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Original Research

The Efficacy and Neural Correlates of ERP-based Therapy for OCD & TS: A Systematic Review and Meta-Analysis

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Abstract

Background: Exposure and response prevention (ERP) is a form of cognitive behavioral therapy that can effectively relieve obsessive-compulsive symptoms and tic symptoms in patients with obsessive-compulsive disorder (OCD) and Tourette syndrome (TS). However, the effect size of ERP-based therapy is still unclear. **Methods**: In this study, we performed a meta-analysis to identify the efficacy of ERP-based therapy for individuals with OCD and TS. The standard mean difference (SMD) with a 95% confidence interval (CI) was calculated to assess the effect size of the efficacy for ERP-based therapy. We used subgroup and meta-regression analyses to explore the heterogeneity of the pooled SMD of ERP-based therapy for OCD. We also summarized the neuroimaging studies for ERP-based therapy for OCD. This meta-analysis was registered within the International Platform of Registered Systematic Review and Meta-analysis Protocols (number: INPLASY2021120112). **Results**: A total of 18 studies including a total of 1057 patients with OCD and 3 studies including 267 with TS/chronic tic disorder were identified. We did not observe any indication of publication bias using Egger's funnel plot ($p = 0.41$). We observed a small-to-medium effect size of ERP for both OCD (SMD = –0.27, 95% CI: –0.53 to –0.01) and TS/chronic tic disorder (SMD = –0.35, 95% CI: –0.59 to –0.1). We found no heterogeneity of ERP-based therapy for OCD between the ERP-based therapy subgroup and medicine subgroup in the subgroup analysis ($p = 0.72$). We found no heterogeneity of ERP-based therapy for OCD between the child subgroup and adult subgroup in the subgroup analysis ($p = 0.37$). We used meta-regression analysis to identify the heterogeneity of ERP-based therapy for OCD and found that the sessions of therapy and publication year did not account for any significant heterogeneity ($p > 0.05$). The neurological mechanism of EPR-based therapy is unclear, but it may lie in changes in the prefrontal cortex and anterior cingulate cortex. **Conclusions**: In conclusion, we found that ERP-based therapy is effective for patients with OCD and TS/chronic tic disorder. We suggest a combination with other therapies and the development of online ERP services that might prove a promising new direction for healthcare providers.

Keywords: exposure and response prevention; cognitive behavioral therapy; obsessive-compulsive disorder; tourette syndrome; tic disorders; meta-analysis

1. Introduction

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by distressing and time-consuming obsessions and compulsions [1]. Obsessions are defined as intrusive and unwanted thoughts, urges, or images, and they are followed by compulsions, which aim to relieve these "uncomfortable feelings" [1,2]. It has been reported that the lifetime prevalence of OCD is approximately 1%–3% [3,4]. Patients are often affected by obsessions and compulsions that interfere with social, at home, educational attainment, and occupational aspects [1,5].

Exposure and response prevention (ERP) is based on cognitive behavioral therapy (CBT) and is the primary psychological treatment for OCD in children, adolescents, and adults [6–10]. ERP involves exposure to feared obsessional stimuli while refraining from engaging in compulsive behaviors [11]. Research indicates that approximately 60%–85% of patients who complete ERP treatment achieve significant success in alleviating obsessive-compulsive symptoms [4,12,13]. Moreover, CBT (including ERP) is recommended as the first-line treatment for mild-to-moderate OCD in youth [14]. Although serotonin reuptake inhibitors (SRIs) are effective in reducing symptoms compared with placebo, only moderate effect sizes are found when compared to CBT (including ERP) [9,15]. Recently, it was reported that the patient dropout rate for ERP was 10.24%, whereas the patient dropout rate for pharmacotherapy was 17.29% [16]. Interestingly, the same study found that patients who did not respond to SRI augmentation with risperidone or placebo showed significant reductions in OCD symptoms and depression when treated with ERP, as well as better quality of life and social functioning [17]. However, ERP-based CBT has no or only partial improvement for many young patients with OCD. For example, one study found that 60% of patients in an ERP-based CBT condition failed to demonstrate clinical remission in a large RCT for children and adolescents with OCD [18]. Although approximately 60% of patients who completed treatment

improved, only 25% of patients were asymptomatic [19]. This suggests that most patients treated with ERP continue to experience OCD symptoms [20]. Based on these studies, the quantitative degree of efficacy of ERP is still unclear, and the factors influencing ERP need to be explored.

Previous research has focused on the neuroimaging findings of OCD. Some studies have indicated that brain function changes pre- and post-ERP-based therapy. A recent study found that OCD patients showed less inhibition-related activation in areas of the frontoparietal cortex, dorsal anterior cingulate cortex (ACC) and anterior insula than controls [21]. Stein *et al*. [22] found that OCD is associated with subtle alterations in cortico-striato-thalamo-cortical, fronto-parietal, and frontolimbic circuits. Few studies have focused on the neurological mechanism of ERP-based therapy for OCD patients [23]. Because of inconsistencies in the changes after interventions [24,25], we surveyed neuroimaging studies of ERP-based interventions for OCD and summarized them in a systematic review.

Furthermore, ERP is applied not only in patients with OCD but also in patients with Tourette syndrome (TS). TS is characterized by sudden motor movements and/or vocalizations (referred to as tics) for at least 12 months [26]. It has been reported that the worldwide prevalence of TS is nearly 1% [27]. TS and OCD often co-occur. They share common dysfunction in symptoms profiles [28] and pathophysiology [29]. The development of ERP for OCD might benefit the ERP for TS. Indeed, ERP has also been recommended as a first-line behavioral therapy in American, Canadian and European guidelines for tic disorders [30–32]. However, the efficacy of ERP for TS needs to be clarified. We can investigate the efficacy of ERP for both OCD and TS which might give us more indications for the development of ERP across different mental disorders.

Several studies on the meta-analysis of CBT for OCD have been conducted [6,33–35]. However, the efficacy of ERP-based therapy for OCD & TS is still unclear. This meta-analysis aimed to find the effect sizes of ERP for OCD & TS. A meta-analysis method provides the opportunity to statistically combine the results of comparable trials [36]. Therefore, in the current meta-analysis, we attempted to identify the efficacy of ERP-based therapy (which included the ERP as the main procedure) for OCD & TS. We used meta-regression and subgroup analyses to determine potential heterogeneities in these approaches.

2. Materials and Methods

2.1 Identification of Included Studies

An extensive literature search was conducted in the following databases: PubMed, Web of Science, PsycINFO, and Google Scholar. We only considered studies published before November 1, 2021. The search terms were as follows: "obsessive-compulsive disorder" or "OCD" or obsessive/compulsive" or "Tourette's syndrome" or "tics" or "tic disorders" and "cognitive behavior therapy" or "exposure and response" or "exposure and ritual prevention" or "ERP" or "EX/RP" or "psychotherapy" and "magnetic resonance imaging" or "MRI". References of related articles were also searched for any other relevant studies.

Inclusion criteria were as follows:

(1) ERP or ERP-based therapy;

(2) The symptoms of OCD measured by a validated scale, such as the Yale-Brown Obsessive-Compulsive Symptom Scale (Y-BOCS) [37] or the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) [38], and the Yale Global Tic Severity Scale (YGTSS) were used to assess the tic symptoms;

(3) Y-BOCS/CY-BOCS or YGTSS was used to assess the efficacy of ERP or ERP-based therapy;

(4) Both adult and child/adolescent OCD and tic disorder patients were included; and

(5) written in English.

Exclusion criteria were as follows:

(1) No Y-BOCS/CY-BOCS data or YGTSS data;

(2) Studies combining ERP with another type of behavioral therapy;

(3) Articles with duplicate records; and

(4) Articles such as case reports, editorials, comments, and review papers.

Notably, the Y-BOCS/CY-BOCS score range of severity for patients who have both obsessions and compulsions was categorized as follows: mild OCD (<13); moderate OCD (13–22); severe OCD (>22) [38]. In addition, we also searched imaging studies for ERP-based therapy for OCD/TS. This meta-analysis was registered within the International Platform of Registered Systematic Review and Meta-analysis Protocols (number: INPLASY2021120112).

2.2 Quality Assessment of Included Studies

The quality of each study was assessed by the modified Jadad scale [39]. Each study was evaluated by using the following criteria: randomization, blinding strategy, withdrawals/dropouts, inclusion/exclusion criteria, adverse effects, and statistical analysis. Two authors independently scored each included trial and discussed with each other to reach a consensus on any differences.

2.3 Data Extraction

We identified a total of 18 studies including 1057 patients diagnosed with OCD. Three studies including 267 patients diagnosed with TS/chronic tic disorder were included. Both children and adults patients were included. We extracted the following information from the included studies: authors, publication years, mean ages, numbers of males/females, sample sizes, diagnostic criteria, comparison group, online or face to face, *in vivo*/imaginal exposure, outcome measurements, the baseline Y-BOCS/CY-BOCS value and YGTSS value, and the number of therapy sessions.

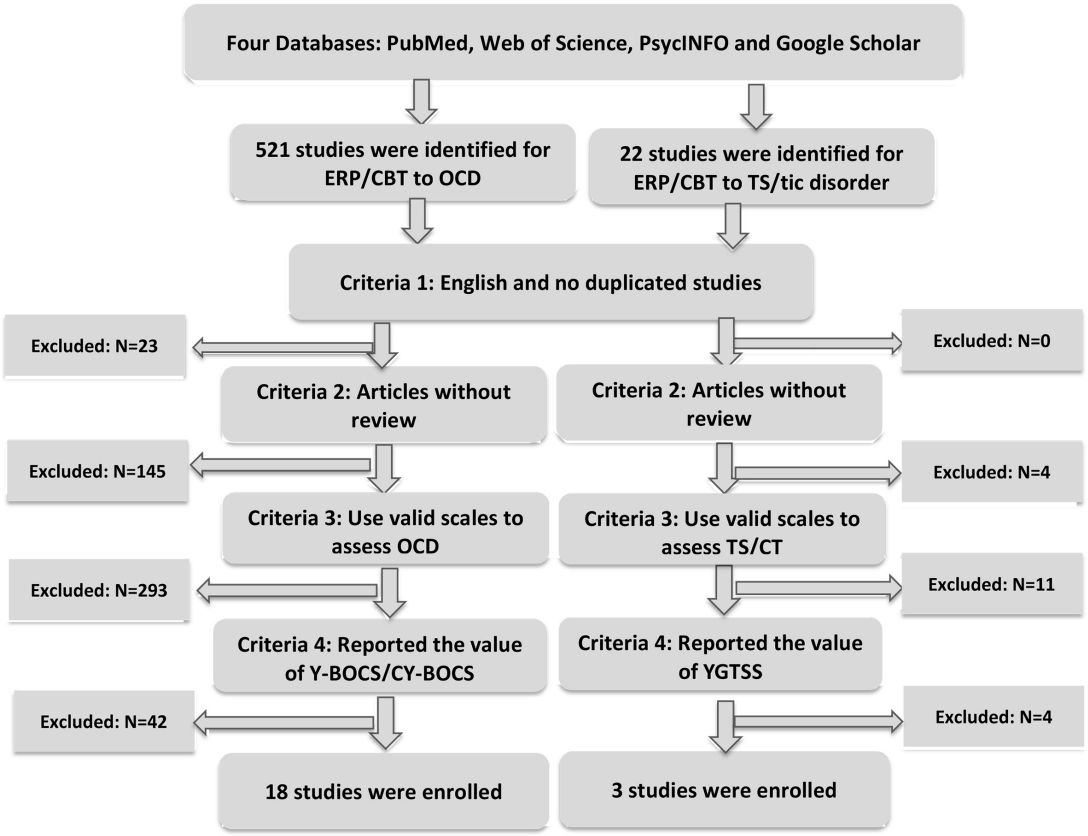

Fig. 1. Flow chart of the included studies. ERP, exposure and response prevention; OCD, obsessive-compulsive disorder; Y-BOCS, the Yale-Brown Obsessive-Compulsive Scale; CY-BOCS, the Children's Yale-Brown Obsessive-Compulsive Scale; YGTSS, the Yale Global Tic Severity Scale.

2.4 Statistic Analysis

A randomized effects model was used to examine the standard mean difference (SMD) of ERP-based therapy. If the SMD was between 0.2 and 0.5, the efficacy of ERP-based therapy was mild-to-moderate, whereas SMD values between 0.5 and 0.8 indicated that the efficacy of ERP-based therapy was moderate-to-large [40]. I^2 and forest plots were used to identify the heterogeneity of the effect size of ERP. If I^2 was greater than 50%, we used a random-effects model [41]. Then, we used subgroup and meta-regression analyses to explore heterogeneities in the effect size for ERP-based therapy. We considered a p value $<$ 0.05 to be statistically significant, and all the analyses were performed in R (version 3.5.3) (https://cran.r-project.org/bin/windows/base/old/3.5.3/) using the "meta" or "metafor" packages.

3. Results

3.1 The Included Studies

Based on the inclusion and exclusion criteria, a total of 18 studies were identified for OCD and 3 studies for TS. For the flowchart to identify the included studies, see Fig. 1. We list the extracted data in the Table 1 (Ref. [18,42–61]). The quality assessment for the included studies was summarized in Table 2 (Ref. [18,42–61]).

3.2 The Effect Size of ERP-based Therapy

The pooled SMD of ERP-based therapy for OCD was –0.27 (95% CI: –0.53 to –0.01), with a heterogeneity (I^2) of 70% (95% CI: 51.1 to 81.4, $p < 0.01$) based on a random effects model (Fig. 2). The pooled SMD of ERP-based therapy for TS/chronic tic disorder was –0.35 (95% CI: –0.59 to –0.1), with a heterogeneity (I^2) of 0% (95% CI: 0.0–89.6, $p = 0.92$) based on the common effects model. For more details see Fig. 2.

3.3 Sensitivity Analysis and Publication Bias

We used sensitivity analysis to explore the heterogeneity of the pooled SMD of ERP-based therapy for OCD. This method omits one study at a time and tracks the change in I^2 to identify the contribution of each study to heterogeneity [62]. In doing so, we observed changes in I^2 to be no more than 5% (**Supplementary Fig. 1**). Moreover, we did not observe any indication of publication bias using Egger's funnel plot ($p = 0.41$) (**Supplementary Fig. 2**).

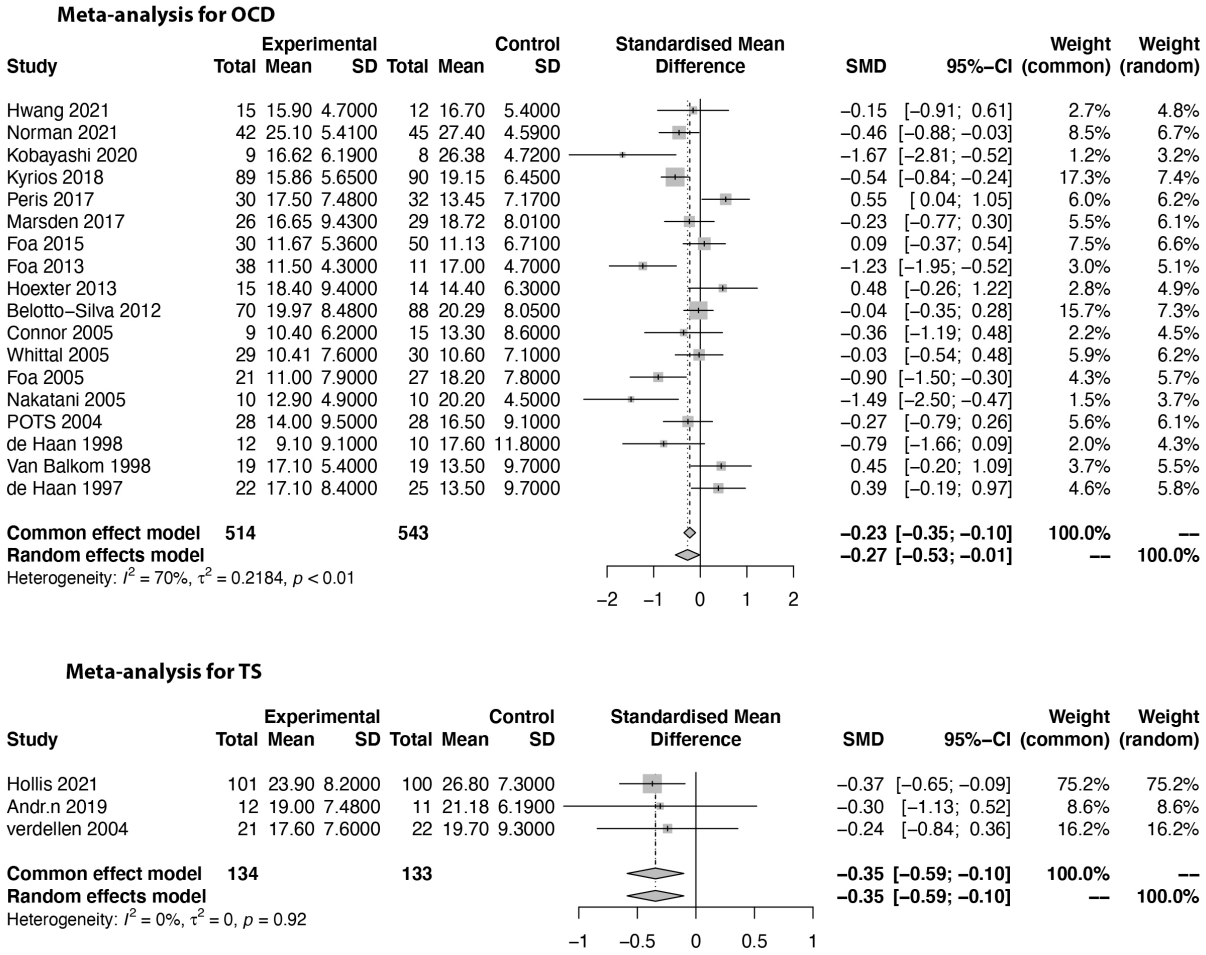

Fig. 2. Forest plots of the meta-analysis of efficacy for ERP-based therapy for OCD and TS.

3.4 Subgroup Analysis

A subgroup analysis of the pooled SMD of ERP-based therapy for OCD was conducted to identify the potential source of heterogeneity by different comparison groups and different age groups. Furthermore, we found no heterogeneity of ERP for OCD between different comparison groups (p = 0.72) (Fig. 3). For the subgroup analysis of the different age groups, heterogeneity was found in both adults (I^2 = 68%) and children (I^2 = 78%), but we found no significant heterogeneity between the two subgroups (p = 0.37) (Fig. 4).

3.5 Meta-regression Analysis

We conducted a meta-regression analysis to explore the heterogeneity of pooled SMD of ERP-based therapy for OCD. The sessions of therapy and publication year did not account for any significant heterogeneity ($p > 0.05$) (Table 3).

3.6 The Imaging Studies of ERP-based Therapy for OCD

Differences in the involved brain areas after ERP interventions between OCD patients and control subjects were detected. Within the ERP group, after-treatment response was significantly associated with greater pretreatment activation within the medial prefrontal and amygdala regions, as well as connectivity increases between the cerebellum and caudate/putamen and between the cerebellum and prefrontal cortices after interventions. Studies about the involved brain areas of ERP for TS were not found. For more details see Table 4 (Ref. [44,51,63–72]).

3.7 The Functional Recovery of ERP

In addition to the relief of clinical core symptoms after ERP, functional recovery is also something we need to discuss. For OCD patients, ERP can help improve family functioning, which including levels of family accommodation and psychological distress. Therefore, we summary the related studies which also report the functional recovery of ERP in **Supplementary Table 1**. These results indicated that the ERP might also improve the patients' social function.

Table 1. The included studies.

Author	Published year	Age (years)	Male/Female	Diagnosis criteria	Sample size	Comparison group	Online or face to face	*In vivo*/imaginal exposure	Outcome measurements	Baseline Y-BOCS/ CY-BOCS or YGTSS	Sessions
Hwang *et al.* [43]	2021	ERP: 24.7 ± 10.7; OCfree CBT: 25.7 ± 7.7	11/16	DSM-5	27	OCfree CBT	Face to Face	N/A	Y-BOCS, BDI, BAI	ERP: 19.5 ± 4.1; OCfree CBT: 21.9 ± 5.7	6 sessions/6weeks
Norman *et al.* [44]	2021	ERP: 24.23 ± 9.13; SMT: 24.52 ± 9.32	30/57	N/A	87	SMT	Face to Face	N/A	Y-BOCS, QIDS, CGI-S, HAM-A	ERP: 25.10 ± 5.41; SMT: 27.40 ± 4.59	12 sessions/12 weeks
Kobayashi *et al.* [45]	2020	ERP: 29.44 ± 8.3; TAU: 30.88 ± 10.1	9/8	DSM-IV	17	TAU	Face to Face	N/A	Y-BOCS, PGI-S, CGI-S, BDI, K6, SDS, EQ5D, FAS-PV, FAS-SR	ERP: 26.67 ± 5.50; TAU: 27.75 ± 3.24	16 sessions/16 weeks
Kyrios *et al.* [46]	2018	ERP: 32.59 ± 9.86; iPRT: 34.23 ± 9.88	61/117	DSM-IV-TR	178	iPRT	Online	N/A	Y-BOCS, GAF, HAM-D, HAM-A	EPR: 22.58 ± 5.53; iPRT: 22.22 ± 5.76	12 sessions/12 weeks
Peris *et al.* [47]	2017	ERP: 13.66 ± 2.75; PFIT: 12.61 ± 2.55	35/27	DSM-IV-TR	62	PFIT	Face to Face	N/A	CY-BOCS, CGI-I, COIS-RP, FAS, FES, PABS	ERP: 25.43 ± 3.33; PFIT: 25.53 ± 3.72	12 sessions/12 weeks
Marsden *et al.* [48]	2017	EPR: 33.31 ± 15.37; EMDR: 30.90 ± 9.79	21/34	DSM-IV	55	EMDR	Face to Face	Both	Y-BOCS, OCI, PHQ-9, GAD-7, WSAS	ERP: 26.65 ± 6.61; EMDR: 25.07 ± 6.23	16 sessions/16 weeks
Foa *et al.* [49]	2015	EX/RP: 34.47 ± 13.09; RIS: 42.25 ± 11.73	17/21	DSM- IV	38	RIS	Face to Face	N/A	Y-BOCS, HDRS	ERP: 27.5 ± 3.88; RIS: 24.13 ± 4.29	17 sessions/8 weeks
Foa *et al.* [50]	2013	EX/RP: 36.1 ± 14.1; SMT: 41.7 ± 11.7	34/15	DSM-IV	49	SSRI	Face to Face	N/A	Y-BOCS, HDRS, HARS, Q-LES-Q, SAS-SR	ERP: 25.1 ± 4.7; SMT: 26.4 ± 4.7	16 sessions/8 weeks
Hoexter *et al.* [51]	2013	ERP: 33.3 ± 10.0; Fluoxetine: 33.1 ± 11.6	11/18	DSM-IV	29	Fluoxetine	Face to Face	N/A	Y-BOCS, DY-BOCS, BDI, BAI	ERP: 27.3 ± 5.2; Fluoxetine: 23.5 ± 4.9	12 sessions/12 weeks
Belotto-Silva *et al.* [52]	2012	E/RP: 33.94 ± 11.1; SSRI: 34.12 ± 10.6	71/87	DSM-IV	158	SSRI	Face to Face	N/A	Y-BOCS	ERP: 25.97 ± 5.48; SSRI: 25.82 ± 5.10	12 sessions/12 weeks
Connor *et al.* [53]	2005	38.3	16/28	DSM-IV	44	CAM	Face to Face	In vivo	Y-BOCS, Padual, CIQ, BAI, BDI	ERP: 19.2 ± 4.4; CAM: 25.5 ± 7.1;	20 sessions/20 weeks
Whittal *et al.* [54]	2005	ERP: 34.24 ± 11.31; CBT: 35.57 ± 9.67	22/37	DSM-IV	59	CBT	Face to Face	N/A	Y-BOCS, BDI	ERP: 21.66 ± 5.9; CBT: 23.50 ± 4.3	12 sessions/12 weeks
Foa *et al.* [42]	2005	ERP: 33.8 ± 8.9; CLOM: 35.7 ± 11.3	19/46	DSM-IV	65	CLOM	Face to Face	Both	Y-BOCS, CGI	ERP: 24.6 ± 4.8; CLOM: 26.3 ± 4.4	12 sessions/12 weeks

Table 1. Continued.

Author	Published year	Age (years)	Male/Female	Diagnosis criteria	Sample size	Comparison group	Online or face to face	*In vivo*/imaginal exposure	Outcome measurements	Baseline Y-BOCS/ CY-BOCS or YGTSS	Sessions
Nakatani *et al.* [55]	2005	E/RP: 32.5 ± 11.2; FLV: 33.0 ± 5.7	6/14	DSM-III-R	20	FLV	Face to Face	N/A	Y-BOCS, CGI-I, CGI-S, GAF, HAM-A/D	E/RP: 29.9 ± 3.1; FLV: 28.4 ± 3.8	12 sessions/12 weeks
POTS [18]	2004	ERP: 11.4 ± 2.8; Sertraline: 11.7 ± 2.4	31/25	DSM-IV	56	Sertraline	Face to Face	N/A	CY-BOCS, CGI	ERP: 26.0 ± 4.7; Sertraline: 22.5 ± 4.7	14 sessions/12 weeks
de Haan *et al.* [56]	1998	ERP: 13.25 ± 2.73; CLOM: 14.28 ± 3.19	11/11	DSM-III-R	22	CLOM	Face to Face	N/A	CY-BOCS, LOI-CV	ERP: 21.5 ± 5.9; CLOM: 23.8 ± 7.2	12 sessions/12 weeks
van Balkom *et al.* [57]	1998	ERP: 13.25 ± 2.73; CT: 14.28 ± 3.19	17/19	DSM-III-R	38	CT	Face to Face	In vivo	CY-BOCS, BDI, SCL-90	ERP: 25.0 ± 7.9; CLOM: 25.3 ± 6.6	16 sessions/16 weeks
de Haan *et al.* [58]	1997	N/A	N/A	DSM-III-R	47	Cognitive	Face to Face	N/A	Y-BOCS, SCL-90, BDI	ERP: 24.7 ± 7.7; Cognitive: 25.0 ± 6.6	16 sessions/16 weeks
Hollis *et al.* [59]	2021	ERP: 12.2 ± 2.0; Psy: 12.4 ± 2.1	177/47	N/A	224	Psychoeducation	Online	N/A	YGTSS, TTSS, C&A-GTS-QOL	ERP: 28.4 ± 7.7; Psy: 28.4 ± 7.1	N/A
Andrén *et al.* [60]	2018	HRT 12.79 ± 2.62; ERP 11.80 ± 2.51	15/8	DSM-5	23	HRT	Online	N/A	YGTSS, CGAS, PUTS, GTS-QOL, PTQ	ERP: 23.75 ± 23.75; HRT: 23.45 ± 6.88	10 sessions/10 weeks
Verdellen *et al.* [61]	2004	HRT: 19.2 ± 11.4; ERP: 22.0 ± 13.0	34/9	DSM-IV	43	HRT	Face to Face	N/A	YGTSS, TF-institute, TF-home	ERP: 26.2 ± 7.2; HRT: 24.1 ± 7.2	10 sessions

Abbreviations: ERP, exposure and response prevention; EX/RP, Exposure and Ritual Prevention; iPRT, internet-based progressive relaxation therapy; TAU, treatment as usual; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; QIDS, Quick Inventory of Depressive Symptomatology; PGI, Patient Global Impression; K6, Kessler Psychological Distress Scale; SDS, Sheehan Disability Scale; EQ5D, EuroQol; FAS-SR, Family Accommodation Scale for OCD Self-Rated version; FAS-PV, Family Accommodation Scale for OCD Patient-Rated version; GAF, Global Assessment of Functioning; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; PFIT, Positive Family Interaction Therapy; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; CGI-I,Clinical Global Impression Scale – Improvement; COIS-RP, Child Obsessive-Compulsive Disorder (OCD) Impairment Scale – Parent-Report Revised; FAS, Family Accommodation Scale; FES, Family Environment Scale; PABS, Parental Attitudes and Behaviors Scale; EMDR, eye movement desensitization and reprocessing; OCI, obsessive compulsive inventory; PHQ-9, measure of depression symptoms; GAD-7, measure of anxiety symptoms; WSAS, work and social adjustment scale; RIS, Risperidone; HDRS, Hamilton Depression Rating Scale; SMT, Stress Management Training; HARS, Hamilton Anxiety Rating Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Scale; SAS-SR, Social Adjustment Scale-Self Report; DY-BOCS, Dimensional Yale–Brown Obsessive–Compulsive Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; CGI, Clinical Global Impressions; E/RP, exposure with response prevention; SSRI, selective serotonin reuptake inhibitor; CAM, Cognitive Appraisal Model; IBA, Inference-based Approach; Padua, Padua Inventory; CIQ, Cognitive Intrusions Questionnaire; CLOM, Clomipramine; FLV, Fluvoxamine; CGI-S, Clinical Global Impressions-Severity of Illness Scale; LOI-CV, Leyton Obsessional Inventory-Child Version; SCL-90, Symptom Check-list; Cognitive, cognitive therapy; Psy, Psychoeducation; HRT: Habit reversal therapy; TTSS, Total Tic Severity Score; C&A-GTS-QOL, Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale; TF-institute, tic frequency observed at the institute; TF-home, tic frequency monitored at home.

Table 2. The modified jadad scores of the included studies.

First author	Published year	Was the research described as randomized?	Was the approach of randomization appropriate?	Was the research described as blinding?	Was the approach of blinding appropriate?	Was there a presentation of withdrawals and dropouts?	Was there a presentation of the inclusion/exclusion criteria?	Was the approach used to assess adverse effects described?	Was the approach of statistical analysis described?	Total
OCD										
Hwang *et al.* [43]	2021	1	1	0	0	1	1	1	1	6
Norman *et al.* [44]	2021	1	1	1	1	1	1	0	1	7
Kobayashi *et al.* [45]	2020	1	1	1	1	1	1	1	1	8
Kyrios *et al.* [46]	2018	1	1	1	1	1	1	0	1	7
Peris *et al.* [47]	2017	1	1	1	1	1	1	0	1	7
Marsden *et al.* [48]	2017	1	1	0	0	1	0	0	1	4
Foa *et al.* [49]	2015	1	1	1	1	1	1	1	1	8
Foa *et al.* [50]	2013	1	1	1	1	1	1	0	1	7
Hoexter *et al.* [51]	2013	1	1	1	1	1	1	1	1	8
Belotto-Silva *et al.* [52]	2012	1	0	1	1	1	1	0	1	6
Connor *et al.* [53]	2005	0	0	1	1	1	1	0	0	4
Whittal *et al.* [54]	2005	1	0	1	1	1	1	0	1	6
Foa *et al.* [42]	2005	1	1	1	1	1	1	1	1	8
Nakatani *et al.* [55]	2005	1	1	1	1	1	1	1	1	8
POTS [18]	2004	1	1	0	0	1	1	1	1	6
de Haan *et al.* [56]	1998	1	0	0	0	1	1	1	1	5
van Balkom *et al.* [57]	1998	1	1	0	0	1	1	1	1	6
de Haan *et al.* [58]	1997	1	1	0	0	1	1	0	1	5
TS										
Hollis *et al.* [59]	2021	1	1	1	1	1	1	1	1	8
Andrén *et al.* [60]	2019	1	1	1	1	1	1	1	1	8
Verdellen *et al.* [61]	2004	1	1	1	1	1	1	0	1	7

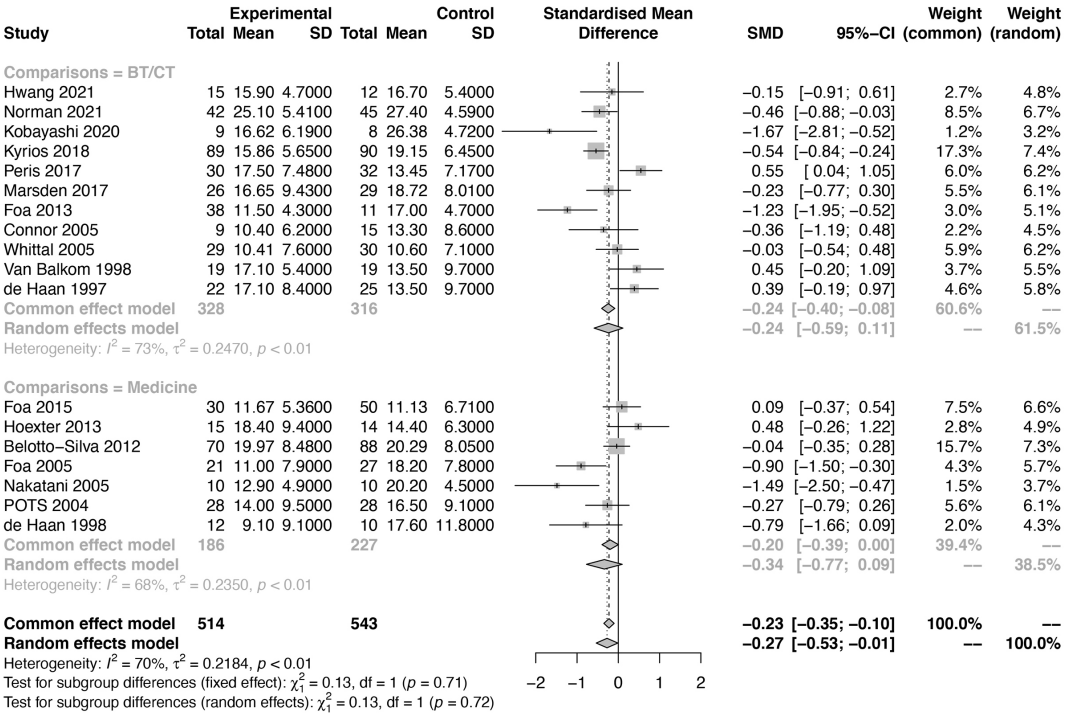

Fig. 3. Forest plots of the subgroup analysis by different comparisons for the efficacy of ERP-based therapy (medicine and BT/CT).

Table 3. Results of meta-regression analysis of the pooled SMD of ERP for OCD.

Predictors	tau^2	I^2	H^2	R^2	The test of moderators (p)
Publication year	0.237	75.37%	4.12	0.00%	0.608
Session	0.240	76.35%	4.23	0.00%	0.998

Note: tau^2, the estimated amount of residual heterogeneity; I^2, the residual heterogeneity; H^2, the unaccounted variability; R^2, the amount of heterogeneity accounted for.

4. Discussion

In this study, we conducted a meta-analysis to identify the efficacy of ERP-based therapy for OCD and TS/chronic tic disorder. A small-to-moderate effect size of ERP-based therapy was found in the experimental groups compared to the control groups. The effect sizes were comparable with the medicine (i.e., risperidone, fluoxetine, clomipramine, and sertraline) and other behavior therapies. The results indicate that ERP-based therapy can be effective in alleviating obsessive-compulsive symptoms and tic symptoms.

In the present study, we found that ERP-based therapy for OCD can be applied in both adults and children. For example, in a randomized controlled trial, ERP-based therapy alone does not differ from sertraline alone (p = 0.24) after 12 weeks of treatment in OCD patients aged 7 through 17 years [18]. For adult patients with OCD, ERP is comparable to first-line pharmacological treatments (e.g., SRIs) [11]. However, to determine whether ERP-based therapy for OCD shows differences between children and adults, more studies including different age groups are needed in the future. Moreover, it should be noted that the I^2 of the pooled SMD of ERP for OCD was 70% (95% CI: 51.1–81.4, p < 0.01), suggesting substantial heterogeneity. In follow-up analyses, however, no associated factors were found to significantly explain the heterogeneity. The potential reasons need to be explored in future studies. In addition, with the development of ERP, we should pay more attention to the remission rather than clinical response. We also need to focus on how to improve the remission rate of ERP in future studies

Currently, modifications of CBT formats, such as CBT augmented with d-cycloserine [73], internet-delivered treatments [74], video teleconferencing methods [75], and Bergen 4-day treatment (B4DT) [76], are also used in OCD patients. The modifications of ERP programs based on different individual needs may require further investigation in the future. Many patients with OCD have no access to ERP [77], and possible barriers include clinician-related factors, aspects of the phenomenology of OCD, willingness to experience unpleasant sensations during ERP, financial barriers, and geographical factors [78,79]. Several options for accessing online CBT have been developed to make it easier to access this treatment [80,81], but further research is needed to extend the reach of ERP online. Furthermore, more research is needed regarding the long-term efficacy of ERP, as longer treatment durations may yield reduced OCD

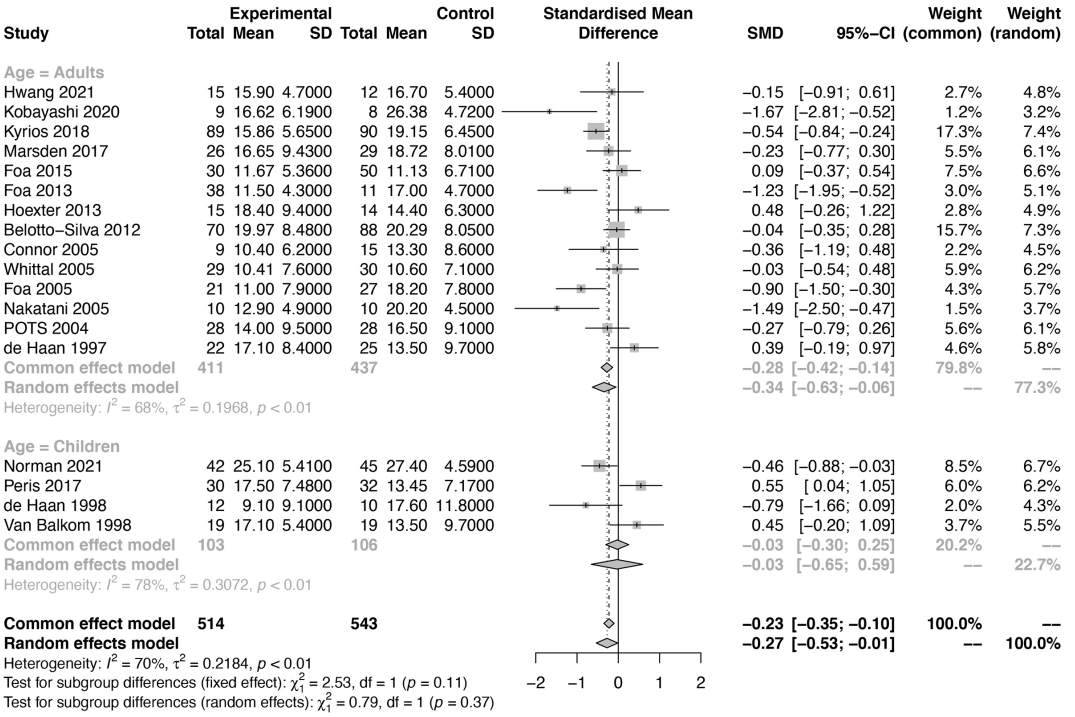

Fig. 4. Forest plots of the subgroup analysis by age group for the efficacy of ERP-based therapy (adults and children).

Table 4. Studies focused on the ERP-based therapy and related brain areas.

Studies	Year	M/F ratio OCD	M/F ratio controls	Mean age of OCD patients	Mean age of controls	Involved brain areas
Cyr *et al.* [63]	2021	12/13	11/12	12.76 (2.92)	11 (3.27)	lateral amygdala/ventromedial prefrontal cortex
Norman *et al.* [44]	2021	14/28	16/29	24.23 (9.13)	24.51 (9.32)	the right temporal lobe/rostral anterior cingulate cortex/ventromedial prefrontal/orbitofrontal/lateral prefrontal/amygdala
Cao *et al.* [64]	2021	22/12	27/23	18–50	28.48 (6.19)	the left lingual gyrus/left middle temporal gyrus/left precuneus/left fusiform gyrus
Pagliaccio *et al.* [65]	2020	14/14	14/13	12.14 (3.34)	11.26 (3.23)	middle and superior frontal/angular/lingual/precentral/ superior temporal/supramarginal gyri
Thorsen *et al.* [66]	2020	12/19	8/18	30.19 (9.21)	31 (10.73)	the right inferior frontal gyrus/the right amygdala/the right inferior frontal gyrus/the pre-supplementary motor area/supplementary motor area
Cyr *et al.* [67]	2020	12/13	11/12	12.8 (2.9)	11.0 (3.3)	left angular gyrus and left frontal pole/frontoparietal/ventral attention/cingulo-opercular/right putamen/posterior insula and posterior insula (auditory network)
Moody *et al.* [68]	2017	22/21	14/10	33 (10.7)	31 (12.0)	the cerebellum/caudate/putamen/dorsolateral/ventrolateral prefrontal
Göttlich *et al.* [69]	2015	5/12	4/15	32.6 (11.6)	30.4 (9.6)	amygdala/superficial amygdala
Olatunji *et al.* [70]	2014	6/6	-	32.25 (9.9)	-	anterior temporal pole/amygdala/dorsolateral prefrontal
Huyser *et al.* [71]	2013	5/12	6/14	13.8 (2.8)	14.6 (2.6)	orbitofrontal
Hoexter *et al.* [51]	2013	5/10	6/8	33.3 (10.0)	33.1 (11.6)	right medial prefrontal
Freyer *et al.* [72]	2011	7/3	6/4	36.1 (9.36)	39.6 (10.48)	orbitofrontal cortex/right putamen/the caudate nucleus/pallidum

Note: OCD, Obsessive-Compulsive Disorder; M/F, males/females.

symptoms. The potential benefits of the combination of behavioral therapy and pharmacotherapy are also required to help patients not responsive to monotherapy or with severe OCD.

In this study, we found evidence to support the efficacy of ERP-based therapy for reducing obsession-compulsion symptoms. Behavioral therapy and SRIs were found to be comparable in improving the symptoms in adults with OCD [6,7], and ERP also exhibited efficacy for reducing tic symptoms. It appears that the mechanisms that underlie the treatment of OCD and tic disorders are similar to some extent. Indeed, OCD and TS overlap in many aspects, such as their clinical phenomenology and tendency to co-occur in affected individuals. A tic-related OCD subtype

in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) may occur in 10%–40% of patients diagnosed with childhood OCD [1,82], and approximately 25%–50% of patients with TS meet the criteria for OCD [83,84]. Similarly, approximately 30% of patients with OCD have a history of combined TS [85,86]. Both animal studies and neuroimaging studies suggest that abnormal function of cortical basal ganglia circuitry results in tics and compulsive behaviors [87–89]. Abnormalities of the dopaminergic system may be the common pathophysiologic mechanism of TS and OCD [90], and based on these similarities, it is perhaps not surprising that ERP was not only effective for mild-to-moderate OCD and TS/chronic tic disorder but may also be a promising behavior therapy for the tic-related OCD subtype.

Patients with tic disorder are trained to endure premonitory urges (PUs), or "uncomfortable bodily feelings", a longing to make things "just right" [91,92] to suppress tic symptoms in ERP. The long period exposed to the unpleasant sensation and to resist the tic symptoms, the patients will learn to endure the sensation [30]. Habit reversal therapy (HRT) is another form of CBT that is effective for the treatment of tic disorder and includes awareness training, relaxation training, and competing-response training as its core procedures. ERP and HRT are both recommended as first-line behavioral treatments for tic disorder [30,31,93], and the combination of the two may be a new direction for behavior therapy in the future. In addition, ERP has also been applied to anorexia nervosa, body dysmorphic disorder, anxiety disorder, hypochondriasis, and repetitive behaviors in autism [8,94–98]. ERP (unlike medication) has essentially no untoward effects and that benefits of ERP are typically retained after termination of treatment. And more follow-up studies are needed in the future.

The neurological mechanism of the effectiveness of EPR is unclear, but it may lie in changes in the prefrontal cortex and anterior cingulate cortex (ACC). A prior study found that the volume of gray matter within the medial prefrontal cortex was correlated with the response to ERP-based CBT in OCD patients [51]. A study found that with intensive ERP-based CBT, the degree of improvement in OCD symptoms significantly increases in right dorsal ACC activity and decreases in bilateral thalamic activity [99]. OCD patients who respond to exposure therapy have thinner rostral ACC than those who do not [100]. Greater conflict-related activity in the anterior insula and anterior and posterior cingulate predicted a greater ERP response in OCD patients [65]. Some associations between brain activation and treatment response were specific to ERP-based CBT [44]. More studies are needed to research the neurological mechanism of ERP for OCD and other psychiatric diseases.

Additionally, study found that the family-based ERP might also help to improve family functioning and quality of life, social functioning [45]. Likewise, TS patients had better quality of life in the ERP group than psychoeducation group at 3 months [59]. We might need more evidence for this dimension of ERP in future studies.

Several limitations are needed to be noted. First, the included studies and sample size were limited, which might reduce the credibility of the results. Second, the validated scales for OCD were restricted to widely used scales of Y-BOCS and CY-BOCS, and the studies that applied the other scales were not included. Third, the studies included not only ERP but also ERP-based therapy, which might increase the heterogeneity of the data. Despite these limitations, this study provided evidence of the treatment effect of ERP on OCD & TS.

5. Conclusions

In summary, we identified a small-to-medium effect size of ERP-based therapy to relieve obsessive-compulsive symptoms and tic symptoms. We suggest that combining ERP with other therapies and online services might be an ideal direction for ERP in the future. The prefrontal cortex and ACC might have associations with the neurological mechanism of the ERP.

Abbreviations

ERP, Exposure and response prevention; CBT, Cognitive behavioral therapy; OCD, Obsessive-compulsive disorder; TS, Tourette syndrome; SMD, standard mean difference; CI, Confidence interval; SRIs, Serotonin reuptake inhibitors; Y-BOCS, Yale-Brown Obsessive-Compulsive Symptom Scale; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; BT/CT, Behavior therapy/cognitive therapy; HRT, Habit reversal therapy; PUs, premonitory urges; MRI, Magnetic Resonance Imaging.

Author Contributions

For this manuscript, YC and YL took the initiative. MW finished the data collection. YL performed the data analysis and JY and LC finished the draft.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2103097.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). 5th edn. American Psychiatric Publishing: Washington DC. 2013.

[2] Franklin ME, Foa EB. Treatment of obsessive compulsive disorder. Annual Review of Clinical Psychology. 2011; 7: 229–243.

[3] Adam Y, Meinlschmidt G, Gloster AT, Lieb R. Obsessive-compulsive disorder in the community: 12-month prevalence, comorbidity and impairment. Social Psychiatry and Psychiatric Epidemiology. 2012; 47: 339–349.

[4] Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Molecular Psychiatry. 2010; 15: 53–63.

[5] Pérez-Vigil A, Fernández de la Cruz L, Brander G, Isomura K, Jangmo A, Feldman I, *et al*. Association of Obsessive-Compulsive Disorder With Objective Indicators of Educational Attainment: A Nationwide Register-Based Sibling Control Study. JAMA Psychiatry. 2018; 75: 47–55.

[6] Ost LG, Havnen A, Hansen B, Kvale G. Cognitive behavioral treatments of obsessive-compulsive disorder. A systematic review and meta-analysis of studies published 1993-2014. Clinical Psychology Review. 2015; 40: 156–169.

[7] Skapinakis P, Caldwell D, Hollingworth W, Bryden P, Fineberg N, Salkovskis P, *et al*. A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive-compulsive disorder in children/adolescents and adults. Health Technology Assessment. 2016; 20: 1–392.

[8] 2019 surveillance of obsessive-compulsive disorder and body dysmorphic disorder: treatment (NICE guideline CG31). National Institute for Health and Care Excellence: London. 2019.

[9] McGuire JF, Piacentini J, Lewin AB, Brennan EA, Murphy TK, Storch EA. A Meta-Analysis Of Cognitive Behavior Therapy And Medication for Child Obsessive-Compulsive Disorder: Moderators Of Treatment Efficacy, Response, And Remission. Depression and Anxiety. 2015; 32: 580–593.

[10] Ost LG, Riise EN, Wergeland GJ, Hansen B, Kvale G. Cognitive behavioral and pharmacological treatments of OCD in children: A systematic review and meta-analysis. Journal of Anxiety Disorders. 2016; 43: 58–69.

[11] Law C, Boisseau CL. Exposure and Response Prevention in the Treatment of Obsessive-Compulsive Disorder: Current Perspectives. Psychology Research and Behavior Management. 2019; 12: 1167–1174.

[12] Abramowitz JS. The psychological treatment of obsessive-compulsive disorder. The Canadian Journal of Psychiatry. 2006; 51: 407–416.

[13] Simpson HB, Foa EB, Liebowitz MR, Huppert JD, Cahill S, Maher MJ, *et al*. Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial. JAMA Psychiatry. 2013; 70: 1190–1199.

[14] Bloch MH, Storch EA. Assessment and management of treatment-refractory obsessive-compulsive disorder in children. Journal of the American Academy of Child and Adolescent Psychiatry. 2015; 54: 251–262.

[15] Ivarsson T, Skarphedinsson G, Kornor H, Axelsdottir B, Biedilae S, Heyman I, *et al*. The place of and evidence for serotonin reuptake inhibitors (SRIs) for obsessive compulsive disorder (OCD) in children and adolescents: Views based on a systematic review and meta-analysis. Psychiatry Research. 2015; 227: 93–103.

[16] Johnco C, McGuire JF, Roper T, Storch EA. A meta-analysis of dropout rates from exposure with response prevention and pharmacological treatment for youth with obsessive compulsive disorder. Depression and Anxiety. 2019; 37: 407–417.

[17] McLean CP, Zandberg LJ, Van Meter PE, Carpenter JK, Simpson HB, Foa EB. Exposure and response prevention helps adults with obsessive-compulsive disorder who do not respond to pharmacological augmentation strategies. The Journal of Clinical Psychiatry. 2015; 76: 1653–1657.

[18] Pediatric OCDTST. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. The Journal of the American Medical Association. 2004; 292: 1969–1976.

[19] Fisher PL, Wells A. How effective are cognitive and behavioral treatments for obsessive-compulsive disorder? A clinical significance analysis. Behaviour Research and Therapy. 2005; 43: 1543–1558.

[20] Melchior K, Franken I, Deen M, van der Heiden C. Metacognitive therapy versus exposure and response prevention for obsessive-compulsive disorder: study protocol for a randomized controlled trial. Trials. 2019; 20: 277.

[21] Norman LJ, Taylor SF, Liu Y, Radua J, Chye Y, De Wit SJ, *et al*. Error Processing and Inhibitory Control in Obsessive-Compulsive Disorder: a Meta-analysis Using Statistical Parametric Maps. Biological Psychiatry. 2019; 85: 713–725.

[22] Stein DJ, Costa DLC, Lochner C, Miguel EC, Reddy YCJ, Shavitt RG, *et al*. Obsessive-compulsive disorder. Nature Reviews Disease Primers. 2019; 5: 52.

[23] Thorsen AL, van den Heuvel OA, Hansen B, Kvale G. Neuroimaging of psychotherapy for obsessive-compulsive disorder: A systematic review. Psychiatry Research. 2015; 233: 306–313.

[24] Nabeyama M, Nakagawa A, Yoshiura T, Nakao T, Nakatani E, Togao O, *et al*. Functional MRI study of brain activation alterations in patients with obsessive-compulsive disorder after symptom improvement. Psychiatry Research. 2008; 163: 236–247.

[25] Riesel A, Endrass T, Auerbach LA, Kathmann N. Overactive Performance Monitoring as an Endophenotype for Obsessive-Compulsive Disorder: Evidence From a Treatment Study. The American Journal of Psychiatry. 2015; 172: 665–673.

[26] Bloch MH, Leckman JF. Clinical course of Tourette syndrome. Journal of Psychosomatic Research. 2009; 67: 497–501.

[27] Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 1: the epidemiological and prevalence studies. Journal of Psychosomatic Research. 2008; 65: 461–472.

[28] Worbe Y, Mallet L, Golmard JL, Behar C, Durif F, Jalenques I, *et al*. Repetitive behaviours in patients with Gilles de la Tourette syndrome: tics, compulsions, or both? PLoS ONE. 2010; 5: e12959.

[29] Hirschtritt ME, Darrow SM, Illmann C, Osiecki L, Grados M, Sandor P, *et al*. Genetic and phenotypic overlap of specific obsessive-compulsive and attention-deficit/hyperactive subtypes with Tourette syndrome. Psychological Medicine. 2018; 48: 279–293.

[30] Verdellen C, van de Griendt J, Hartmann A, Murphy T. European clinical guidelines for Tourette Syndrome and other tic disorders. Part III: behavioural and psychosocial interventions. European Child & Adolescent Psychiatry. 2011; 20: 197–207.

[31] Steeves T, McKinlay BD, Gorman D, Billinghurst L, Day L,

Carroll A, *et al*. Canadian Guidelines for the Evidence-Based Treatment of Tic Disorders: Behavioural Therapy, Deep Brain Stimulation, and Transcranial Magnetic Stimulation. The Canadian Journal of Psychiatry. 2012; 57: 144–151.

[32] Pringsheim T, Okun MS, Müller-Vahl K, Martino D, Jankovic J, Cavanna AE, *et al*. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology. 2019; 92: 896–906.

[33] Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ, Henk HJ. Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. Psychopharmacology. 1998; 136: 205–216.

[34] Abramowitz JS, Whiteside SP, Deacon BJ. The effectiveness of treatment for pediatric obsessive-compulsive disorder: A meta-analysis. Behavior Therapy. 2005; 36: 55–63.

[35] Olatunji BO, Davis ML, Powers MB, Smits JA. Cognitive-behavioral therapy for obsessive-compulsive disorder: A meta-analysis of treatment outcome and moderators. Journal of Psychiatric Research. 2013; 47: 33–41.

[36] Fagard RH, Staessen JA, Thijs L. Advantages and disadvantages of the meta-analysis approach. Journal of Hypertension Supplement. 1996; 14: S9–S12; discussion S13.

[37] Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, *et al*. The Yale-Brown Obsessive Compulsive Scale. i. Development, use, and reliability. Archives of General Psychiatry. 1989; 46: 1006–1011.

[38] Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, *et al*. Children's Yale-Brown Obsessive Compulsive Scale: Reliability and Validity. Journal of the American Academy of Child & Adolescent Psychiatry. 1997; 36: 844–852.

[39] Jadad AR, Moher D, Klassen TP. Guides for Reading and Interpreting Systematic Reviews: II. How did the authors find the studies and assess their quality? Archives of Pediatrics & Adolescent Medicine. 1998; 152: 812–817.

[40] Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Lawrence Earlbaum Associates: Hillsdale NJ. 1988.

[41] Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions. Version 510 2011, The Cochrane Collaboration. 2011. Available at: www.cochrane-handbook.org (Accessed: 21 February 2022).

[42] Foa EB, Liebowitz MR, Kozak MJ, Davies S, Campeas R, Franklin ME, *et al*. Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. The American Journal of Psychiatry. 2005; 162: 151–161.

[43] Hwang H, Bae S, Hong JS, Han DH. Comparing Effectiveness Between a Mobile App Program and Traditional Cognitive Behavior Therapy in Obsessive-Compulsive Disorder: Evaluation Study. JMIR Mental Health. 2021; 8: e23778.

[44] Norman LJ, Mannella KA, Yang H, Angstadt M, Abelson JL, Himle JA, *et al*. Treatment-Specific Associations between Brain Activation and Symptom Reduction in OCD Following CBT: a Randomized fMRI Trial. American Journal of Psychiatry. 2021; 178: 39–47.

[45] Kobayashi Y, Kanie A, Nakagawa A, Takebayashi Y, Shinmei I, Nakayama N, *et al*. An Evaluation of Family-Based Treatment for OCD in Japan: A Pilot Randomized Controlled Trial. Frontiers in Psychiatry. 2019; 10: 932.

[46] Kyrios M, Ahern C, Fassnacht DB, Nedeljkovic M, Moulding R, Meyer D. Therapist-Assisted Internet-Based Cognitive Behavioral Therapy Versus Progressive Relaxation in Obsessive-Compulsive Disorder: Randomized Controlled Trial. Journal of Medical Internet Research. 2018; 20: e242.

[47] Peris TS, Rozenman MS, Sugar CA, McCracken JT, Piacentini J. Targeted Family Intervention for Complex Cases of Pediatric Obsessive-Compulsive Disorder: a Randomized Controlled Trial. Journal of the American Academy of Child & Adolescent Psychiatry. 2017; 56: 1034–1042.e1.

[48] Marsden Z, Lovell K, Blore D, Ali S, Delgadillo J. A randomized controlled trial comparing EMDR and CBT for obsessive-compulsive disorder. Clinical Psychology & Psychotherapy. 2018; 25: e10–e18.

[49] Foa EB, Simpson HB, Rosenfield D, Liebowitz MR, Cahill SP, Huppert JD, *et al*. Six-Month Outcomes from a Randomized Trial Augmenting Serotonin Reuptake Inhibitors with Exposure and Response Prevention or Risperidone in Adults with Obsessive-Compulsive Disorder. The Journal of Clinical Psychiatry. 2015; 76: 440–446.

[50] Foa EB, Simpson HB, Liebowitz MR, Powers MB, Rosenfield D, Cahill SP, *et al*. Six-Month Follow-up of a Randomized Controlled Trial Augmenting Serotonin Reuptake Inhibitor Treatment with Exposure and Ritual Prevention for Obsessive-Compulsive Disorder. The Journal of Clinical Psychiatry. 2013; 74: 464–469.

[51] Hoexter MQ, Dougherty DD, Shavitt RG, D'Alcante CC, Duran FLS, Lopes AC, *et al*. Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive–compulsive disorder. European Neuropsychopharmacology. 2013; 23: 569–580.

[52] Belotto-Silva C, Diniz JB, Malavazzi DM, Valério C, Fossaluza V, Borcato S, *et al*. Group cognitive-behavioral therapy versus selective serotonin reuptake inhibitors for obsessive-compulsive disorder: a practical clinical trial. Journal of Anxiety Disorders. 2012; 26: 25–31.

[53] O'Connor KP, Aardema F, Bouthillier D, Fournier S, Guay S, Robillard S, *et al*. Evaluation of an inference-based approach to treating obsessive-compulsive disorder. Cognitive Behaviour Therapy. 2005; 34: 148–163.

[54] Whittal ML, Thordarson DS, McLean PD. Treatment of obsessive-compulsive disorder: cognitive behavior therapy vs. exposure and response prevention. Behaviour Research and Therapy. 2005; 43: 1559–1576.

[55] Nakatani E, Nakagawa A, Nakao T, Yoshizato C, Nabeyama M, Kudo A, *et al*. A randomized controlled trial of Japanese patients with obsessive-compulsive disorder–effectiveness of behavior therapy and fluvoxamine. Psychotherapy and Psychosomatics. 2005; 74: 269–276.

[56] de Haan E, Hoogduin KA, Buitelaar JK, Keijsers GP. Behavior therapy versus clomipramine for the treatment of obsessive-compulsive disorder in children and adolescents. Journal of the American Academy of Child and Adolescent Psychiatry. 1998; 37: 1022–1029.

[57] van Balkom AJ, de Haan E, van Oppen P, Spinhoven P, Hoogduin KA, van Dyck R. Cognitive and behavioral therapies alone versus in combination with fluvoxamine in the treatment of obsessive compulsive disorder. The Journal of Nervous and Mental Disease. 1998; 186: 492–499.

[58] de Haan E, van Oppen P, van Balkom AJ, Spinhoven P, Hoogduin KA, Van Dyck R. Prediction of outcome and early vs. late improvement in OCD patients treated with cognitive behaviour therapy and pharmacotherapy. Acta Psychiatrica Scandinavica. 1997; 96: 354–361.

[59] Hollis C, Hall CL, Jones R, Marston L, Novere ML, Hunter R, *et al*. Therapist-supported online remote behavioural intervention for tics in children and adolescents in England (ORBIT): a multicentre, parallel group, single-blind, randomised controlled trial. The Lancet Psychiatry. 2021; 8: 871–882.

[60] Andrén P, Aspvall K, Fernández de la Cruz L, Wiktor P, Romano S, Andersson E, *et al*. Therapist-guided and parent-guided internet-delivered behaviour therapy for paediatric Tourette's disorder: a pilot randomised controlled trial with long-term

follow-up. BMJ Open. 2019; 9: e024685.
[61] Verdellen CWJ, Keijsers GPJ, Cath DC, Hoogduin CAL. Exposure with response prevention versus habit reversal in Tourettes's syndrome: a controlled study. Behaviour Research and Therapy. 2004; 42: 501–511.
[62] Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of Inhaled and Oral Corticosteroids and the Long-term Risk of Cataract. Ophthalmology. 2009; 116: 652–657.
[63] Cyr M, Pagliaccio D, Yanes-Lukin P, Goldberg P, Fontaine M, Rynn MA, *et al*. Altered fronto-amygdalar functional connectivity predicts response to cognitive behavioral therapy in pediatric obsessive-compulsive disorder. Depression and Anxiety. 2021; 38: 836–845.
[64] Cao, R., Yang, X., Luo, J., Wang, P., Meng, F., Xia, M., ... & Li, Z. The effects of cognitive behavioral therapy on the whole brain structural connectome in unmedicated patients with obsessive-compulsive disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2021; 104, 110037.
[65] Pagliaccio D, Cha J, He X, Cyr M, Yanes-Lukin P, Goldberg P, *et al*. Structural neural markers of response to cognitive behavioral therapy in pediatric obsessive-compulsive disorder. Journal of Child Psychology and Psychiatry. 2020; 61: 1299–1308.
[66] Thorsen A L , Wit S , Hagland P , et al. Stable inhibition-related inferior frontal hypoactivation and fronto-limbic hyperconnectivity in obsessive–compulsive disorder after concentrated exposure therapy[J]. NeuroImage: Clinical, 2020; 28:102460.
[67] Cyr, M., Pagliaccio, D., Yanes-Lukin, P. et al. Altered network connectivity predicts response to cognitive-behavioral therapy in pediatric obsessive–compulsive disorder. Neuropsychopharmacol. 2020; 45: 1232–1240
[68] Moody TD, Morfini F, Cheng G, Sheen C, Tadayonnejad R, Reggente N, *et al*. Mechanisms of cognitive-behavioral therapy for obsessive-compulsive disorder involve robust and extensive increases in brain network connectivity. Translational Psychiatry. 2017; 7: e1230.
[69] Göttlich, M., Krämer, U. M., Kordon, A., Hohagen, F., & Zurowski, B. Resting-state connectivity of the amygdala predicts response to cognitive behavioral therapy in obsessive compulsive disorder. Biological Psychology, 2015; 111, 100-109.
[70] Olatunji, B. O., Ferreira-Garcia, R., Caseras, X., Fullana, M. A., Wooderson, S., Speckens, A., ... & Mataix-Cols, D. Predicting response to cognitive behavioral therapy in contamination-based obsessive–compulsive disorder from functional magnetic resonance imaging. Psychological medicine, 2014; 44(10), 2125-2137.
[71] Huyser, C., van den Heuvel, O. A., Wolters, L., de Haan, E., Lindauer, R., & Veltman, D. J. A longitudinal VBM study in paediatric obsessive–compulsive disorder at 2-year follow-up after cognitive behavioural therapy. The World Journal of Biological Psychiatry, 2014; 15(6), 443-452.
[72] Freyer T, Klöppel S, Tüscher O, Kordon A, Zurowski B, Kuelz A, *et al*. Frontostriatal activation in patients with obsessive-compulsive disorder before and after cognitive behavioral therapy. Psychological Medicine. 2011; 41: 207–216.
[73] Storch EA, Wilhelm S, Sprich S, Henin A, Micco J, Small BJ, *et al*. Efficacy of Augmentation of Cognitive Behavior Therapy with Weight-Adjusted d-Cycloserine vs Placebo in Pediatric Obsessive-Compulsive Disorder: a Randomized Clinical Trial. JAMA Psychiatry. 2016; 73: 779–788.
[74] Lenhard F, Andersson E, Mataix-Cols D, Rück C, Vigerland S, Högström J, *et al*. Therapist-Guided, Internet-Delivered Cognitive-Behavioral Therapy for Adolescents with Obsessive-Compulsive Disorder: a Randomized Controlled Trial. Journal of the American Academy of Child & Adolescent Psychiatry. 2017; 56: 10–19.e2.
[75] Comer JS, Furr JM, Kerns CE, Miguel E, Coxe S, Elkins RM, *et al*. Internet-delivered, family-based treatment for early-onset OCD: a pilot randomized trial. Journal of Consulting and Clinical Psychology. 2017; 85: 178–186.
[76] Hansen B, Kvale G, Hagen K, Havnen A, Öst L. The Bergen 4-day treatment for OCD: four years follow-up of concentrated ERP in a clinical mental health setting. Cognitive Behaviour Therapy. 2019; 48: 89–105.
[77] Krebs G, Heyman I. Obsessive-compulsive disorder in children and adolescents. Archives of Disease in Childhood. 2015; 100: 495–499.
[78] Keleher J, Jassi A, Krebs G. Clinician-reported barriers to using exposure with response prevention in the treatment of paediatric obsessive-compulsive disorder. Journal of Obsessive-Compulsive and Related Disorders. 2020; 24: 100498.
[79] Reid AM, Garner LE, Van Kirk N, Gironda C, Krompinger JW, Brennan BP, *et al*. How willing are you? Willingness as a predictor of change during treatment of adults with obsessive-compulsive disorder. Depression and Anxiety. 2017; 34: 1057–1064.
[80] Babiano-Espinosa L, Wolters LH, Weidle B, op de Beek V, Pedersen SA, Compton S, *et al*. Acceptability, feasibility, and efficacy of Internet cognitive behavioral therapy (iCBT) for pediatric obsessive-compulsive disorder: a systematic review. Systematic Reviews. 2019; 8: 284.
[81] Wootton BM. Remote cognitive-behavior therapy for obsessive-compulsive symptoms: a meta-analysis. Clinical Psychology Review. 2016; 43: 103–113.
[82] Leckman JF, Denys D, Simpson HB, Mataix-Cols D, Hollander E, Saxena S, *et al*. Obsessive-compulsive disorder: a review of the diagnostic criteria and possible subtypes and dimensional specifiers for DSM-V. Depression and Anxiety. 2010; 27: 507–527.
[83] Lebowitz ER, Motlagh MG, Katsovich L, King RA, Lombroso PJ, Grantz H, *et al*. Tourette syndrome in youth with and without obsessive compulsive disorder and attention deficit hyperactivity disorder. European Child & Adolescent Psychiatry. 2012; 21: 451–457.
[84] Cohen SC, Leckman JF, Bloch MH. Clinical assessment of Tourette syndrome and tic disorders. Neuroscience and Biobehavioral Reviews. 2013; 37: 997–1007.
[85] Nikolajsen KH, Nissen JB, Thomsen PH. Obsessive-compulsive disorder in children and adolescents: symptom dimensions in a naturalistic setting. Nordic Journal of Psychiatry. 2011; 65: 244–250.
[86] Torresan RC, Ramos-Cerqueira ATA, Shavitt RG, do Rosário MC, de Mathis MA, Miguel EC, *et al*. Symptom dimensions, clinical course and comorbidity in men and women with obsessive-compulsive disorder. Psychiatry Research. 2013; 209: 186–195.
[87] Graybiel AM. Habits, rituals, and the evaluative brain. Annual Review of Neuroscience. 2008; 31: 359–387.
[88] Lewis M, Kim S. The pathophysiology of restricted repetitive behavior. Journal of Neurodevelopmental Disorders. 2009; 1: 114–132.
[89] Muehlmann AM, Lewis MH. Abnormal repetitive behaviours: shared phenomenology and pathophysiology. Journal of Intellectual Disability Research. 2012; 56: 427–440.
[90] Denys D, de Vries F, Cath D, Figee M, Vulink N, Veltman DJ, *et al*. Dopaminergic activity in Tourette syndrome and obsessive-compulsive disorder. European Neuropsychopharmacology. 2013; 23: 1423–1431.
[91] Leckman JF, Walker DE, Goodman WK, Pauls DL, Cohen DJ. "Just right" perceptions associated with compulsive behavior in Tourette's syndrome. The American Journal of Psychiatry. 1994; 151: 675–680.

[92] Prado HS, Rosário MC, Lee J, Hounie AG, Shavitt RG, Miguel EC. Sensory phenomena in obsessive-compulsive disorder and tic disorders: a review of the literature. CNS Spectrums. 2008; 13: 425–432.
[93] Murphy TK, Lewin AB, Storch EA, Stock S. Practice parameter for the assessment and treatment of children and adolescents with tic disorders. Journal of the American Academy of Child and Adolescent Psychiatry. 2013; 52: 1341–1359.
[94] Steinglass JE, Albano AM, Simpson HB, Wang Y, Zou J, Attia E, *et al*. Confronting fear using exposure and response prevention for anorexia nervosa: a randomized controlled pilot study. The International Journal of Eating Disorders. 2014; 47: 174–180.
[95] Whiteside SPH, Deacon BJ, Benito K, Stewart E. Factors associated with practitioners' use of exposure therapy for childhood anxiety disorders. Journal of Anxiety Disorders. 2016; 40: 29–36.
[96] Visser S, Bouman TK. The treatment of hypochondriasis: exposure plus response prevention vs cognitive therapy. Behaviour Research and Therapy. 2001; 39: 423–442.
[97] Zarafshan H, Salmanian M, Aghamohammadi S, Mohammadi MR, Mostafavi S. Effectiveness of Non-Pharmacological Interventions on Stereotyped and Repetitive Behaviors of Pre-school Children with Autism: a Systematic Review. Basic and Clinical Neuroscience. 2017; 8: 95–103.
[98] Boyd BA, Woodard CR, Bodfish JW. Feasibility of exposure response prevention to treat repetitive behaviors of children with autism and an intellectual disability: a brief report. Autism. 2013; 17: 196–204.
[99] Saxena S, Gorbis E, O'Neill J, Baker SK, Mandelkern MA, Maidment KM, *et al*. Rapid effects of brief intensive cognitive-behavioral therapy on brain glucose metabolism in obsessive-compulsive disorder. Molecular Psychiatry. 2009; 14: 197–205.
[100] Fullana MA, Cardoner N, Alonso P, Subirà M, López-Solà C, Pujol J, *et al*. Brain regions related to fear extinction in obsessive-compulsive disorder and its relation to exposure therapy outcome: a morphometric study. Psychological Medicine. 2014; 44: 845–856.