified as the most important in this model: EWSAS-C, CHOCI-R-C (child-rated) impairment subscale, CDI-S, age of OCD onset, duration of OCD. Accuracy was 75% [95% CI (43–95%)].
4. *Support Vector Machines.* A Support Vector Machine with radial kernel was fit. Three variables were identified as most important: duration of OCD, CGI-I, and EWSAS-C. Accuracy was 75% [95% CI (43–95%)].

3.2.1 | Post hoc *analyses of most important predictors*

The variable age of OCD onset was identified as one of the most important variables in three of the four machine learning models. *Post hoc* analyses revealed that treatment responders had on average a later onset [mean (M) = 11.3 years, standard deviation (SD) = 1.8] than treatment non-responders (M = 9.3 years, SD = 2.8). The variables duration of OCD occurred in two of four machine learning analyses as an important predictor. Treatment non-responders had on average a 2.3 years longer course of OCD [95% CI (0.60–3.96)]. A Pearson correlation of onset of OCD and duration of OCD revealed, as expected, that the two variables were highly correlated with each other, r = 0.82, indicating that patients with earlier onset usually also experience longer duration of OCD. CGI-I and EWSAS-C was identified as important predictors in two of the machine learning analyses. Treatment responders had on average a slightly lower CGI-I at baseline of 0.39 [95% CI (0.79–0.02)], and had on average a 2.99 points lower EWSAS-C score at baseline [95% CI (8.27–2.28)], compared to treatment non-responders. CY-BOCS-rated avoidance, CHOCI-R-C and CDI-S were identified once each as important predictors in the analyses. Treatment responders had on average a 0.57 point lower score on avoidance [95% CI (0.05–1.09)], two points lower score on the CHOCI-R-C impairment subscale [95% CI (1.94–5.95)] and a 1.5 points lower score on the CDI-S [95% CI (0.33–3.33]), compared to treatment non-responders.

4 | DISCUSSION

The aim of this study was to predict the outcome of ICBT in paediatric OCD. Critically, we compared a traditional regression analytic approach with a novel machine learning approach. Results showed that the traditional regression approach was not able to find any stable predictors of treatment response. The machine learning models however were able to predict treatment response with good to excellent accuracy. More specifically, the predictive models that were trained in a subset of the sample could then accurately predict treatment response in 75 to 83% of previously unseen cases in the test sample. The degree of accuracy is in line with previous machine learning studies in adults with OCD (Askland et al., 2015) and children with ADHD (Kim et al., 2015). The Linear Model with best subset predictor selection had slightly higher accuracy than the other three models, perhaps indicating superiority of the model and at the same time providing good interpretability due to linear modelling. To allow for better guidance when choosing machine learning approach, the different models should be re-evaluated in other samples with more appropriate sample sizes. All in all, the results from this study provide tentative support for machine learning as an efficient way to guide us in clinical decisions of which patients to offer this novel ICBT treatment. This may in turn pave the way to personalized psychiatric care for the paediatric population with OCD. This could be especially important within the field of ICBT, as it is a relatively new intervention for children and adolescents, and not much is known about which patients should receive ICBT. On a broader scale, previous attempts to predict face-to-face CBT outcome have produced inconclusive results, and machine learning could be one way to approach prediction in a methodically different, and perhaps more efficient way.

Regarding the clinical relevance of our results, one of the repeatedly identified predictors across analyses was onset of OCD symptoms, indicating that the earlier the onset of OCD the less chance of responding to ICBT. This finding is clinically important, as it indicates the importance to tailor ICBT interventions especially to younger

adolescents and children. Interestingly, the previous literature of face-to-face CBT has not shown any convincing results on onset as a predictor of outcome.

Related to onset of OCD, and indeed highly correlated, we found that duration of OCD was an important predictor in two of the analyses. Two previous studies and one meta-analysis have found the same association between longer duration of OCD and less favourable treatment outcome (Mancebo et al., 2014; Micali et al., 2010; Stewart et al., 2004). However, several studies of ICBT in adult OCD have reported large treatment effects, on par with effects found in face-to-face CBT (Andersson et al., 2011, 2012, 2015; Wootton, Dear, Johnston, Terides, & Titov, 2013). Thus, despite adults with OCD usually experience a significantly longer duration of OCD than children and adolescents, ICBT still produces large effects in adults, which contradicts the importance of duration of OCD as a predictor. A methodological observation is that onset of OCD and OCD duration were found significant predictors in the univariate logistic regression analyses, but non-significant in the multivariate model, and it could very well be that the non-significant result was due to the substantial inter-correlation of the two variables.

The results from this study also suggest that patients with a more severe clinical presentation did less well in the ICBT treatment. It would be a reasonable assumption that ICBT might suit patients with moderate symptom severity better, and that patients with severe symptoms should receive face-to-face treatment. As initially mentioned in Table 1, the literature on face-to-face CBT is currently inconclusive about whether symptom severity and comorbidity may affect treatment outcome. To give informed clinical recommendations regarding which patients should receive ICBT and which standard face-to-face CBT, randomized trials are needed that directly compare the two interventions in efficacy as well as predictors and moderators of treatment outcome.

Given the encouraging results from the present study, machine learning methods could lend themselves to better understand the complex interaction of different predictors. In the study of Kim et al. (2015), a variety of predictors, both psychometric, biological and environmental, contributed to the predictive model of methylphenidate treatment outcome. As the current model of OCD proposes a multifactorial interplay between genes, environment, neurofunctional, cognitive and behavioural pathways (Pauls, Abramovitch, Rauch, & Geller, 2014), it would be interesting to take those different types of variables into account when trying to identify a more personalized approach to treatment outcome. The ICBT field has demonstrated the potential to conduct large-scale clinical trials, often much faster than clinical trials of face-to-face treatment, and usually in combination with rich online data collection and little data loss. In combination with collections of genetic and imaging material, there could be great potential that machine learning algorithms help us identify meaningful patterns in the data that previously were not detected with traditional methods, and thus guide us towards personalized mental health care.

4.1 | Limitations

Importantly, our results are limited by a moderately sized sample. The classical regression analysis was not able to show significance for any predictor in the multivariate model, which could have been due to non-sufficient statistical power or collinearity of the remaining predictors. Within machine learning, sample size calculations are not straightforward and few rules of thumb are available in the literature. Generally, sample size is expected to be associated with algorithm performance, with increasing accuracy and tighter confidence intervals when moving from small samples to larger samples (Figueroa, Zeng-Treitler, Kandula, & Ngo, 2012). One simulation study from the somatic field showed that acceptable predictive performance could be achieved in sample sizes of 5 to 25. However, in order to build reasonably reliable classification models the authors concluded that sample size should start at 75 to 100 samples, and sample sizes much larger than that in order to establish superiority of one classification algorithm over the other (Beleites, Neugebauer, Bocklitz, Krafft, & Popp, 2013). Other factors that are thought to affect the requirements for sample size in machine learning is the complexity of the model (with higher complexity demanding more samples) and the distribution of the outcome variable (with a unbalanced distributions demanding more samples) (Dobbin, Zhao, & Simon, 2008). Thus, considering these sample size requirements, the sample size in the current study is clearly suboptimal. Our results should be seen as preliminary and warrant further validation in larger samples.

Also, we chose to build our regression and machine learning models on baseline total scores of clinician-, self- and parent-rated scales of OCD and comorbid symptoms. This might have caused suboptimal machine learning results, as we did not make item level information available for the learning algorithms. One could assume that a richer dataset with a higher resolution of information would have resulted in more accurate predictions. We chose however to not provide item level information as we aimed to make the same data available to the machine learning algorithms that we had used in the regression analyses. Moreover, as exemplified by Kim et al.'s (2015) study on methylphenidate response, we did not include other potentially important predictors, such as genetic, neuropsychological or neuroimaging data. It is possible that the inclusion of different types of data further would refine the predictive models.

In addition, the sample in this study was selected for participation in a clinical trial of ICBT. A high proportion of self-referred patients and an above-average percentage of highly educated parents indicate that the sample might differ from patients typically seen in clinical practice. Methodologically such a selection might also result in a restriction in variability of baseline characteristics in the sample, thus affecting model performance. To further increase generalizability of the results it would therefore be necessary to test the machine learning approach in regular clinic settings. We do not know if the results reported herein might be specific for ICBT interventions or generalizable to CBT in general. Therefore, an important next step would be to employ machine learning methods to predict outcomes with traditional face-to-face CBT.

5 | CONCLUSIONS

Our results suggest that machine learning methodology could lend itself to predict treatment outcome in ICBT for paediatric OCD. In spite of a moderately sized sample, the machine learning models could repeatedly identify important predictors with good to excellent predictive accuracy, whereas classical multivariate regression essentially

failed at doing so. Variables with high importance for the machine learning models were age of OCD onset, duration of OCD, self- and clinician-rated symptom severity, functional impairment, avoidance and depressive symptoms. These preliminary promising findings warrant validation and replication within the ICBT field, in larger samples as well as in different patient populations.

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DECLARATION OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTION

Dr Lenhard contributed with conception and design of study, data collection, trial management, interpretation of data and drafting the article. Dr Sauer contributed with the statistical analyses, interpretation of data. Drs Andersson, Månsson, Mataix-Cols, Rück and Serlachius contributed with conception and design of study and interpretation of data. All authors were involved in revising the manuscript critically for important intellectual content, and approved the final version.

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